Title: Risk factors for visual field deterioration in the United Kingdom Glaucoma Treatment Study

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Running head: Risk factors for glaucoma progression in the UKGTS

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Abstract

Objective: The United Kingdom Glaucoma Treatment Study (UKGTS) investigated the visual field (VF) preserving effect of medical treatment in open-angle glaucoma (OAG). The objective of this analysis was to identify risk factors associated with VF deterioration.
Design: Randomized, double masked, placebo-controlled, multicentre trial.
Participants: Five hundred sixteen participants with previously untreated OAG were prospectively recruited in 10 UK centres.
Methods: Eligibility criteria were modeled on those for the Early Manifest Glaucoma Trial. Study participants were randomized to either latanoprost 0.005% or placebo eye drops. The observation period was 2 years and involved, among other procedures, VF testing and intraocular pressure (IOP) measurement at 11 scheduled visits, with clustering of tests at baseline, 18 months, and 24 months. Guided Progression Analysis pattern deviation maps were used to determine VF deterioration. Cox regression was used to compute the hazard ratios (HRs) and respective 95% confidence intervals (CIs) whilst accounting for the correlation within sites. Model selection was guided by backwards stepwise selection conducted on the model containing all variables which were significant at the 0.2 level in the univariable analysis. Follow-up variables which showed collinearity with baseline values were not retained in the final model.
Main Outcome Measures: Time-to-VF deterioration.
Results: Treatment with latanoprost reduced the HR for VF deterioration by 58% (HR 0.42; 95% CI 0.27-0.67, P=0.001). Factors associated with deterioration were bilateral disease (HR 1.59 for yes versus no; 95% CI 1.02-2.50, P=0.041), higher baseline IOP (HR 1.07 per mmHg; 95% CI 1.02-1.12, P=0.008) and disc haemorrhage at visit 1 (HR 2.08; 95% CI 1.07-4.04, P=0.030). Smoking (current or previous) was associated with a reduced HR for VF deterioration (HR 0.59; 95% CI 0.37-0.93, P=0.023). No other evaluated factors were found to be statistically significant in the multivariable analysis.
Conclusions: In the UKGTS, treatment with latanoprost halved VF deterioration risk. Bilateral disease, higher IOP and disc haemorrhage were confirmed as risk factors for deterioration; smoking history appeared to be protective against VF deterioration.

Introduction

Glaucoma is a progressive optic neuropathy characterised by accelerated retinal ganglion cell death.[1] Functional damage in glaucoma is a gradual, irreversible loss of the visual field, usually identified in the mid-periphery in the early stages and progressing to central visual field loss in the later stages of the disease. Evidence suggests that individuals with glaucoma experience a measurable loss in vision-specific quality of life, which continues to decline with increasing severity of visual field damage.[2] Clinical guidelines from different parts of the world are in agreement that the main objective of glaucoma management is the preservation of visual function and related quality of life through the individual's lifetime.[3-5]

Evidence-based risk assessment is essential for individualised glaucoma management.[6,7] Knowledge of risk factors for visual field deterioration allows the identification of 'high-risk' individuals who can be targeted for closer monitoring or more aggressive treatment. In a broader scientific sense, risk factors can provide insight into disease mechanisms and may help identify potential treatment targets. Four large randomized controlled trials have previously investigated risk factors for the progression of established open-angle glaucoma (OAG): the Early Manifest Glaucoma Trial (EMGT),[8] the Advanced Glaucoma Intervention Study,[9] the Collaborative Initial Glaucoma Treatment Study[10] and the Collaborative Normal Tension Glaucoma Study.[11,12] Older age,[8-10] higher intraocular pressure (IOP),[8-11] and disc haemorrhages[8,12] have been consistently associated with the progression of OAG. Other factors, such as bilateral disease and central corneal thickness, have been associated with glaucoma progression in the EMGT,[8] but have not been confirmed or evaluated in the other trials of manifest glaucoma. The EMGT, which was the only study with a sizable population with pseudoexfoliation, has also found a strong association between pseudoexfoliation and glaucoma progression.[8]

To our knowledge, the United Kingdom Glaucoma Treatment Study (UKGTS) is the first randomized, double-masked, placebo-controlled trial to evaluate the efficacy of medical treatment in preserving visual function in OAG.[13-15] The baseline characteristics for eligible patients and eyes have been previously presented[14] and found to be similar to those of the largely population-ascertained EMGT cohort.[16] The UKGTS has provided evidence on the protective effect on vision for latanoprost 0.005%, which is a prostaglandin analogue.[15] Prostaglandins represent the most frequently prescribed class of drugs to lower intraocular pressure (IOP).[17] At 2 years, visual field preservation was longer in the latanoprost than the placebo group (HR 0·44, 95% CI 0·28-0·69; P=0·0003).[15] The trial design enabled this difference to become evident at 12 months, compared with typical 4 to 5-year observation periods in previous trials. The purpose of the current report is to identify factors associated with visual field deterioration in the UKGTS cohort.

Materials and Methods

The UKGTS methodology has been described in detail elsewhere.[13] The UKGTS is a randomized, double-masked, placebo-controlled trial for the medical treatment of OAG, undertaken in ten participating centres throughout the UK (trial registration no.: ISRCTN96423140). The trial was approved by the Moorfields and Whittington Research Ethics Committee (June 1, 2006; reference no.: 09/H0721/56). All study procedures adhered to the tenets of the Declaration of Helsinki for research involving human subjects and all participants provided written informed consent before screening investigations. An independent Data and Safety Monitoring Committee was appointed by the trial steering committee.

A total of 516 participants >18 years old with newly detected, previously untreated OAG in at least one eye were randomized in a 1:1 ratio to receive either latanoprost 0.005% or placebo once in the evening in both eyes for 24 months or until reaching an end point. Pfizer provided latanoprost and placebo drops in identical containers with tear-off labels identifying the container contents; the tear-off labels were removed by the Moorfields Pharmaceutical Manufacturing Unit and were replaced with the study identification number (according to the randomization schedule) before packaging.[13] Eligibility criteria were closely modeled on those from the EMGT[16] to allow comparison and meta-analysis. Primary open angle glaucoma and pseudoexfoliative glaucoma were both among the inclusion criteria. Exclusion criteria included pigmentary glaucoma, advanced glaucoma (visual field mean deviation worse than –10 dB in the better eye or –16 dB in the worse eye), mean baseline IOP of 30 mm Hg or higher, Snellen visual acuity worse than 6/12, and poor image quality (>40 µm mean pixel height standard deviation) with the Heidelberg retina tomograph (Heidelberg Engineering, Heidelberg, Germany).

Definition of glaucoma

Open-angle glaucoma was defined as the presence of glaucomatous visual field defects in at least one eye with corresponding damage to the optic nerve head (cup-to-disc ratio of ≥0.7, focal narrowing of the neural rim, or both), with an open iridocorneal drainage angle on gonioscopy and the absence of retinal or neurologic condition that could account for visual field loss. A glaucomatous visual field defect was defined as a reproducible (in at least 2 consecutive reliable post-screening visual fields) reduction in sensitivity at 2 or more contiguous points with P<0.01 loss or more, 3 or more contiguous points with P< 0.05 loss or more, or a 10 dB difference across the nasal horizontal midline at 2 or more adjacent points in the total deviation plot.[18] The reliability criteria were a false-positive rate of less than 15% and 20% fixation losses (for fixation losses >20%, reliability was based on subjective judgment, including assessment of the eye tracker trace).

Study procedures

Study procedures have been described in detail elsewhere.[13,14] Study participants underwent visual field testing, IOP measurement and imaging at 11 scheduled visits over 24 months. The tests were clustered at baseline, 18 months, and 24 months to improve the accuracy and precision of the rate of deterioration estimate;[19] 16 visual fields test were scheduled over 24 months. Visual field testing was done with the Humphrey Field Analyser Mark II (or II-i) with the Swedish interactive threshold algorithm standard 24–2 programme (Carl Zeiss Meditec, Dublin, CA, USA).[20] At each visit, IOP measurements were made in both eyes with Goldmann applanation tonometry (Haag Streit, Koeniz, Switzerland), Pascal dynamic contour tonometry (DCT - Ziemer Ophthalmic Systems AG, Zurich, Switzerland) and the Ocular Response Analyzer (ORA - software version 2.10; Reichert, Inc, Buffalo, NY). The latter was also used for corneal-corrected IOP and corneal hysteresis readings with good-quality traces.

At visit 1 (after treatment allocation) study participants were interviewed for demographic data (age, sex, and ethnicity), family history of glaucoma, history of systemic diseases (systemic hypertension, cardiovascular disease, diabetes, heart attack, stroke, sleep apnoea, migraine, Raynaud's phenomenon, vasospasm, angina, claudication) and smoking. The following investigations were also undertaken: systolic and diastolic blood pressure measured with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan), weight, height, slit-lamp examination, refractive error measured either with an autorefractor or from spectacle focimetry (when neither was available, the

spherical equivalent of the trial lens was used in the visual field test, based on participants' age), axial length measured with the IOL Master (software version 5.4.3.0002; Carl Zeiss Meditec) and central corneal thickness (CCT) measured with an ultrasound pachymeter.

Definition of end-points

The UKGTS included the following end points (1) visual field deterioration (therapeutic end point); (2) IOP >35 mmHg on 2 successive occasions (safety end point); and (3) decline of best-corrected visual acuity to less than 20/60 (non-glaucomatous end point). Visual field progression analysis was performed in the Humphrey Field Analyzer II-i Guided Progression Analysis software. Visual field deterioration was defined as at least three visual field locations worse than baseline at the 5% levels in two consecutive reliable visual fields and at least three visual field locations worse than baseline at the 5% levels in the two subsequent consecutive reliable visual fields; the locations identified in the first and second pair were not required to be identical. Time to visual field deterioration was defined as time from baseline to the fourth visual field that confirmed deterioration. This means that visual field change compared to baseline was confirmed with three additional visual field tests. The primary end point was assessed on the day of each visit and then verified by the Reading Centre.[13] An endpoint committee consisting of independent ophthalmologists judged whether endpoints were consistent with glaucoma.[13,15]

Statistical analysis

For the purposes of this report, the statistical analysis was closely modeled on the risk factors analysis for long-term progression in the EMGT.[8] The following variables were included in the univariable analysis: age, sex, ethnicity, family history of glaucoma, body mass index (calculated as weight divided by the square of height), systolic and diastolic blood pressure, systolic ocular perfusion pressure (defined as systolic blood pressure minus IOP), 'ever smoked' (defined as a positive response to "have you ever smoked as much as one cigarette a day for as long as a year?"), present smoking (defined as a positive response to "do you smoke cigarettes now?"), systemic hypertension (defined as systolic blood pressure higher than 160 mmHg or diastolic blood pressure higher than 95 mmHg or medical history of hypertension), cardiovascular disease, diabetes, heart attack, stroke, sleep apnoea, migraine (defined according to the diagnostic criteria by the International Classification of Headache Disorders),[21] Raynaud's (defined as a positive response to at least one of the following: "do your fingers change colour when they are exposed to cold?" or "do your fingers or toes turn white then blue?"), cold hands and feet (defined as a positive response to at least one of the following: "do you suffer from cold hands and feet?" or "are your fingers or toes unusually sensitive to cold?"), vasospasm (defined as any of the following: migraine, migraine with aura, Reynaud's or cold hands and feet), angina (defined according to the Rose classification),[22] claudication (defined according to the Edinburgh Claudication Questionnaire),[23] symptomatic cardiovascular disease (defined as any of the following: angina, claudication, heart attack or stroke), treatment assignment, eligibility of both eyes, mean deviation in the visual field, baseline mean Goldmann IOP (defined as the mean reading on 2 pre-randomization visits), visit 1 (6 weeks after treatment allocation) mean Goldmann IOP, visit 1 mean ORA IOP, visit 1 mean DCT IOP, central corneal thickness, corneal hysteresis, refractive error (spherical equivalent), axial length, disc haemorrhage at visit 1 and disc haemorrhage at any visit.

Cox regression was used to compute the hazard ratios (HRs) and respective 95% confidence intervals (CI) while accounting for the correlation within sites. Model selection was guided by

backwards stepwise elimination conducted on the model containing all variables with P< 0.2 in the univariable analysis. While follow-up variables were considered (IOP at visit 1 and disc haemorrhage at any visit), these showed collinearity with baseline values and were not retained in the final model.

Results

Baseline characteristics of study participants have been published previously.[14] Baseline characteristics and ocular parameters of study participants were mostly similar between treatment groups.[15] Data were analysed for the 461 study participants with follow-up data (230 in the latanoprost and 231 in the placebo group).[15] Within 24 months, 94 participants reached a visual field end point (35 in the latanoprost and 59 in the placebo group). Six participants reached a safety end point, two of whom also reached a visual field endpoint, whereas no patient reached a visual acuity reduction endpoint.

Baseline and other clinical characteristics of those who reached the visual field end point compared to those who did not are presented in table 1. Age, sex, ethnicity and family history of glaucoma were similar for the two groups. A higher proportion among 'never smokers' had visual field deterioration than among 'ever smokers' [24% (95% CI 19%-29.7%) versus 16.4% (95% CI 12.1%-22%) respectively]. For most systemic diseases considered in this analysis, the proportions of those with visual field deterioration were similar for those with and without the disease. However, for diabetes, heart attack, claudication and symptomatic cardiovascular disease, the proportion of those who progressed was higher among those without the disease, than among those who had the disease (table 1). The proportion of those with visual field deterioration was 25.7% (95% CI 20.4%-31.7%) in the placebo group versus 15.2% (95% CI 11.1%-20.4%) in the latanoprost group, and 23.6% (95% CI 18.5%-29.5%) among those who had both eyes eligible for the study versus 17.4% (95% CI 13%-22.8%) those who had only one eye eligible. The mean baseline Goldmann IOP was 20.5 (5.2) mmHg in those who progressed versus 19.6 (4.4) mmHg in those who did not; the mean value of the mean deviation in the visual field test was -4.2 (3.2) dB and -4.1 (3.4) dB, respectively. The proportion of those who progressed was higher among those with a disc haemorrhage at visit 1 (33.3%, 95% CI 20.6%-49.1%) or at any visit (28.1%, 95% CI 20.8%-36.7%), than among those who did not have a disc haemorrhage at visit 1 (19.2%, 95% CI 15.7%-23.2%) or at any visit (17.6%, 95% CI 14%-22.1%).

The Figure presents differences in the time-to-visual field deterioration between the treated and the untreated group stratified by age (a), baseline IOP (b) and smoking (c). Figure (a) suggests a similar time-to-visual field deterioration in the younger and older age groups in the placebo arm, but a shorter time-to-visual field deterioration in the older, compared to the younger, age group in the treated arm. However, as mentioned below, age was not statistically significant when entered as an interaction term in the multivariable model. The treatment effect on the time-to-visual field deterioration was more evident in those with baseline IOP ≥ 21 mmHg, compared to those with baseline IOP < 21 mmHg, and in those who ever smoked, compared to those who never smoked. Deterioration rates were similar between those with mean deviation better than -4.5 dB and those with mean deviation equal or worse than -4.5 dB (supplemental material).

The univariable analysis (table 1) suggested associations of visual field deterioration with smoking (current or previous) (HR 0.60; 95% CI 0.40-0.92, P=0.018), treatment with latanoprost (HR 0.50; 95% CI 0.33-0.76, P=0.001), baseline Goldmann mean IOP (1.05 per mmHg; 95% CI 1.00-1.09, P=0.032), visit 1 Goldmann mean IOP (HR 1.06 per mmHg, 95% CI 1.02-1.11, P=0.005), visit 1 ORA

mean corneal compensated IOP (HR 1.06 per mmHg; 95% CI 1.03-1.10, p<0.001), visit 1 DCT mean IOP (HR 1.05 per mmHg, 95% CI 1.00-1.09, P=0.034), corneal hysteresis (HR 0.86, 95% CI 0.77-0.96, P=0.008), disc haemorrhage at visit 1 (HR 1.87, 95% CI 1.04-3.36, P=0.036) and disc haemorrhage at any visit (HR 1.54, 95% CI 1.01-2.34, P=0.045).

Table 2 presents the results of the final multivariable analysis on factors associated with visual field deterioration. Treatment with latanoprost reduced the HR for visual field deterioration by 58% (HR 0.42; 95% CI 0.27-0.67, P=0.001). Participants with both eyes eligible (HR 1.59 for yes versus no; 95% CI 1.02-2.50, P=0.041), higher baseline mean IOP (HR 1.07 per mmHg; 95% CI 1.02-1.12, P=0.008) and disc haemorrhage at visit 1 (HR 2.08; 95% CI 1.07-4.04, P=0.030) were associated with increased likelihood of visual field deterioration. Smoking (current or previous) was associated with reduced HR for visual field deterioration (HR 0.59; 95% CI 0.37-0.93, P=0.040). Sex and history of heart attack were included in the multivariable analysis but were not statistically significant.

Discussion

In the UKGTS, after adjustment for relevant factors: 1) treatment with latanoprost more than halved the risk of visual field deterioration, 2) bilateral disease, baseline mean IOP and disc haemorrhage at visit 1 were confirmed as risk factors for visual field deterioration, and 3) an inverse association was found between 'ever smoked' and visual field deterioration.

Baseline characteristics of study participants were similar to those of the EMGT.[14] In the UKGTS we used continuous variables in all analyses, whereas in the EMGT the investigators used the median split to determine cut-off values. Based on multivariable models, treatment reduced the risk of visual field deterioration by 58% in the UKGTS (HR 0.42; 95% CI 0.27-0.67 for latanoprost versus placebo) and by 47% in the EMGT (HR 0.53; 95% CI 0.39-0.72 for argon laser trabeculoplasty plus betaxolol versus no treatment). Higher IOP[8-11] and the presence of disc haemorrhage,[8,12] which have been consistently associated with the progression of OAG, were confirmed as progression factors in the UKGTS cohort. Also, visual field deterioration was associated with bilateral disease, which was a strong risk factor for progression in the EMGT.[8] The previously reported associations of visual field deterioration with older age,[8-10] systolic ocular perfusion pressure[8] and central corneal thickness[8] were not confirmed in the UKGTS cohort. Also, we were not able to confirm the association of visual field deterioration with pseudoexfoliation,[8] because the latter was rare in the UKGTS participants (0.5%) and, therefore, was not included in the analysis.

Older age is an established risk factor for the onset of glaucoma.[24-27] Also, older age has been strongly associated with the progression of OAG in the EMGT[8], the AGIS[9] and the CIGTS.[10] Therefore, the lack of association between older age and visual field deterioration in the UKGTS is an unexpected finding. This discrepancy cannot be explained by differences in age distribution, which is actually larger in the UKGTS than in the EMGT, and only 2 years younger on average (mean age 66 (11) years in the UKGTS and 68 (5) years in the EMGT). Interestingly, using 68 years as a cut-off value for age at baseline, visual field deterioration rates in the UKGTS were similar between the older and younger groups (Figure a), whereas the EMGT found higher progression rates in the older group. In addition to dichotomizing the time-to-visual field deterioration by age, we also plotted age against time-to-visual field deterioration (data not shown); there was no significant association and no outliers. Additional possible explanations are the difference in the proportion of patients with pseudoexfoliation in the UKGTS and EMGT cohorts and the impact of a burdensome trial protocol on participation, possibly resulting in a healthier cohort of older participants in the UKGST than other

studies. Based on the above, there was no evidence in the UKGTS data for an association of older age with visual field deterioration.

In the final multivariable model, 'ever smoked' was found to be protective against visual field deterioration. This finding requires careful interpretation due to potential confounding by unmeasured variables (e.g nicotine replacement therapy). Given the definition of 'ever smoked' ("have you ever smoked as much as one cigarette a day for as long as a year?") and the small number of current smokers in the study (Table 1), the above association is driven by previous smokers. Therefore, it is possible that previous smoking is a surrogate for the cessation of smoking and related factors, e.g. the decision to adopt an overall healthier lifestyle. The proportion of those with follow-up less than 21 months and no evidence of progression (loss to follow-up, early trial termination or protocol amendment-related) was similar between the 'ever smokers' (31.5% (69/219); 95% CI 25.7-37.9) and the 'never smokers' (33.5% (81/242); 95% CI 27.8-39.6). Death rates during the study were also similar between the groups, 0.9% (2/219; 95% CI 0.03-3.5) among the 'ever smokers' and 0.8% (2/242; 95% CI 0.03-3.2) among the never smokers. In addition, we found no evidence of interaction between treatment group and smoking (P = 0.143).

There are thousands of active compounds in tobacco smoke, most of which are toxic to the ocular tissues, triggering ischemic or oxidative mechanisms.[28] Smoking has been associated with increased risk of several ocular diseases,[28] including age-related macular degeneration (AMD) and its subtypes,[29] age-related cataract[30] and thyroid eye disease.[31] It is possible that smokers with cataract and AMD did not qualify for inclusion for the UKGTS. The 'ever smoked' cohort in the UKGTS may, therefore, be healthier than smokers in general. Counter-intuitively, the United Kingdom Prospective Diabetes Study (UKPDS) found that current smokers had lower risk of incidence of retinopathy and progression of retinopathy compared with those who had never smoked.[32] According to the UKPDS investigators, the strength of the association suggests that this is unlikely to be chance alone and there could be an independent effect of nicotine itself or of one of the many other active compounds found in tobacco smoke. The relationship between smoking and OAG remains unclear. Some population-based studies found no association between smoking and the prevalence of OAG,[33-38] whereas other studies have reported increased risk of OAG with smoking.[39-41] In the Nurses' Health Study and the Health Professionals Follow-up Study, an inverse association was found between pack-years of smoking and glaucoma incidence, which is in accordance with our findings.[42] In a more recent report from the National Health and Nutrition Examination Survey, in the unadjusted analysis current smokers had a lower odds of glaucoma compared to both ex-smokers and non-smokers.[43] The association lost statistical significance in adjusted analyses, which showed that, among smokers, heavy smoking is associated with higher odds of glaucoma. The authors formed the hypothesis that the protective effects of smoking, if there are any, may be eliminated in heavy smoking.

Further to the above, there seems to be an inverse dose-response relationship between Parkinson's disease and smoking,[44] which is supported by meta-analyses.[45,46] A protective effect of smoking on neurodegenerative diseases, including glaucoma, cannot be excluded. In addition to the many harmful effects of tobacco smoke on ocular and other tissues, protective effects have also been described. Increased blood flow to the optic nerve through nicotine induced arteriole dilatation,[47] release of nitric oxides and activation of nicotinic acetylcholine receptors[48] are all possible mechanisms of neuroprotection associated with tobacco smoking. If the inverse association between smoking and glaucoma were to be confirmed, further research into the implicated mechanisms could provide better understanding of the disease and, ultimately, help us identify

treatment targets. Although the finding of a protective effect of 'ever smoked' is consistent with some epidemiological evidence for glaucoma and other neurodegeneratios, the evidence is mixed and complex. Therefore, additional investigations would help clarify associations.

We found no evidence for CCT as a risk factor for visual field deterioration in the UKGTS in the univariable analysis (HR 1.00, 95% CI 0.99 – 1.00, p = 0.34). CCT has been referred to as an independent risk factor for the conversion of ocular hypertension to glaucoma[49] and glaucoma progression.[8,50] However, CCT is a known confounder of IOP measurement by GAT[51,52] and the interaction of CCT with the corneal biomechanical properties[53] means that IOP measurements cannot be corrected for CCT without knowing the corneal material properties. The confounding of GAT IOP measurements may account for the previously found association of CCT with the development of glaucoma[49] and glaucoma progression[8] in multivariable analyses of clinical trial data. In clinic-based studies, the confounding of IOP measurement additionally influences treatment decisions; patients with lower measured GAT IOP likely receive less intensive treatment.[50] Confounding of treatment decisions does not apply in trials such as the UKGTS and the EMGT.

Corneal hysteresis has also been reported to be associated with risk of glaucoma progression.[54,55] This was found in the univariable analysis of the UKGTS (HR 0.86, 95% CI 0.77-0.96, P = 0.008) and may be explained by the fact that CH is strongly associated with CCT and IOP,[56] with lower CH values being associated with a thinner cornea and higher IOP. In a similar manner to CCT, CH acts as a confounder of IOP measurement by GAT and may confound treatment decisions in clinic-based studies. This needs to be taken into account in previously reported associations between CH and progression.

Strengths and limitations of the UKGTS have been discussed in detail elsewhere.[15] With regard to this specific report, we investigated a large number of possible risk factors for visual field deterioration, including ocular, systemic and cardiovascular parameters. Given the similarities between the UKGTS and the EMGT, comparisons between study results are appropriate and may help in interpretation of findings. There are also limitations in this analysis. All information on family history of glaucoma and systemic diseases was self-reported, thus, the accuracy of this information cannot be confirmed. In addition, the information on cigarette smoking was not detailed enough to allow further analysis, such as exploring the association with pack-years of smoking and nicotine replacement.

In conclusion, in the UKGTS, after adjustment for possible confounders, treatment with latanoprost more than halved the risk of visual field deterioration. Bilateral disease, baseline mean IOP and the presence of disc haemorrhage were confirmed as risk factors for visual field deterioration. There was no evidence for an association of older age with visual field deterioration, and this was an unexpected finding. The analysis also revealed an inverse association between cigarette smoking and visual field deterioration. Although this finding requires careful interpretation, there is evidence to suggest that a protective effect of smoking on neurodegeneration, including glaucoma, is biologically plausible.

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Contributorship

Conception and design: DFG-H, CB
Data acquisition: DFG-H
Data analysis: PF, CB, DFG-H
Interpretation of data: PF, CB, AK, CJD, JMN, DFG-H
Drafting the work: PF, CB, DFG-H
Revising the work critically for important intellectual content: PF, CB, AK, CJD, JMN, DFG-H
Final approval of the version to be published: PF, CB, AK, CJD, JMN, DFG-H
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: PF, CB, AK, CJD, JMN, DFG-H

Competing Interests

PF – no relevant competing interests. Lecturing honorarium from Thea. Travel support from the Ophthalmica Institute, Greece.

CB – no relevant competing interests. Research funded/supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London.

AK – no relevant competing interests. Consultant to Novartis, Aerie, Santen, Allergan. Lecturing honorarium from Grafton Optical. Travel support from Thea.

CJD – no relevant competing interests.

JMN - no relevant competing interests.

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Table 1. Potential factors for visual field deterioration in the United Kingdom Glaucoma Treatment Study with Univariable Hazard Ratios.					
Variable	**N[1]**	**In subjects without visual field deterioration** Mean (standard deviation) or percentage (N=367)	**In subjects with visual field deterioration** Mean (standard deviation) or percentage (N=94)	**Univariable Hazard Ratio (95% Confidence Intervals)**	**p-value**
Age (years)	461	65.2 (10.2)	65.7 (11.3)	1.00 (0.98, 1.03)	0.65
Ethnicity					
white	417	79.4%	20.6%	1.04(0.50, 2.14)	0.92
other	44	81.8%	18.2%		
Sex					
female	222	82.0%	18.0%	1.31 (0.87, 1.98)	**0.19**
male	239	77.4%	22.6%		
Family history of glaucoma					
yes	153	79.1%	20.9%	1.01 (0.66, 1.55)	0.96
no	304	80.3%	19.7%		
BMI (kg/m^2)	450	27.8 (7.9)	26.8 (5.1)	0.98 (0.93, 1.02)	0.27
Systolic blood pressure (mmHg)	451	135 (19.4)	137.7 (20.9)	1.01 (1.00, 1.02)	**0.19**
Diastolic blood pressure (mmHg)	451	80.6 (10.8)	81.8 (10.3)	1.01 (0.99, 1.03)	0.38
Systolic ocular perfusion pressure (mmHg)[2]	451	115.4 (19.6)	117.1 (21.4)	1.00 (0.99, 1.01)	0.43
Ever smoked[3]					
yes	219	83.6%	16.4%	0.60 (0.40, 0.92)	**0.018**
no	242	76.0%	24.0%		
Present smoking[4]					
yes	34	82.3%	17.7%	0.82 (0.36, 1.88)	0.64
no	426	79.6%	20.4%		
Systemic hypertension[5]					

yes	179	81.6%	18.4%	0.88 (0.58, 1.36)	0.59
no	282	78.4%	21.6%		
Cardiovascular disease					
yes	123	79.7%%	20.3%	1.05 (0.66, 1.66)	0.84
no	338	79.6%%	20.4%		
Diabetes					
yes	43	83.7%	16.3%	0.86 (0.40, 1.86)	0.70
no	418	79.2%	20.8%		
Heart attack					
yes	24	95.8%	4.2%	0.22 (0.03, 1.56)	**0.13**
no	437	78.7%	21.3%		
Stroke					
yes	14	78.6%	21.4%	1.20 (0.38, 3.78)	0.76
no	447	79.6%	20.4%		
Sleep apnoea					
yes	10	80%	20.0%	0.96 (0.24, 3.91)	0.96
no	442	79.9%	20.1%		
Migraine[6]					
yes	71	80.3%	19.7%	0.90 (0.51, 1.59)	0.72
no	377	79.3%	20.7%		
Raynaud's[7]					
yes	76	78.9%	21.1%	1.09 (0.63, 1.87)	0.76
no	360	80.0%	20.0%		
Cold hands and feet[8]					
yes	162	79.0%	21.0%	1.13 (0.73, 1.74)	0.58
no	273	80.6%	19.4%		
Vasospasm[9]					
yes	201	79.6%	20.4%	1.01 (0.67, 1.53)	0.95

no	253	79.4%	20.6%		
Angina[10]					
yes	10	80%	20%	1.14 (0.28, 4.64)	0.85
no	451	79.6%	20.4%		
Claudication[11]					
yes	14	92.9%	7.1%	0.31 (0.04, 2.20)	0.24
no	447	79.2%	20.8%		
Symptomatic cardiovascular disease[12]					
yes	51	88.2%	11.8%	0.59 (0.26, 1.34)	0.21
no	410	78.5%	21.5%		
Treatment assignment					
Latanoprost	231	84.8%	15.2%	0.50 (0.33, 0.76)	**0.001**
Placebo	230	74.3%	25.7%		
Both eyes eligible					
yes	225	76.4%	23.6%	1.37 (0.91, 2.06)	**0.13**
no	236	82.6%	17.4%		
Mean deviation (dB)	461	-4.1 (3.4)	-4.2 (3.2)	0.97 (0.92, 1.03)	0.38
Baseline GAT mean IOP (mmHg)	461	19.6 (4.4)	20.5 (5.2)	1.05 (1.00, 1.09)	**0.032**
Visit 1 GAT mean IOP (mmHg)	452	16.3 (4.4)	17.4 (4.7)	1.06 (1.02, 1.11)	**0.005**
Visit 1 ORA mean IOP (mmHg)	440	19.9 (5.7)	22.3 (6.5)	1.06 (1.03, 1.10)	**<0.001**
Visit 1 DCT mean IOP (mmHg)	439	18.3 (4.6)	19.3 (5.3)	1.05 (1.00, 1.09)	**0.034**
Central corneal thickness (µm)	443	542.6 (34.7)	538.4 (29.8)	1.00 (0.99, 1.00)	0.34
Hysteresis (mmHg)	439	9.2 (2.0)	8.6 (1.7)	0.86 (0.77, 0.96)	**0.008**
Refractive error (spherical equivalent) (D)	461	-0.8 (2.9)	-0.4 (2.9)	1.05 (0.98, 1.13)	**0.17**
Axial length (mm)	436	24.1 (1.3)	24.0 (1.1)	0.94 (0.80, 1.10)	0.43
Disc haemorrhage (at visit 1)					

yes	39	66.7%	33.3%	1.87 (1.04, 3.36)	**0.036**
no	422	80.8%	19.2%		
Disc haemorrhage (at any visit)					
yes	121	71.9%	28.1%	1.54 (1.01, 2.34)	**0.045**
no	340	82.4%	17.6%		

[1]Available covariate

[2]Defined as systolic blood pressure minus intraocular pressure

[3]Defined as a positive response to “have you ever smoked as much as one cigarette a day for as long as a year?”

[4]Defined as a positive response to “do you smoke cigarettes now?”

[5]Defined as systolic blood pressure higher than 160 mmHg or diastolic blood pressure higher than 95 mmHg or medical history of hypertension

[6]Defined according to the diagnostic criteria by the International Classification of Headache Disorders[21]

[7]Defined as a positive response to at least one of the following: "do your fingers change colour when they are exposed to cold?" or "do your fingers or toes turn white then blue?"

[8]Defined as a positive response to at least one of the following: "do you suffer from cold hands and feet?" or "are your fingers or toes unusually sensitive to cold?"

[9]Defined as any of the following: migraine, migraine with aura, Reynaud's or cold hands and feet

[10]Defined according to the Rose classification[22]

[11]Defined according to the Edinburgh Claudication Questionnaire[23]

[12]Defined as any of the following: angina, claudication, heart attack or stroke

GAT=Goldmann applanation tonometry; IOP=intraocular pressure; ORA=ocular response analyser; IOPcc=corneal compensated intraocular pressure; DCT=dynamic contour tonometry

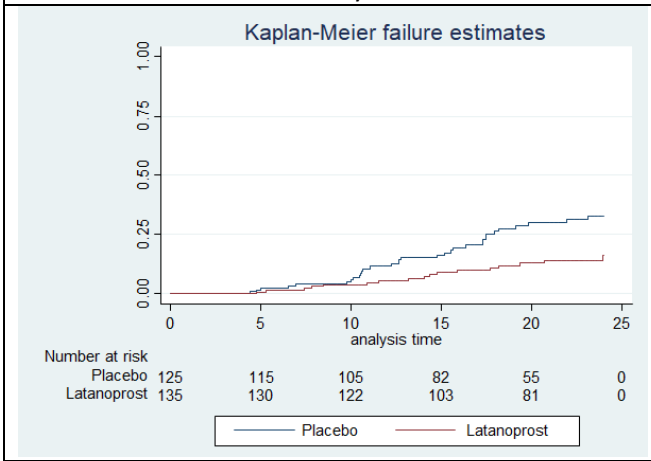
Values in bold indicate variables included in the multivariable backwards elimination Cox regression model with $P < 0.20$

Table 2. Multivariable analysis of baseline factors associated with visual field deterioration*		
Variable	**Hazard Ratio (95% Confidence Intervals)**	**p-value**
Treatment assignment (latanoprost vs placebo)	0.42 (0.27, 0.67)	**0.001**
Both eyes eligible (yes vs no)	1.59 (1.02, 2.50)	**0.041**
Baseline GAT mean IOP (mmHg)	1.07 (1.02, 1.12)	**0.008**
Female sex	1.49 (0.95, 2.33)	0.08
Disc haemorrhage at visit 1 (yes vs no)	2.08 (1.07, 4.04)	**0.030**
History of heart attack (yes vs no)	0.25 (0.03, 1.82)	0.17
Ever smoked (yes vs no)	0.59 (0.37, 0.93)	**0.023**
*Final model fitting study site as a random effect GAT=Goldmann applanation tonometry; IOP=intraocular pressure Values in bold indicate statistical significance		

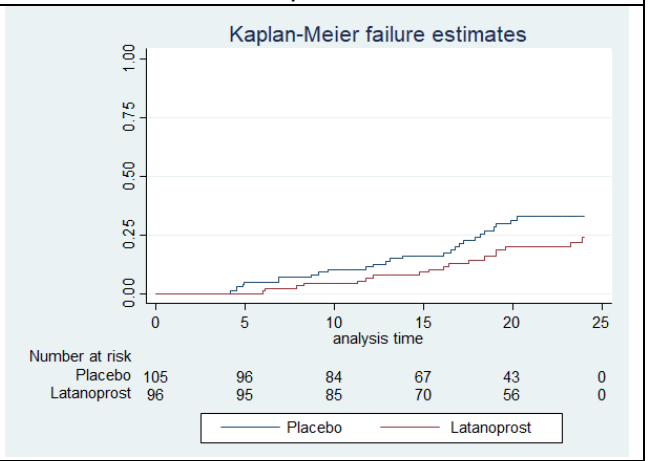
Figure. Visual field deterioration across time stratified by a) age, b) baseline IOP and c) smoking

a. Age

<68 years old

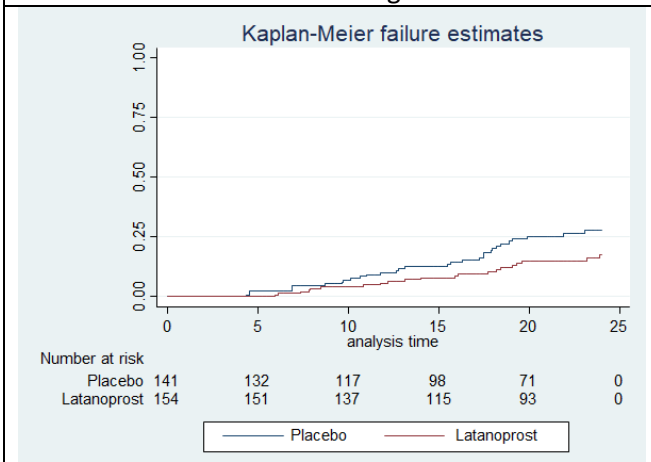


≥68 years old

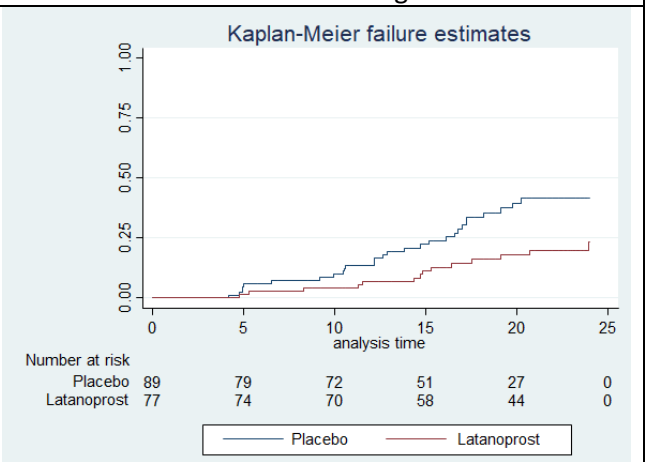


b. Baseline intraocular pressure

< 21 mmHg

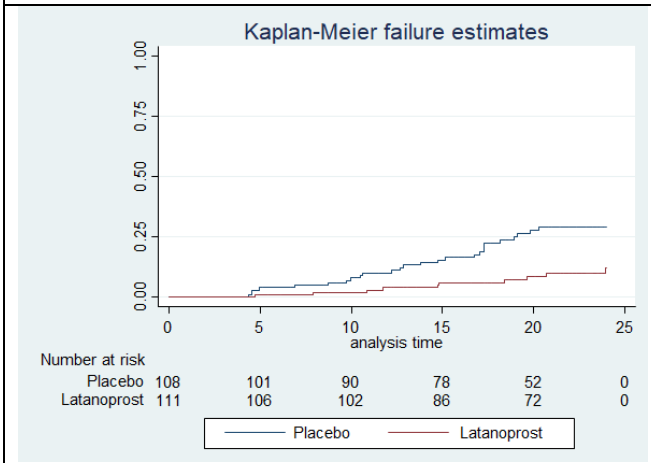


≥ 21 mmHg

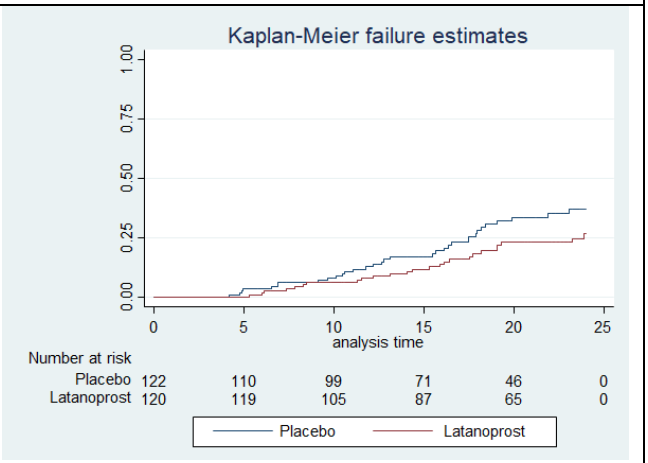


c. Smoking

Ever smoked



Never smoked

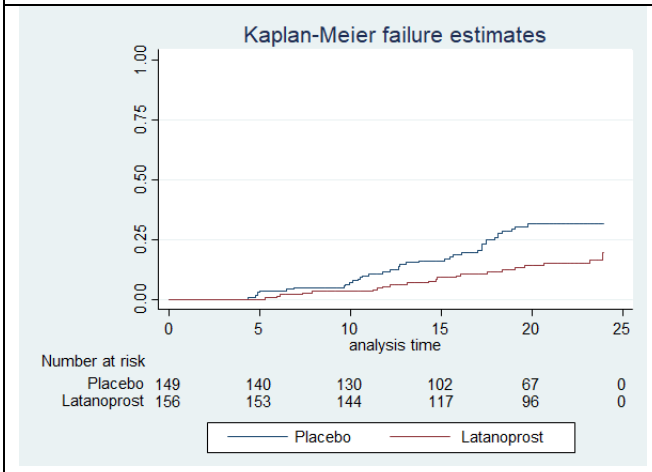


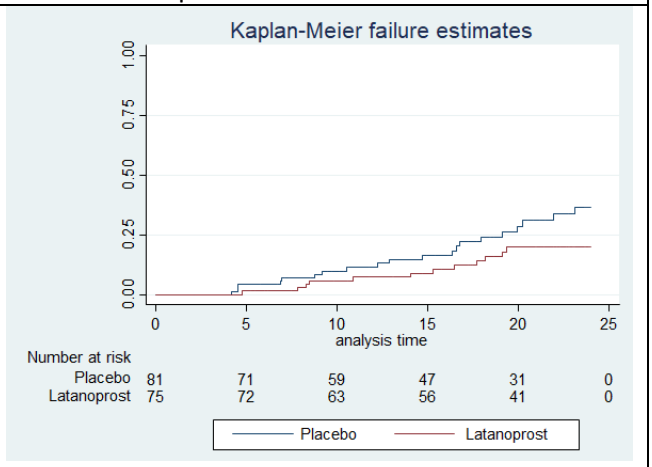
The survival curve analysis and the values used to dichotomize the data were chosen from: Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M; Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002 Oct;120(10):1268-79.
The x-axis shows the length of follow-up in months.
The y-axis shows the proportion of those with visual field deterioration(x100%).

The numbers of participants at risk are provided below each graph.

Supplemental figure. Visual field deterioration across time stratified by baseline mean deviation in the visual field.

Baseline mean deviation	
Better than -4.5 dB	Equal or worse than -4.5 dB





The survival curve analysis and the value used to dichotomize baseline mean deviation were chosen from: Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M; Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002 Oct;120(10):1268-79.

The x-axis shows the length of follow-up in months.
The y-axis shows the proportion of those with visual field deterioration(x100%).
The numbers of participants at risk are provided below each graph.