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Published in:
Ophthalmology

DOI:
10.1016/j.ophtha.2016.01.039

2016

Document Version:
Peer reviewed version (aka post-print)

Link to publication

Citation for published version (APA):
Öhnell, H., Heijl, A., Brenner, L., Anderson, H., & Bengtsson, B. (2016). Structural and Functional Progression in the Early Manifest Glaucoma Trial. *Ophthalmology*, *123*(6), 1173-1180. https://doi.org/10.1016/j.ophtha.2016.01.039

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Structural and functional progression in the Early Manifest Glaucoma Trial

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Abstract

Objective—To elucidate the temporal relationship between detection of glaucomatous optic disc progression, as assessed by fundus photography, and visual field progression.

Design—Prospective, randomized, longitudinal trial.

Subjects—Three hundred and six study eyes with manifest glaucoma with field loss and 192 fellow eyes without any field defect at the start of the trial, of a total of 249 subjects included in the Early Manifest Glaucoma Trial (EMGT) were assessed.

Methods—Evaluation of visual field progression and optic disc progression during an 8-year follow-up period. Three graders independently assessed optic disc progression in optic disc photographs. Visual field progression was assessed using glaucoma change probability maps and the EMGT progression criterion.

Main outcome measures—Time to detection of visual field progression and optic disc progression.

Results—Among study eyes with manifest glaucoma, progression was detected in the visual field first in 163 eyes (52%), in the optic disc first in 39 eyes (12%) and in 1 eye (0%) it was found simultaneously with both modalities.

Among fellow eyes with normal fields, progression was detected in the visual field first in 28 eyes (15%), in the optic disc first in 34 eyes (18%) and in 1 eye (1%) it occurred simultaneously.

Conclusion—In eyes with manifest glaucoma, progression in the visual field was detected first more than four times as often as progression in the optic disc. Among fellow eyes without visual

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Conflict of Interest: Both Dr Bengtsson and Dr Heijl are consultants of Carl Zeiss Meditec. Dr Heijl reports grants from Allergan, Santen and MSD outside the submitted work.

This article contains additional online-only material. The following should appear online-only: Figure 1.

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field loss at baseline, progression was detected first as frequently in the optic disc as in the visual field.

Introduction

Glaucomatous progression can be observed as increasing functional loss in a series of visual fields or as increasing structural change in the optic nerve head or in the retinal nerve fiber layer. The relationship between structural and functional findings has been the object of many scientific papers.[1–13] A common, but not unanimous, contemporary opinion is that glaucomatous structural changes are detected more commonly early in the disease while functional progression is seen more commonly at later stages of the disease, although there is variation among patients as to which of the two appears first.[14–17]

This temporal relationship is relevant in order to be able to make appropriate decisions on when and how to use available instrumentation to diagnose, or how to decide when to treat or to change treatment in patients during different stages of the disease.

In the Early Manifest Glaucoma Trial (EMGT), glaucoma patients were followed using computerized perimetry and optic disc photography over long periods of follow-up; the present analysis includes prospective data collected during up to 11 years. Thus, the EMGT offers an unusual opportunity to study the temporal relationship between structural and functional findings using regular fundus photography and visual field testing throughout the study.

The aim of the present paper is to elucidate the temporal relationship between optic disc progression and visual field progression among patients in EMGT, and to compare the results obtained in study eyes, that had visual field defects at the beginning of the trial, and fellow eyes lacking such loss at study inception.

Method

As detailed in previous reports,[18] the EMGT (National institutes of Health ClinicalTrials.gov identifier NTC00000132. Date of registration: September 23, 1999) included 255 glaucoma patients aged 50 to 79 years at the time of study enrollment. Patients included in the study were mainly recruited from a large population-based screening and were equally randomized either to treatment with argon laser trabeculoplasty plus betaxolol (Betoptic®, Alcon, Fort Worth, Texas), or to no treatment until progression was observed. Participants were followed every 3 months for the first four years. Thereafter, some of the patients were seen every 6 months but the vast majority continued follow-up with 3-month intervals.

The study was conducted according to the tenets of the Declaration of Helsinki, and approved by the Ethics Committee of the University of Lund, Sweden, and also by the Committee on Research Involving Human Subjects of the State University of New York at Stony Brook. All patients provided informed consent.

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Eligibility criteria for inclusion in the EMGT included the presence of reproducible glaucomatous visual field defects as determined by the Glaucoma Hemifield Test (GHT) of the Humphrey perimeter (Carl Zeiss Meditec, Dublin, CA.).

Monoscopic fundus photographs were obtained at baseline and at the month 3 and month 6 visits, and every six months thereafter. Visual fields were obtained at each study visit.

The EMGT criterion for visual field progression was applied,[18] i.e. progression was determined to be definite only if three or more of the same test locations showed statistically significant progression in three consecutive visual fields, compared to baseline. The method of assessment was Glaucoma Change Probability Maps.[19] The date of the last of the three visual fields showing progression was defined as the date of progression. All patients showing visual field progression were subsequently evaluated to rule out alternative explanations for the observed progression. Also, if the three or more test locations did not indicate change in the subsequent visual fields, it was not considered true progression.

We evaluated all disc photographs that had been obtained between the time of each patient's first three-month visit and the year 2005, when our camera technique changed. All evaluated photographs were obtained through a dilated pupil, using a modified 30° Zeiss fundus camera and Kodachrome 64 film. Baseline images were defined to be the photographs taken at the three-month visit, rather than those of the pre-randomization baseline visit, in order to avoid inclusion of any possible immediate changes in optic disc configuration caused by the introduction of pressure-lowering treatment.[20, 21] Photographs obtained with the new camera technique used after 2005 were not evaluated, because this would have prevented masking of the temporal order of the images.

All studied photographs were digitized, and three disc readers, two experienced (A.H., B.B) and one more recently trained, (H.M.O) independently evaluated each optic disc while masked as to the temporal order and to all other patient data. AH and BB are senior scientists with long experience in optic disc interpretation, including teaching and performing longitudinal studies on optic disc topography and comparisons with perimetric data.[22, 23] HMO is a resident who has been working with this study for two years together with the senior authors. During this time period, HMO has had frequent opportunity to work with optic disc reading together with one or both of the senior authors. At an early stage, HMO went through an internet-based training course for the appraisal of optic disc progression prior to assessment of the eyes in the study. [24] High quality computer screens were used in the assessment where disc readers had the ability to magnify photographs to desired size. Progression was mainly recognized as changes in the course of small vessels on the optic disc surface. Increasing pallor, peripapillary atrophy or optic disc hemorrhages were not considered proof of optic disc progression. A random sample of optic discs thus determined to have progressed is presented in Fig. 1 (available at http://www.aaojournal.org).

Photo evaluation was done in the following order:

1. We looked for progression in pairs of fundus photographs, in which one photo came from the three-month visit and the second photo was the last available

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photograph of reasonable quality. The two photographs were masked as to temporal order and presented for evaluation in randomized order with study eyes and fellow eyes intermingled. One-fifth of the evaluated photo pairs were control pairs, in which two separate fundus photographs of study eyes obtained on the same date were used.

2. One disc reader (H.M.O) thereafter studied all full-sequences of photographs of all eyes to rule out that optic disc progressions had been missed in the pair-analysis.

3. If an eye was judged to have progressed and the temporal order was correctly determined, we evaluated the whole series of that patient's photographs sorted in chronological order, and the date of the first photograph where progression could be seen was recorded. Progression had to be sustainable throughout the series unless the earliest photograph showing progression also was the one that had originally shown progression in step 1.

4. Any disagreement among readers was settled through consensus, both regarding the existence of progression and the date of progression.

The same three disc readers evaluated the three-month photographs of fellow eyes in order to assess whether or not the optic nerves were glaucomatous. Fundus photographs from study-eligible glaucoma eyes were mixed randomly with fellow eyes. These eyes were classified as having pre-perimetric glaucoma when an optic disc hemorrhage was present or the disc showed convincing signs of glaucomatous damage, e.g., a clear notch or increased excavation and rim thinning.

In further analyses, fellow eyes were divided in three groups: 1) eyes with normal intraocular pressure and no signs of glaucoma in their optic discs or visual fields, 2) eyes with ocular hypertension, and 3) eyes designated as having pre-perimetric glaucoma because of abnormal optic discs or disc hemorrhages.

To compute inter-rater agreement among the disc readers, Cohen's kappa values and prevalence adjusted, bias adjusted kappa (PABAK) were calculated.[25] The arithmetic mean was used for both measures of inter-rater agreement.[26, 27] Cumulative incidence functions were calculated for the competing events; visual field progression first, optic disc progression first, and death occurring within six months from the last available follow-up in patients without progression.[28] Some patients had both eyes included as study eyes. To determine 95% confidence intervals for the various cumulative incidences at 96 months (median follow-up time) a bootstrap technique was used with 1000 repetitions and patient as cluster.[29] The conditional probability for visual field progression or optic disc progression to occur first, given that a progression has occurred, was calculated, with 95% confidence intervals. For study eyes robust 95% confidence intervals were determined with patient as cluster variable.[30] Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM Corp. released 2013. IBM statistics for Macintosh, version 22.0. Armonk, NY: IBM Corp.) and Stata (StataCorp. 2015. Stata: Release 14. Statistical Software. College Station, TX: StataCorp LP.)

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Results

The 255 glaucoma patients included in the EMGT had a median age of 68 years at baseline, 66% were female. Twelve eyes of 6 patients were excluded because follow-up was too short to be able to reach progression according to the criteria used in EMGT. That is to say, we were unable to include eyes having fewer than two fundus photographs and/or fewer than three visual fields obtained after baseline.

Of the 498 eyes analyzed, 306 had manifest glaucoma and 192 eyes were defined as fellow eyes, i.e., eyes without visual field defects at baseline. Of the 192 fellow eyes, 116 (60%) had seemingly normal discs and normal intraocular pressure, 39 (20%) were ocular hypertensive eyes (intraocular pressure >21 mmHg) and 37 (19%) were classified in the present analysis as having pre-perimetric glaucoma, four of those on the basis of an optic disc hemorrhage only.

Median follow-up time was 96 months (8 years) with a minimum of 9 months and a maximum of 132 months, for both study and fellow eyes. The median value of perimetric mean deviation (MD) at baseline was −4.0 dB for study eyes and −0.6 dB for fellow eyes. The median intraocular pressure at the three-month visit was 17 mmHg for study eyes and 19 mmHg for fellow eyes.

Inter-rater agreement calculations resulted in a Light's kappa (arithmetic mean of Cohen's kappa) of 0.487 and the arithmetic mean of the prevalence adjusted and bias adjusted kappa (PABAK) was 0.636, considered to represent substantial agreement.[31]

The disc readers did not mark any of the control pairs as "progression" but erroneously marked progression in the wrong temporal order in 9 of the 498 disc pairs. When assessing full series of photographs the three readers individually changed "progression" to "no progression" in 29 cases, 14 cases and 13 cases respectively, as the change first seen in the disc pairs was not judged to have been sustained in subsequent photographs and could thus have been a result of shifts in parallax. The disc reader assessing all full-sequence photographs found two more progressions, not detected in the pair analysis.

Among all study eyes, visual field progression was detected first more than four times as often as disc progression, Table 1. Three eyes showing non-glaucomatous visual field progression were marked as "no visual field progression" in our analysis; one had developed homonymous hemianopia caused by a stroke, and in the other two eyes, observed visual field progressions were not sustained. The conditional probability, given that a progression occurred, that the first type of progression to be detected in the visual field was 81% (95% CI 74.6% – 85.6%) and 19% for the optic disc (95% CI 14.4% – 25.4%). The difference is thus statistically significant since confidence intervals do not include the value 50%. The cumulative incidence at month 96 for visual field progression first was 54% (95% CI 48.1%– 59.7%) and for optic disc progression first 12% (95% CI 8.6%– 15.7%). The cumulative incidence for death before progression at the same month was 5% (95% CI 2.4%– 8.3%), Fig 2. Twenty-five percent of study eyes showed progression in both the visual field and the optic disc, and among these 66% showed progression first in the visual field and 32% in the optic disc, Table 2.

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Among fellow eyes the proportion of eyes where detection of progression was noted first with either of the two modalities was similar, Table 1. Another two fellow eyes showing non-glaucomatous visual field progression were not considered to have glaucomatous visual field progression in our analysis; one was the fellow eye of the hemianopic stroke patient mentioned earlier, and in another eye, progression was not sustained. The conditional probability for a progression to be detected in the visual field first was 45% (95% CI 33.0%– 57.9%) and 55% for the optic disc (95% CI 42.1%– 67.0%), thus not a statistically significant difference. The cumulative incidence for visual field progression at month 96 was 14% (95% CI 9.6%– 19.7%) and for optic disc progression 18% (95% CI 12.3%– 23.5%). The cumulative incidence for death at month 96 was 6% (95% CI 3.1%– 9.9%), Fig 3. Seventeen fellow eyes (9%) showed progression in both modalities and among these progression was detected first in the visual field in 41% of eyes and in the optic disc in 53%, Table 2.

There was no statistically significant difference between the conditional probability of optic disc progression first and visual field progression first in neither of the three subgroups of fellow eyes: eyes having normal optic discs and also normal intraocular pressure, eyes with intraocular pressures above 21 mmHg, and eyes having pre-perimetric glaucoma. Thus the conditional probability for optic disc progression to occur first for apparently normal eyes was 52% (95% CI 31.0%– 72.6%), for ocular hypertensive eyes it was 72% (95% CI 45.3%– 89.0%) and for pre-perimetric fellow eyes it was 43% (95% CI 22.6%– 65.8%). The cumulative incidences are shown in figure 4.

Discussion

The EMGT was a randomized, controlled, prospective study with long follow-up and regular documentation of both optic disc and visual field status. Long-term studies are necessary to make temporal comparisons of structural and functional detection of progression. Because fellow eyes were examined according to the same protocol used for study eyes, it was possible to compare patterns of detection of progression in glaucomatous eyes with those found in eyes having normal fields at baseline. Our results describe the first type of progression detected during follow-up. In EMGT it was possible to change treatment after progression, and therefore, any possible progression in the other modality after this point could theoretically be postponed. Thus no further analyses after the first type of progression could be performed.

In eyes with manifest glaucoma, visual field progression was detected first more than four times as often as optic disc progression with a conditional probability of 81%, while in fellow eyes without visual field loss at baseline, the two types of progression were noted first with similar frequency and no statistically significant difference in conditional probability. When dividing fellow eyes into three subgroups, i.e., apparently normal eyes, eyes with ocular hypertension and eyes with pre-perimetric glaucoma, there was no clear trend towards either modality to detect progression being more important in any of these subgroups.

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We used side-by-side comparison of fundus photographs for assessment of optic disc progression. The quality of the photographs was mostly good, but still identification of discrete changes was sometimes difficult, as noted also in other studies.[32–38] In the present study, three disc readers assessed optic disc progression independently, and in a masked fashion. We did not include pallor in our assessment for progression, because colors recorded photographically can change with, e.g., different exposure, cataract development and cataract extraction. We also chose to disregard changes in peripapillary atrophy. Presence of optic disc hemorrhages was not defined to be indicative of progression. Inspection of the course of small and large vessels in the optic disc was very thorough though, and even minute changes in the course of a vessel were regarded as signs of progression if they were sustained in later photographs. Such signs could consist of, e.g., a sharper or deeper bend over the disc rim, a bend over the rim occurring closer to the disc margin, or a smaller distance between two adjacent vessels. The initial pair-assessment strived for high sensitivity to minimize the risk of missing optic disc progressions. An indication of this is the relatively high number of changes from “progression” to “no progression” among disc readers when viewing the full series of photographs. A random selection of twelve eyes that were judged as showing disc progressions is displayed in Fig 1 (available at http://www.aaojournal.org), to give an indication of our criteria for indicating such change. We cannot rule out that very small optic disc changes are due to ageing but it would be unlikely that ageing would produce such localized changes. All three readers missed some progressions; therefore kappa values did not show perfect agreement. In cases of disagreement among readers, consensus was reached in a separate session. Such rigorous examinations of fundus photographs would not be realistic in standard clinical care.

Automated imaging techniques with built in computerized interpretation tools are, of course, free from subjectivity, but these devices were not available when EMGT started. A number of studies have reported that the diagnostic accuracy of some automated imaging techniques is similar to that of glaucoma experts.[38–42] The evidence of the role of imaging devices to predict visual field loss is conflicting. Several studies with up to eleven years of follow up showed promising ability to predict visual field loss among glaucoma suspects, [43–48] and possibly also in glaucoma patients, [49] while several other studies reported rather poor predictive ability[2, 3, 9, 12,] but none with follow up longer than six years. There are also indications that the agreement between visual field progression and progression in optic disc photographs may be better than that between optic disc photographs and automated imaging results.[4] Monoscopic photographs was the method available to us, and is commonly used in clinical practice. While stereoscopic photographs often are regarded as the “gold standard”, stereoscopic classification has not shown any convincing advantage as compared with monoscopic classification in the ability to assess glaucoma likelihood.[50, 51]

In an earlier paper about progression in eyes included in the EMGT we reported that almost all progression was first seen in the visual fields.[52] At that time optic disc progression analyses came from a dedicated optic disc reading center, where technicians based their judgments on flicker chronoscopy,[53] and patients had been followed for an average of 6 years. EMGT’s optic disc reading center was closed on the basis of these findings by the Data Safety and Monitoring Committee, since it was clear that perimetric findings had been much more important for study outcomes. The average follow-up time for the current report

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was 8 years, and we used a different technique for analyzing the photographs. In the first EMGT report only one study eye per subject was included, while all study eyes were included in the current report. These differences may explain the differences in results.

Different methods used for detecting structural or functional progression have different sensitivities and specificities. Differences in study population (ocular hypertensives, glaucomas, and mixtures thereof) also affect results, as do follow-up time, and criteria for optic disc and visual field progression. The percentage of progression detected depends strongly on how long patients have been followed, and any temporal relationship can easily be missed if trials have relatively short follow-up times.

In our study, the EMGT criterion for visual field progression was applied, where the last of the three visual field test defined the date of progression. Concerning date of optic disc progression, the first photograph were progression could be detected was defined as date of progression. Still, we noted substantially more progressions first in the visual field among study eyes.

To the best of our knowledge there are few longitudinal studies on the temporal relationship between structural and functional detection of progression in glaucoma. In one study glaucoma patients' time to detection of progression was found to be the same for Heidelberg retina tomograph (HRT) imaging as it was for visual field testing, but more progressions were noted with the HRT in total.[2] That study also reported an 81% concordance between progressions found through HRT and optic disc photography. Our findings are similar to those presented in a study from 1996 that found visual field progression considerably more often than disc progression in eyes with manifest glaucoma.[5] They are also in agreement with those of the Collaborative Normal-Tension Glaucoma Study (CNTGS), which reported 25% detection of either optic disc or perimetric progression during the study, with 2.9% only in the optic disc.[54]

Among our fellow eyes with no visual field defects at baseline, we found approximately the same number of progressions first in fields and discs. The majority of these eyes seemed healthy at start, while 19% were considered to have pre-perimetric glaucoma based on disc appearance, and 20% had ocular hypertension. This, therefore, is a mixed group and progression results are not quite comparable to studies on patients with ocular hypertension. They are also fellow eyes to glaucoma eyes and thus one could expect a higher level of conversion to glaucoma.[55] The high proportion of fellow eyes appearing normal could be attributable to the fact that patients were recruited through a population-based screening and thus picked up at an earlier stage of glaucoma than an average glaucoma patient in clinical practice. In the Ocular Hypertension Treatment Study (OHTS) after 72 months, conversion to glaucoma had been seen in the optic disc first in 55% of eyes, versus 35% in the visual field. 10 % of progressions were detected simultaneously in both modalities.[6] In a later OHTS report with 8 years of follow-up 41% showed visual field progression before optic disc progression, and 29% showed progression in the optic disc first among those who had both types of progression.[7] Medeiros and co-workers found that out of the glaucoma suspects showing progressive damage during follow up of eight years, 75% had progressive optic disc damage, and 74% had visual field damage but only half overlapped and had both

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types of progression. A temporal advantage to the finding of optic disc progression was described.[56] In the European Glaucoma Prevention Study[8] the results were the opposite; conversion to glaucoma was more commonly seen in the visual fields than in optic disc photographs, 60% and 40% respectively. In the Malmö ocular hypertension study[57] progression was detected in 14 out of 131 eyes with ocular hypertension after a mean follow-up time of 40 months. In 12 of these eyes progression was detected both in the disc and the visual field, in 9 of these 12 eyes progression was noted in the disc first. But it should be noted that the perimetric technique used in that study was less advanced than present techniques and tools for interpretation.[58]

When analyzing the different subgroups of fellow eyes, the group with apparently normal eyes without raised intraocular pressure or glaucomatous optic discs developed somewhat less optic disc and visual field progression, as expected. There was no significant difference in the proportion of visual field versus optic disc progression found in these eyes - an argument against the notion that structural changes are regularly seen before visual field abnormalities in the earliest stage of glaucoma.

It is important to distinguish between *detection* of progression and *actual* progression. We know that *actual* progression over the course of a day or a month, e.g. loss of a single ganglion cell, is too small for us to detect using present techniques. Our ability to detect either structural or functional progression is completely dependent upon the present state of the art, the methods used, the amount of time since the baseline examination, the interpretation criteria applied, and sometimes the skill and diligence of the practitioner.

In summary, visual field progression was noted first considerably more often than change in the optic disc in glaucomatous eyes with field loss. On the other hand, fellow eyes without visual field loss at baseline showed structural and functional changes first with similar frequency.

The current results indicate that when visual field loss already is present, perimetry will find progression more frequently. We examined fellow eyes consisting of a mixture of ocular hypertensive eyes, eyes with pre-perimetric glaucoma and apparently normal eyes, and among these, perimetry and optic disc photography had similar abilities to detect progression.

Our results suggest that if health care resources are limited then standard automated perimetry is preferable to optic disc photography for detection of progression in eyes with manifest glaucoma, while in eyes without field loss both modalities should be of similar value.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: This study was supported by the Swedish Research Council K98-27X and the National Eye Institute, Bethesda, Maryland, grants no U10-EY10260 and U10EY10261 and the Järnhardt Foundation. The

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National Eye Institute and the Swedish Research Council participated in the design of the Early Manifest Glaucoma Trial. The other sponsor had no role in the design or conduct of this research.

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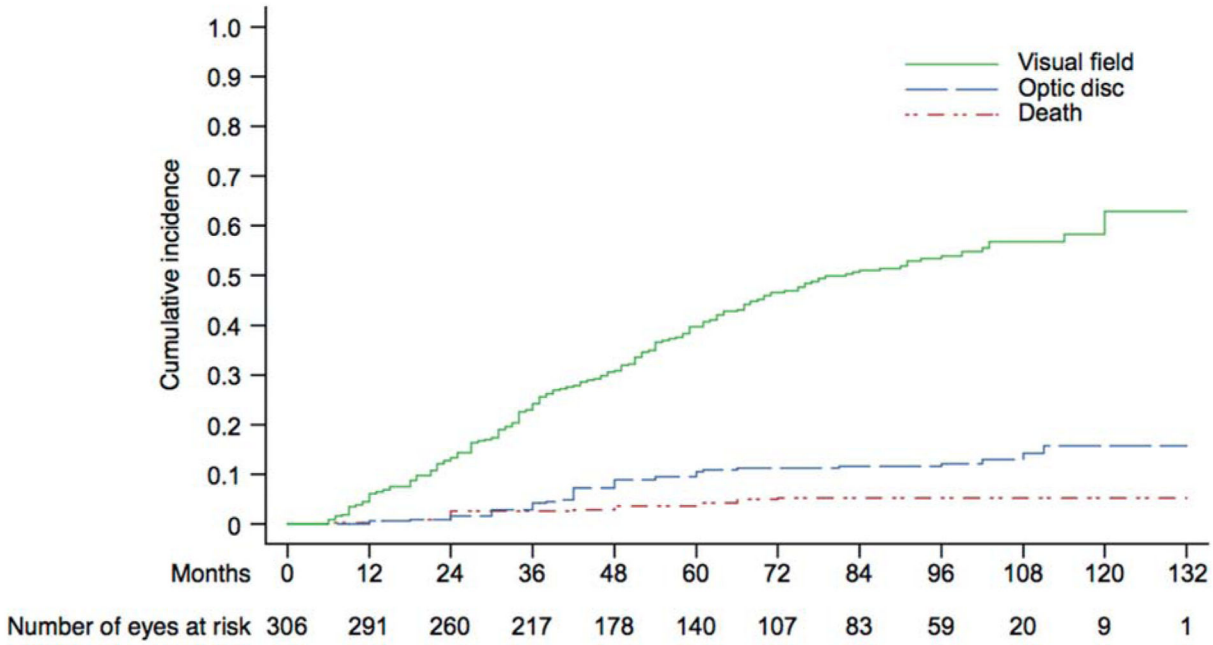

Fig. 2.

Study eyes: Cumulative incidence for visual field and optic disc progression to be detected first for the 306 study eyes, that all had manifest glaucoma with visual field loss. Visual field progression was considerably more common to be detected first. Death occurring within 6 months from the last visit where any progression had not been detected is shown as competing risk. The row below the x-axis denotes the number of eyes still at risk.

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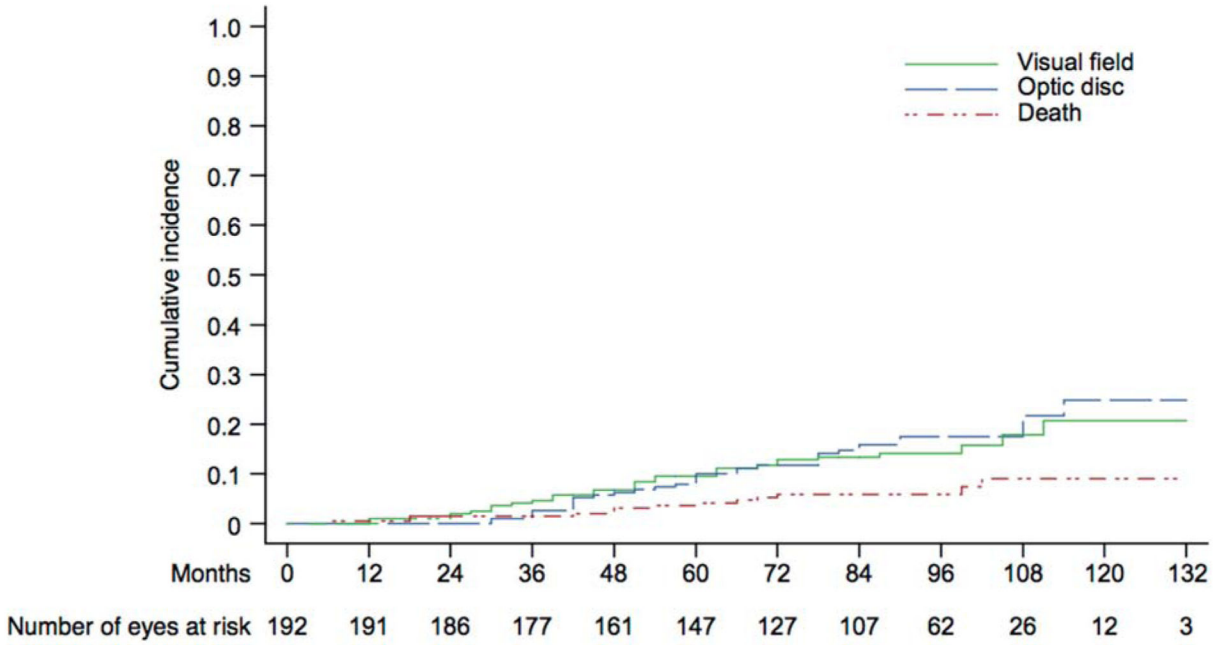

Fig. 3.

Fellow eyes: Cumulative incidence for visual field and optic disc progression to be detected first for 192 fellow eyes with no visual field defects at baseline. Visual field and optic disc progression occurred first with similar frequencies. There was no statistically significant difference. Death occurring within 6 months from the last visit where any progression had not been detected is shown as competing risk. The row below the x-axis denotes the number of eyes still at risk.

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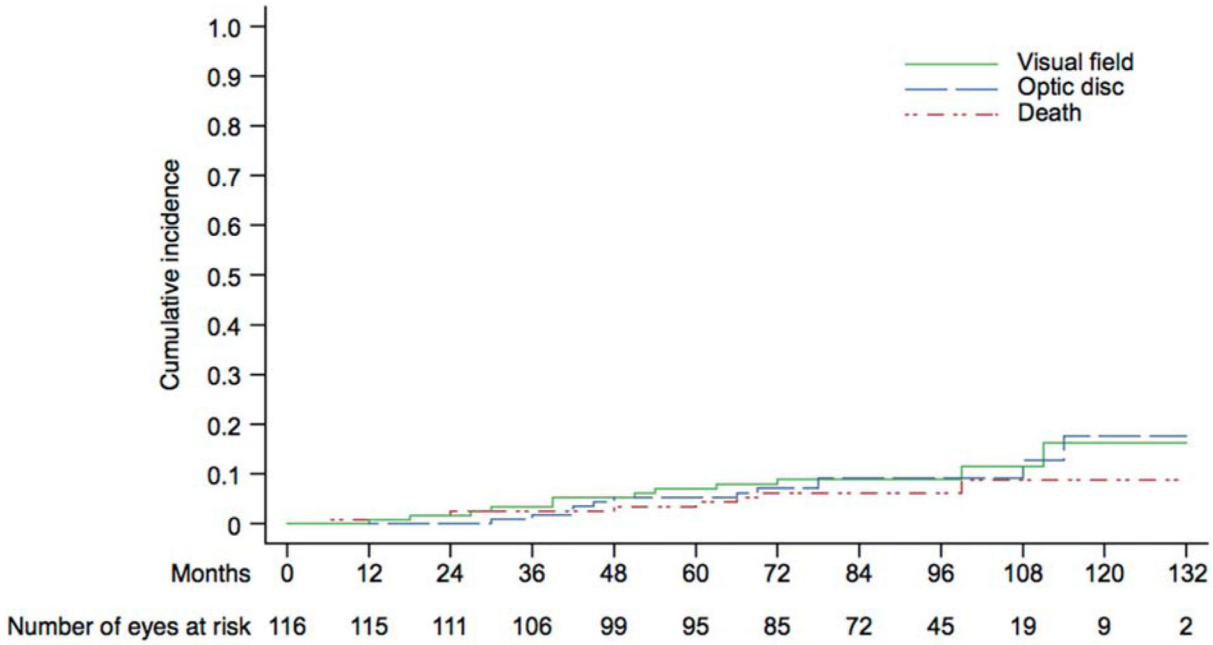

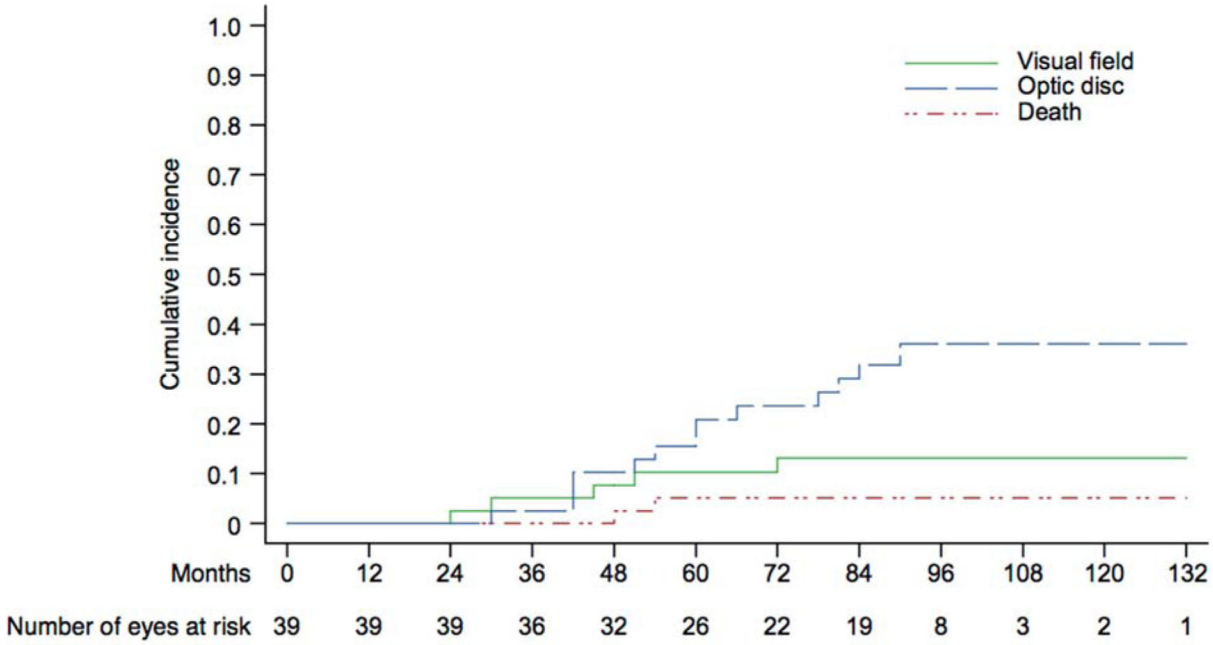

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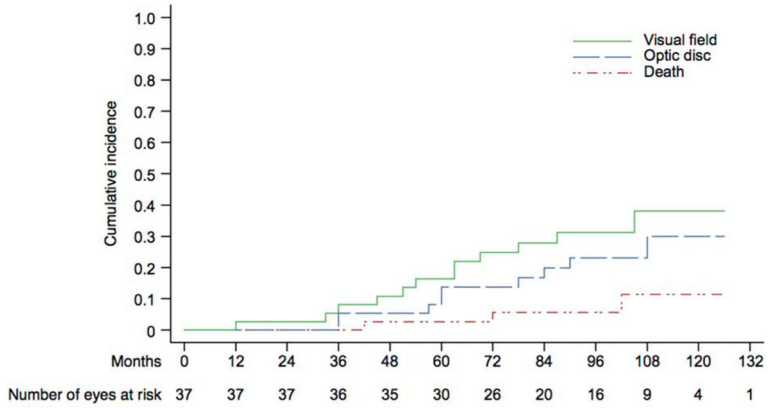

Fig. 4.

Fellow eyes, apparently normal (4a), Fellow eyes with ocular hypertension (4b), Fellow eyes, pre-perimetric (4c): Cumulative incidence for visual field and optic disc progression to be detected first for 116 fellow eyes without disc changes or raised intraocular pressure, (4a), for 39 ocular hypertensive fellow eyes, (4b) and for 37 fellow eyes with pre-perimetric glaucoma, (4c). Fewer progressions were seen in apparently normal fellow eyes without raised intraocular pressure or optic disc changes (4a), than in eyes with optic disc signs or elevated intraocular pressure. There was no statistically significant difference for the cumulative incidence between the two modalities for any of the three subgroups. Death occurring within 6 months from the last visit where any progression had not been detected is shown as competing risk. The row below the x-axis in each figure denotes the number of eyes still at risk.

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Table 1

Type of progression detected first in all eyes.

	Optic disc progression (%)	Visual field progression (%)	Simultaneous progression in visual field and optic disc (%)
Study eyes	39 (12%)	163 (52%)	1 (0%)
Fellow eyes	34 (18%)	28 (15%)	1 (1%)
Normal appearing fellow eyes	12 (10%)	11 (10%)	1 (1%)
Ocular hypertensive fellow eyes	13 (33%)	5 (13%)	0
Pre perimetric fellow eyes	9 (24%)	12 (32%)	0

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Table 2

Type of progression detected first in eyes with progression in both modalities.

	Optic disc progression (%)	Visual field progression (%)	Simultaneous progression in visual field and optic disc (%)
Study eyes	25 (32%)	51 (66%)	1 (1%)
Fellow eyes	9 (53%)	7 (41%)	1 (6%)