Does the Visual Field Improve After Initiation of Intraocular Pressure Lowering in the United Kingdom Glaucoma Treatment Study?

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• PURPOSE: Evidence to support the hypothesis that visual field (VF) status can improve after initiation of intraocular pressure (IOP) reducing treatment is controversial. We take advantage of participant eligibility data from the United Kingdom Glaucoma Treatment Study (UKGTS) to test this hypothesis in newly diagnosed glaucomatous patients randomized to IOP-lowering therapy or placebo.

• DESIGN: Multicentre, randomized, triple-masked, placebo-controlled trial.

• METHODS: Participants were newly diagnosed open-angle glaucoma patients in the UKGTS with eligibility and baseline data (n = 202 and n = 205 participants from the treatment and placebo groups, respectively).

UKGTS eligibility data, including two reliable VFs (Humphrey 24-2 SITA Standard) and IOP measurements were compared to UKGTS trial baseline data acquired after allocation to treatment (topical prostaglandin analog) or placebo eye drops. Mean change in VF mean deviation (MD) and proportion of eyes that improved MD by more than different thresholds were compared across this interval in the treatment and placebo groups. Secondary analyses included stratifying the groups by level of IOP, level of VF loss, and age, along with pointwise analyses including change in subsets of VF locations. The main outcome measure was the mean change in VF MD.

• RESULTS: Mean (standard deviation [SD]) time between eligibility/baseline visits and reduction in IOP was 12 (3) weeks and 4.8 (4.2) and 1.0 (3.6) mmHg for the treated and placebo eyes, respectively. Mean (SD) change in MD was almost the same for the treated (–0.03 [1.45] dB) and placebo groups (+0.08 [1.72] dB; *P* = .47). The proportions of participants with an MD improvement of 1 dB or more were similar for both groups (*P* = .25). No association was found between MD improvement and magnitude of IOP lowering. Stratifying data by IOP, level of VF loss and age did not reveal any differences between the treated and placebo groups, nor did any of the pointwise VF analyses.

• CONCLUSIONS: Initial short-term VF changes in the treatment and placebo arms of UKGTS were the same. In these newly diagnosed patients with non-advanced glaucoma, we found no evidence to support the hypothesis that VF status improves after initial lowering of IOP by medical therapy. (Am J Ophthalmol 2025;269: 346–354. © 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/))

INTRAOCULAR PRESSURE (IOP) LOWERING IS THE established treatment for slowing disease worsening in glaucoma. Treatment emphasis is solely on slowing progression because visual field (VF) that has been lost to glaucoma cannot be recovered. However, this concept has been challenged with the idea that VF sensitivity can improve or recover after initiation of IOP-lowering medical or surgical treatment. An accumulation of experimental and clinical evidence supporting this idea has recently been reviewed.[1] A key limitation of any evidence from patients showing that VF sensitivity can improve after starting IOP-lowering treatment comes from the perimetry learning effect: that is, VF status seemingly improves over time with practice.[2,3]

Untangling whether a patient's VF could truly get "better" rather than the patient becoming "better" at performing the VF test is immune to any simply done experiment. VF measurements are notoriously variable, and observational studies showing VF status improving are confounded by several factors.[4,5] For example, very few studies addressing this question have had control data, which is vital to differentiate possible VF improvement due to IOP lowering from other confounding factors. To our knowledge, the only study using data from a randomized controlled trial for glaucoma was reported by Bengtsson and Heijl.[6] These in-

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vestigators used data from 255 newly diagnosed glaucoma patients randomised to IOP-lowering therapy or no treatment in the Early Manifest Glaucoma Trial (EMGT).[7,8] Patients were regularly monitored with perimetry, including at screening/eligibility visits before patients were randomized, allowing for an untreated control group that was assumed to experience the same VF learning as that randomized to treatment. Using these, at the time, unique clinical data, the investigators did not find any association between therapeutic lowering of IOP and "real" improvement in the VF. For the highest level of evidence for a clinical effect, more than one study is required. Data from the United Kingdom Glaucoma Treatment Study (UKGTS), a randomized clinical trial to investigate the effects of IOP lowering in newly diagnosed open-angle glaucoma patients, offers a similar opportunity to examine the question, especially because repeat VFs were acquired in patients before they were randomized.[9] These data would also add new knowledge because, unlike EMGT, the controls in UKGTS took placebo treatment and the trial was multicenter and triple masked. We take advantage of the UKGTS design to reassess the hypothesis of the VF improving after initiation of IOP-lowering treatment.

The purpose of this study is to compare the increase in VF sensitivity in newly diagnosed glaucoma patients shortly after they were randomized to therapeutic IOP lowering compared to those randomized to placebo, using a post hoc analysis on data from UKGTS. In other words, we test the hypothesis that the VF can improve in people with glaucoma after initial IOP lowering.

METHODS

• **UKGTS:** The UKGTS was a randomized, multicenter, triple-masked, parallel-group, placebo-controlled clinical trial and has been described elsewhere in detail.[9-11] In short, participants were adults with newly detected open-angle glaucoma who had not yet been treated, consecutively identified from ten UK hospital clinics in the United Kingdom. Participants were first invited for a trial eligibility visit, after which the eligible participants were enrolled in the study and randomized (1:1). Participants received either eye drops with 0.005% latanoprost (Pfizer, New York, NY) or latanoprost vehicle eye drops (placebo). After randomisation, participants received regular follow-up visits at which, among other measurements, IOP was measured using Goldmann applanation tonometry (Haag Streit, Koeniz, Switzerland) and standard automated perimetry (SAP) was performed with the Swedish interactive thresholding algorithm (SITA) standard 24-2 of the Humphrey Field Analyser (HFA) Mark II (Carl Zeiss Meditec, Dublin, CA). Participants were recruited between December 2006 and March 2010. The UKGTS (trial registration identifier ISRCTN96423140) adhered to the tenets of the Declaration of Helsinki. Ethics committee approval was granted by the Moorfields and Whittington Research Ethics Committee (ethics approval reference no 09/H0721/56). All participants provided written informed consent.

At the designated eligibility visit, two VF tests were performed, together with optic nerve head assessment to determine eligibility for the study. Participants needed to have repeatable VF defects that fit a diagnosis of glaucoma. A full list of trial exclusion criteria is given elsewhere, [9-11] but included advanced glaucoma (VF mean deviation [MD] worse than –10 dB in the better eye or –16 dB in the worse eye), mean intraocular pressure of ≥30 mmHg, visual acuity worse than 6/12, concomitant cataract, and previous intraocular surgery (other than uncomplicated cataract extraction >1 year previously).

Most UKGTS participants had early VF loss. Median (interquartile range [IQR]) MD (average of the two baseline VFs for each eye) of the better and worse eyes was –2.0 (–1.2 to –3.3) dB and –3.5 (–2.1 to –5.9) dB, respectively.[11] Mean (standard deviation [SD]) IOP for all eligible eyes was 19.5 (4.5) mmHg.[11]

VF testing, IOP measurement, and imaging was done at 11 scheduled visits over 24 months. The primary outcome for UKGTS was time to VF deterioration within 24 months; this was significantly longer in the treatment group than in the placebo group, with an adjusted hazard ratio of 0.44 (95% confidence interval [CI] 0.28–0.69; $P = .0003$). Again, a detailed description of these results is given in the main outcome paper.[9] For the present study, we were interested in the data, collected about two to three months apart, before (eligibility visit) and just after (baseline visit) initiation of treatment or placebo.

• **DATA ACQUISITION:** For the purpose of this study, we acquired the UKGTS eligibility VF data which were archived at Moorfields Eye Hospital, London, as paper only (HFA printout) copies. All available copies were individually scanned by one of the study authors (S.R.K.) and transferred as PDFs, along with other study data (digital format), to City, University of London under a data transfer agreement. Pointwise sensitivity thresholds (52 points; dB) were digitized from these scans with previously developed purpose-written software, using an optical character recognition algorithm.[12] Other information, such as the HFA mean deviation (MD), pattern standard deviation (PSD) and false-positive (FP) rate, were manually entered into a spreadsheet. All of the resulting data were independently and manually checked against the VF scans by 2 of the study authors (S.R.K., P.F.R.).

For the purpose of this study, we selected participants with at least two reliable SITA Standard VFs at both eligibility and baseline visits. Some participants had three VF tests performed at either visit; in these cases, we excluded the first recorded test. Nearly all eligibility VFs were acquired on the same day; for participants with eligibility VFs on different days, we excluded those for which the time interval between the two VFs was a long period (>60 days).

Some eligibility VFs were acquired in some participants using HFA SITA Fast; these participants were also excluded because of known systematic differences with values acquired from HFA SITA standard algorithm (used at baseline for all).[13,14] We excluded VFs with ≥15% false-positive responses; we did not make exclusions based on fixation losses or false-negatives, because good evidence suggests that these metrics are not as useful as false-positives for measuring VF reliability.[5,15] Some VFs were also missing from the baseline visit, as participants failed to attend the visit. Flowcharts showing detailed inclusion/exclusion numbers are given in the supplementary material in Supplemental Figures 1 and 2.

Aside from the VF inclusion criteria, we included only participants with IOP recordings from the eligibility (Goldmann applanation tonometry) and the baseline visit. At the latter, IOP phasing was used; if there were no two tests taken at a single time during phasing, the participant was also excluded. IOP measurement for each participant was calculated as the mean of two separate recordings at the eligibility visit and the mean of between two and ten recorded measurements at the baseline visit. We also scrutinized and recorded dates for randomization and commencement of intervention (treatment or placebo) in relation to the eligibility and baseline visits. We excluded participants if the interval between randomization and baseline visit was <40 or >180 days. Flowcharts showing detailed inclusion/exclusion numbers are given in the Supplemental Figures 1 and 2.

Use of our inclusion criteria meant that we had complete data for 407 (79%) of the 516 UKGTS participants originally enrolled and reported on. For all the VFs (eligibility and baseline), we recorded HFA MD. Age-corrected threshold values (total deviations) and their corresponding probability values were calculated from the recorded pointwise sensitivity (dB) values using the "visualfields"[16,17] package in R (R Foundation for Statistical Computing, Vienna, Austria). We chose to analyze one eye per participant; this was selected to be the eye with the worse mean MD measured at the baseline visit following the same procedure as in the main UKGTS analysis. In 200 of the 407 participants (49%), only one eye was available, so in these cases the available eye was used regardless of the status of MD.

• **DATA ANALYSIS:** We tested the null hypothesis that short-term increases in overall VF sensitivity (dB) were the same regardless of whether a participant was initiated on IOP-lowering treatment or placebo. Our primary analysis was similar to that of Bengtsson and Heijl.[6] Changes in MD were calculated as the difference between the mean MD value at the eligibility and baseline visits for each participant. Differences in change in MD for the treated and placebo groups were compared. We also repeated this analysis for the PSD index (PSD is meant to summarize local sensitivity loss, while correcting for overall VF loss). We also counted the numbers of participants who improved in MD by more than 1, 2, and 3 dB and compared groups. We repeated the primary analysis on data stratified by participant's age, level of VF loss (average MD across both visits), and mean IOP at the eligibility visit; this allowed us to explore whether any of these factors affected short-term increases in overall VF sensitivity. For example, the VF improvement may occur only in younger patients or in those in whom IOP started at a higher level before randomization. Again, we simply examined the differences in MD between treatment and placebo in these stratified groups. IOP reduction for a participant was calculated as the difference between the mean IOP value at the eligibility and baseline visits. The association between this IOP reduction and change in MD was assessed separately for the treated and placebo groups, thus testing the hypothesis that increases in VF sensitivity might be related to the magnitude of IOP reduction.

We also conducted a series of secondary analyses. It might be possible that an increase in sensitivity occurs only at certain VF locations. Therefore, these secondary analyses investigated subsets of VF locations (pointwise analyses) rather than the overall MD value. First, we considered damaged locations on the assumption that IOP lowering could not improve VF locations with normal sensitivity; this replicated an analysis done by Bengtsson and Heijl.[6] Thus, we considered only changes in sets of VF locations that had a defect at the $P \leq 1\%$ level (the mean of the two total deviation probability values was smaller than or equal to the 1% level). Overall change in total deviation (dB) was then compared between the treated and placebo groups at these locations. Given that VF sensitivity improvement might not occur in areas of advanced loss, we repeated this analysis but excluded locations where sensitivity values were recorded to be <15 dB. The latter threshold was chosen because it has been proposed by some that sensitivity values below this approximate point are unreliable and that retinal ganglion cell responses saturate with noise overwhelming measurement signal.[18,19] Further secondary analyses also considered the subset of defective locations (still defined by the $P \leq 1\%$ level on total deviation) directly neighboring these defective points (one location away either horizontally, vertically, or diagonally, and within the same hemifield on the VF plot). For our next secondary analysis, we identified subsets of VF locations that had the largest increase in sensitivity from eligibility to baseline (due to treatment or learning) and examined for a difference between the treated and placebo groups. For example, we considered the five locations where the sensitivity (dB) increased the most for each participant, and examined whether this subset of locations differed between the treated and placebo groups. Finally, we considered whether an effect might occur in the central 16 locations of the 24-2 grid only (approximately the central 10-degree VF).

Differences in mean effects between the treated and placebo groups were assessed by independent two-sample

TABLE 1. Characteristics of Participants Treated With Latanoprost vs Placebo at the Eligibility and Baseline Visits Used in This Study, With a Comparison to the Complete UKGTS Data

	Participants in Current Study		Participants Reported in UKGTS	
	Placebo Group (n = 205)	Treated Group (n = 202)	Placebo Group (n = 258)	Treated Group (n = 258)
Mean age, y	66 (10)	65 (11)	66 (10)	65 (11)
Eligibility visit: mean IOP (mmHg)	19.9 (5.0)	19.5 (5.0)	20.1 (4.8)	19.6 (4.6)
Baseline visit: mean IOP (mmHg)	18.8 (4.9)	14.7 (3.3)	–	–
Eligibility visit: mean MD (dB)	-4.4 (3.3)	-4.2 (3.0)	–	–
Baseline visit: mean MD (dB)	-4.3 (3.4)	-4.2 (3.2)	-4.4 (3.4)	-4.3 (3.4)

dB = decibel; IOP = intraocular pressure; MD = mean deviation; mmHg = millimetres of mercury; UKGTS = United Kingdom Glaucoma Treatment Study.

Data are shown as: mean (SD).

t tests. Comparison of proportions was done with a χ^2 test. Associations were calculated using the Pearson correlation coefficient. A *P* value <0.05 was considered to be statistically significant. Data handling and analysis were done with Python version 3.7.0 (Python Software Foundation) using the "pandas" (v 1.1.5), "numpy" (v 1.21.3), "matplotlib" (v 3.5.1), and "scipy" (v 1.7.3) packages.

RESULTS

Data from 202 and 205 participants randomized to IOP-lowering treatment and to placebo, respectively, were included in this study. Mean (SD) age in years (at enrollment), IOP (mmHg), and MD (dB) for the eligibility and baseline visit for the two groups are given in Table 1. Means for the baseline visit were almost identical to the corresponding values for the complete data in the main trial report (Table 1), reassuring us that there was nothing systematically different about the missing data.

Median (IQR) false-positive responses were the same for the treatment and placebo group at the eligibility visit (1% [0% to 3%] vs 1% [0% to 3%]) and baseline visit (1% [0% to 2%] vs 1% [0% to 3%]). Median (IQR) time between the eligibility and baseline visit for participants randomized to treatment and to placebo was 76 (63 to 97) and 77 (65 to 98) days, respectively. Participants were randomized to treatment or placebo shortly after their eligibility visit (median [IQR] 8 [3 to 13] days). Median (IQR) time from the randomization date (ie, date at which participants received their eye drops) to their baseline date was 67 (55 to 82) days and 68 (56 to 85) days for the treatment and placebo groups, respectively. This means that the participants had about 2.5 months between their eligibility and baseline visit, and had their eye drops (treatment or placebo) for just over 2 months before their second visit.

For our main result, mean (SD) change in MD was −0.03 (1.45) dB and +0.08 (1.72) dB for the treated and placebo groups, respectively. These mean values were almost the same (~0) and not statistically different ($P = .47$), indicating that any improvement in MD was the same for the treated and placebo group (Figure 1). Similarly, there was no difference ($P = .26$) in mean (SD) change in PSD for the treated (+0.05 [1.29] dB) and placebo (−0.11 [1.45] dB) groups, with a positive effect indicating worsening in this index. The proportion of participants with an improvement of MD of ≥1 dB was 20% and 25% for the treated and placebo groups, suggesting, if anything, a slightly larger proportion showing improvement in the patients allocated to placebo; however, these differences were not statistically significant ($P = .25$). The proportion of participants exhibiting larger degrees of improvement in VF sensitivity (MD) was also similar between groups. An improvement of ≥2 dB was seen in 5% and 10% ($P = 0.11$) of the treated and placebo groups, respectively, and an improvement of ≥3 dB was seen in 2% and 5% ($P = 0.11$) of the treated and placebo groups, respectively.

An example of results from a repeat of the primary analysis on data stratified by participant age, level of VF loss, and pre-randomization IOP is shown in Table 2. In this case, we divided each group into tertiles; there were no statistically significant differences between the lowest and highest tertiles for any comparison. Furthermore, these data were also split into quartiles and quintiles for a similar analysis; however, this did not lead to any statistically significant differences either (Supplemental Tables 1 and 2).

As expected, and despite the short follow-up, IOP was reduced much more in the participants in the treated group compared to the participants receiving placebo (Figures 1 and 2). Mean (SD) IOP reduction from baseline was 4.8 (4.2) and 1.0 (3.6) mmHg in the treated and placebo group, respectively. Median (IQR) IOP reduction relative to IOP at the enrollment (eligibility visit) was 23% (12% to 33%) in the treated participants. Despite a clear reduction of IOP among most treated participants, there was no statistically significant association ($r = −0.11$, $P = .12$) between magni-

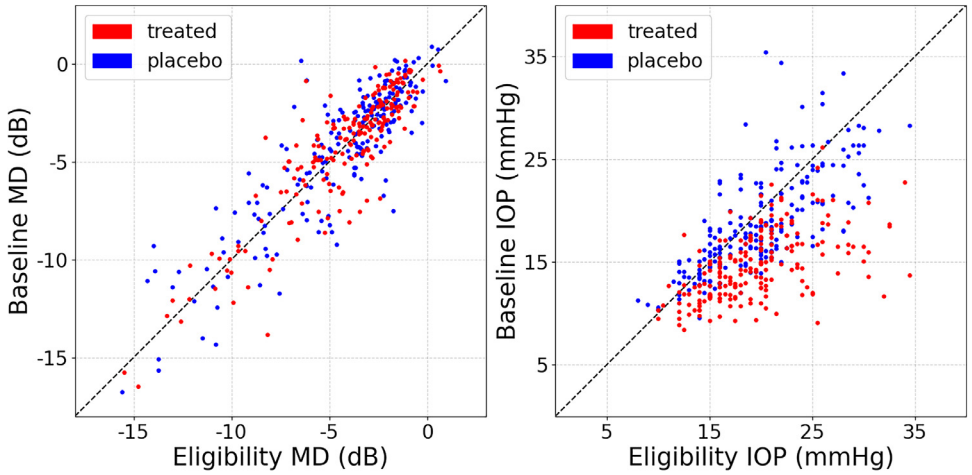

FIGURE 1. Changes in mean deviation (MD; left panel) and intraocular pressure (IOP; right panel) between the eligibility and baseline visit for treated (red symbols) and untreated (placebo) participants (blue symbols), with the diagonal representing the line of equality.

TABLE 2. Changes in MD in the Highest and Lowest Tertiles of Age, Screening Visit MD, and Screening Visit IOP

	Range Median (IQR)	Placebo Group Mean (SD) Change in MD, dB	Treated Group Mean (SD) Change in MD, dB	*P* Value
Youngest	56 (50 to 59 y)	+0.36 (1.73)	+0.08 (1.41)	.29
Oldest	76 (74 to 79 y)	−0.27 (1.84)	−0.13 (1.45)	.61
Least VF damage	−1.6 (−2.1 to −1.1) dB	+0.21 (1.06)	+0.18 (0.87)	.84
Most VF damage	−6.9 (−9.7 to −5.5) dB	−0.02 (2.02)	−0.30 (1.83)	.39
Lowest IOP	15.0 (14.0 to 16.0) mm Hg	+0.02 (1.77)	−0.05 (1.20)	.78
Highest IOP	24.0 (22.0 to 27.0) mmHg	−0.15 (1.72)	−0.18 (1.72)	.94

dB = decibel; IOP = intraocular pressure; IQR = interquartile range; MD = mean deviation; mmHg = millimetres of mercury; VF = visual field.

tude of IOP reduction and immediate improvement in MD values between the eligibility and baseline visit in the treatment group. This means that MD improvement was not related to the magnitude of IOP lowering in this group of patients, in which average IOP lowering was 23% although a significant number of patients had greater reductions. No association between change in IOP and VF improvement was seen in the placebo group ($r = 0.02$, $P = .82$). We repeated this analysis of association using deviation of VF locations that had a defect at the $P \leq 1\%$ only rather than overall MD. The results are presented in Supplemental Figure 3. Again, we found no association between reduction in IOP and deviation change when using this surrogate of VF status.

Median (IQR) whole number of VF locations with a mean total deviation probability value at the $P \leq 1\%$ level was 8 (3 to 17) at the eligibility and 9 (3 to 16) at the baseline visit in the treatment group. Corresponding counts for the placebo group were 8 (3 to 17) and 8 (3 to19). Changes in VF sensitivity at these points were slightly more likely to be positive, indicating improvement; however, the average change was unremarkable, and the level of improvement was the same in both groups. To be more exact, the mean (SD) improvement was −0.02 (2.97) and +0.22 (2.81) dB for the treatment and placebo groups, respectively; these values were not statistically different ($P = .43$). In a repeat of this analysis, excluding locations with values <15 dB, we still found no statistically significant difference ($P = .58$) in mean (SD) sensitivity improvement (−0.05 [1.70] and +0.06 [1.88] dB for the treatment and placebo groups, respectively). This analysis of a subset of VF locations for each patient therefore suggests that the VF improvement at defective points cannot be attributed to IOP-lowering treatment.

None of our other secondary analyses of subsets of VF locations provided evidence for VF improvement in treated participants compared to those receiving placebo. First, we considered a subset of points that were neighboring those with significantly depressed age-corrected threshold values (if a neighboring point was already classed as defective, it was not double counted and it was excluded). The median (IQR) whole number of VF locations satisfying this crite-

rion was 13 (8 to 17) at the eligibility and 13 (7 to 18) at the baseline visit in the treatment group. Corresponding counts for the placebo group were 12 (8 to 18) and 12 (7 to 18). The mean (SD) improvement at these locations was +0.05 (1.39) dB and +0.01 (1.25) dB for the treated and placebo group, respectively; these values were not statistically different ($P = .75$).

Next, we considered subsets of locations in individual VFs that improved the most between the eligibility and baseline visit. For example, the mean (SD) improvement of the 5 locations with the greatest improvement was +5.20 (2.93) dB for the treated group and +5.46 (3.70) dB for the placebo group; these values were not statistically different ($P = .42$). We repeated this analysis for different numbers of the "most improving" locations (from 2 to 15); none of the comparisons between the treatment and placebo groups yielded a statistically significant result (Supplemental Table 3).

Finally, we considered the effect at the central 16 locations of the 24-2 VF grid approximately representing the central 10 degrees of the VF. The mean (SD) improvement in sensitivity at these central points was −0.02 (1.29) and +0.07 (1.53) dB for the treatment and placebo groups, respectively; however, again, any observed differences were not statistically significant ($P = .53$).

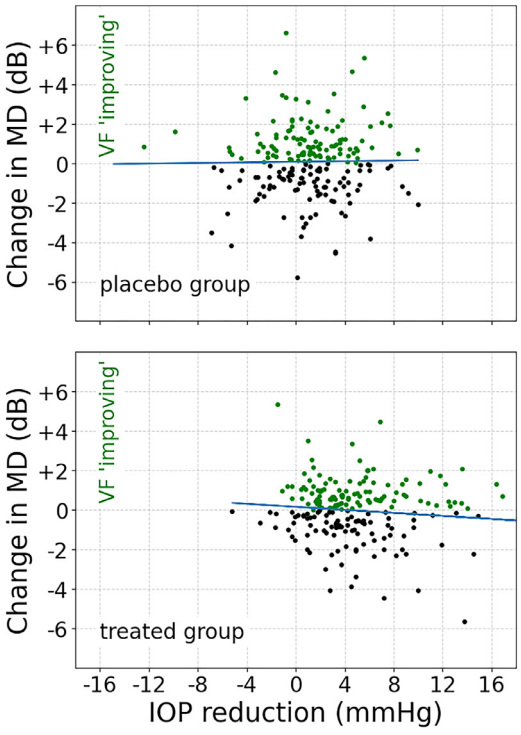

FIGURE 2. Changes in mean deviation (MD) vs intraocular pressure (IOP) reduction among untreated (placebo) participants (above) and treated participants (below). Least squares linear regression line shown in blue.

DISCUSSION

In the UKGTS, newly diagnosed glaucoma patients were randomized to treatment (IOP lowering) or placebo. These patients also underwent IOP and VF testing before they were randomized, as part of an eligibility assessment. These data afford an opportunity to examine potential immediate improvements in the VF following IOP lowering with, critically, a direct comparison to a group receiving placebo; this latter group can be assumed to have VF learning effects similar to those in the treatment group. Our results demonstrated that there was no evidence for VF improvement in the participants allocated to the treatment group compared to those in the placebo group. Our analyses included stratifying these data by participant age, level of VF loss, and pre-randomization IOP because it has been previously suggested that these factors might influence the likelihood of VF improvement after IOP lowering.[20,21] We also performed a series of secondary analyses in which we considered possible increases in sensitivity at particular VF locations. None of these additional analyses yielded any evidence of VF improvements occurring more often in the treatment group compared to the placebo group. Moreover, we could not find any evidence demonstrating an increase in VF sensitivity being associated with IOP reduction.

Several mechanisms have been proposed that broadly suggest that retinal ganglion cell dysfunction in the glaucomatous process can be reversed. These proposed mechanisms are sensible and well supported by experimental and animal models.[1] However, the evidence from studies in patients is less clear. Our results provide new knowledge by confirming the findings of Bengtsson and Heijl,[6] who found no evidence to support an association between therapeutic lowering of IOP and short-term improvement in the VF in treatment-naive glaucoma patients in the EMGT cohort. Their data are strikingly similar to ours. They reported no statistically significant effects in change in MD between treated and placebo eyes during the three-month period between the screening (prior to randomization) and the first trial visit three months later. For example, mean (SD) change in MD was −0.15 (1.52) dB and −0.44 (2.05) dB for the treated and placebo eyes, and no association was seen between IOP reduction and change in MD. The average IOP reduction in their cohort was 23%, and this is the same as the IOP reduction in our data. It may be that the medical IOP lowering in these trials is insufficiently large to induce VF recovery. Moreover, the UKGTS and EMGT cohorts had comparable average (early) VF loss. Similarities in the results are reassuring, given the similar design of the two studies. Nevertheless, the additional evidence for no effect is important, given that UKGTS was placebo controlled and triple masked; this adds to the strength of

our confirmatory evidence. One other study similar to ours was conducted by Anderson and Stainer,[22] with a post hoc analysis on data from the Ocular Hypertension Treatment Study. Although treated patients (ocular hypertensive) experienced a significant reduction in IOP, there was no statistically significant difference in the average improvement in VF indices of the treated compared to the placebo participants.

Our results should be further discussed in the context of other published studies considering the relationship between VF improvement after IOP lowering, specifically in clinical studies. Most of the evidence for VF improvement as a potential result of IOP lowering in patients comes from small observational studies[23-26] or case reports.[27-29] None of these studies were of particularly strong experimental design. Other studies, of varying experimental design, have demonstrated VF improvement after trabeculectomy (surgical intervention); however, none were designed to correct for the confounding perimetry learning effect. Wright et al[21] found the number of improving VF points in a group of 30 surgically treated glaucoma patients to be greater than those found in a group of 28 "stable" ("control") patients. As an observational study, the patients were not randomized to the groups, and the results may also be explained by regression to the mean. That is, patients chosen (non-randomly) for intensified treatment (surgery) may be chosen because of observed VF deterioration; VF measurements are noisy, so one would expect randomly worse values to be nearer to the true underlying value on repeat testing. The same problem exists for evidence from similar recent studies.[30] These studies included patient groups with prior VF experience, with the reasonable assertion that VF learning would be less likely; however, it has been shown that VF learning can be sustained for a long period.[3] Other studies noting VF improvements after surgical intervention for lowering IOP have no control arm, rendering the evidence less robust,[31] especially given what is known about VF learning, and others primarily examining structural changes have led to equivocal findings.[32-34] Waisbourd et al[35] reported evidence of structural changes and VF improvement as qualitatively graded by two observers; however, there is often poor agreement in grading images and VFs even between expert clinicians.[36,37] There are examples of other published studies of better design that have shown improvements in visual function as a response to immediate IOP lowering, although they did not use perimetry.[1,38-41] It is worth adding that studies that have shown some evidence of functional improvement have considered patients who have undergone surgical lowering of IOP, where it might be assumed the pressure lowering is more immediate or greater than what was seen in our data.

Results from our study are relevant for patients and clinicians. There is good evidence that patients diagnosed with glaucoma struggle with the concept that it is a chronic condition requiring a lifetime of treatment.[42] Misunderstanding about the effect of treatment actually improving vision or maintaining a level of stable vision within a lifetime is also likely. Our current study shows improvement in the VF after the initiation of IOP lowering treatment is unlikely, certainly in eyes with normal to moderately increased pretreatment pressures. We think that this is an important message and might help patients to understand better that long-term treatment is the only option for preserving the VF, as evidenced by these data from trials such as UKGTS and EMGT.

One obvious strength of this study is the use of UKGTS data, because they were yielded by a triple-masked, multicenter, randomized, placebo-controlled trial. Each participant performed at least two VF tests before and after randomization, and this allowed us to carry out this analysis of improvements in VF due to IOP-lowering treatment against placebo. Moreover, the study sample was large, and our post hoc data analyses were exhaustive. For example, we used multiple analyses of different sets of locations of VF, and we stratified these data by participant age, level of VF loss, and pre-randomization IOP.

Our study also has some limitations. Critically, our results cannot be generalized to what might happen to participants with very high IOP, because such participants (IOP >35 mmHg) were excluded from UKGTS. The trial was of medical IOP lowering, so no participants had surgical IOP reduction, which is the context in which most other studies have reported a VF improvement.[1] Moreover, UKGTS used SAP to identify changes in the VF; it might be that SAP is insufficiently sensitive to identify subtle changes. Other studies that reported changes used photopic negative response or spatial contrast sensitivity, for example.[38,41] Finally, UKGTS was not designed primarily to answer the question that we have examined in the current study, and this was a post hoc analysis of data. For example, we did not recover all of these data from the eligibility visit, and although the large sample size allows for detecting relevant effects if they exist, the study may not have enough power to identify very small effects.

In summary, we were not able to find any increase in VF sensitivity in newly diagnosed glaucoma patients in the short term after initiation of medical IOP lowering compared to VFs in those randomised to placebo, using data from UKGTS. Because no VF improvement was seen in the UKGTS, nor the EMGT cohort (studies avoiding bias arising from regression-to-the-mean and perimetry learning effects), there is strong evidence that the VF, as measured by SAP, does not improve as a result of medical IOP lowering. Larger IOP changes might be needed to expose such a phenomenon, if it exists.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Peter F. Reddingius: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Stephen R. Kelly:** Data curation. **Giovanni Ometto:** Software, Data curation. **David F. Garway-Heath:** Writing – review & editing, Investigation, Data curation. **David P. Crabb:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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