Early Manifest Glaucoma Trial

Design and Baseline Data

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Objectives: The Early Manifest Glaucoma Trial (EMGT) will evaluate the effectiveness of reducing intraocular pressure (IOP) in early, previously untreated open-angle glaucoma. Its secondary aims are to explore factors related to glaucoma progression and to study the natural history of the disease. This article describes the EMGT design and presents baseline data.

Design: Randomized, clinical trial.

Participants: Newly diagnosed patients 50 to 80 years of age with early glaucomatous visual field defects were mainly identified from a population-based screening of more than 44,000 residents of Malmö and Helsingborg, Sweden. Exclusion criteria were advanced visual field loss; mean IOP greater than 30 mmHg or any IOP greater than 35 mmHg; visual acuity less than 0.5; and inability to complete follow-up protocols.

Interventions: After informed consent, patients were randomized to treatment or no initial treatment with close follow-up. Treated patients had laser trabeculoplasty and started receiving topical betaxolol twice daily in eligible eyes. Follow-up visits include computerized perimetry and tonometry every 3 months and fundus photography every 6 months. Decisions to change or begin treatment are made jointly with the patient when EMGT progression occurs and also later if clinically needed.

Main Outcome Measures: The EMGT progression is defined by sustained increases of visual field loss in three consecutive C30-2 Humphrey tests, as determined from computer-based analyses, or by optic disc changes, as determined from flicker chronoscopy and side-by-side comparisons of fundus photographs performed by masked, independent graders.

Results: A total of 255 patients were randomized between 1993 and 1997 and will be followed for at least 4 years. All had generally good health status; mean age was 68.1 years, and 66% were women. At baseline, mean IOP was 20.6 mmHg and 80% of eyes had IOP less than 25 mmHg.

Conclusions: The Early Manifest Glaucoma Trial is the first large randomized, clinical trial to evaluate the role of immediate pressure reduction, as compared to no initial reduction, in patients with early glaucoma and normal or moderately elevated IOP. Its results will have implications for: (1) the clinical management of glaucoma; (2) understanding the role of IOP and the natural history of glaucoma; and (3) evaluating the rationale for glaucoma screening. *Ophthalmology 1999;106:2144–2153*

The pathogenesis of primary open-angle glaucoma (OAG) remains uncertain. A higher than average intraocular pressure (IOP) often accompanies OAG and was once thought to be the cause of the disease, but this concept has been challenged by evidence from various sources. First, one third to approximately half of glaucoma cases have IOP at or below 21 mmHg, as shown repeatedly in large epidemiologic studies.[1] Second, an elevated IOP alone (ocular hypertension without visual field or optic disc damage) is present in approximately 10% of adults, depending on the population studied, and usually does not lead to glaucoma.[2] Still, the level of IOP is considered to be a major risk factor for developing OAG,[3,4] and the goal of medical and surgical treatments for glaucoma is to reduce pressure.

Although the association between IOP and glaucoma risk seems clear, the role of IOP reduction in preventing field loss is not well-established. Although newly diagnosed patients usually receive IOP-lowering treatment, the effectiveness of such an approach has never been shown in a randomized, clinical trial. In several trials of patients with ocular hypertension,[5–9] it has proved difficult to show the benefit of treatment in decreasing the risk of glaucoma damage. These inconclusive results may be because of obstacles in showing a treatment effect (e.g., because of the low risk of damage or insufficient change in IOP). For

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Table 1. Early Manifest Glaucoma Trial Design Synopsis

Aims	
Primary	To compare the effect of immediate therapy to lower the IOP, versus later treatment or no treatment, on the progression of newly detected open-angle glaucoma, as measured by increasing visual field loss and/or optic disc changes
Secondary	To determine the extent of IOP reduction attained by treatment To explore factors that may influence glaucoma progression To describe the natural history of newly detected glaucoma
Treatment groups	Topical medication with beta-blockers and argon laser trabeculoplasty Follow-up without treatment or later treatment
Outcome measures	
Perimetric endpoint	Significant progression of the same 3 or more points in pattern deviation change probability maps in 3 consecutive C30-2 Humphrey fields
Optic disc endpoints	Comparison of baseline and follow-up photographs by flicker chronoscopy with confirmation by side-by-side gradings in 3 follow-up photographs
Patient eligibility	
Inclusion criteria	Newly detected and untreated chronic open-angle glaucoma with repeatable visual field defects by Humphrey perimetry Age 50–80 yrs
Exclusion criteria	Advanced visual field loss (MD ≤16 dB) or threat to fixation Mean IOP >30 mmHg or any IOP >35 mmHg in at least one eye VA <0.5 in either eye Any condition precluding reliable fields of photos, use of study treatment or 4-year follow-up
Treatment assignment	Person-based randomization
Level of masking	Masking of technicians, disc photograph graders
Follow-up	Every 3 mos, for a minimum of 4 yrs; extra follow-up visits to confirm visual field progression, repeat photographs, confirm IOP elevation (≥25 mmHg in treated group; ≥35 mmHg in control group)
Mode of support	National Eye Institute (Clinical Center and Data Center) Swedish Medical Research Council (Clinical Center)

IOP = intraocular pressure; VA = visual acuity.

OAG, only one small study[10] has addressed this issue, with largely negative results. In a recently published multicenter study of normal-tension glaucoma, similar difficulties in interpretation were found when comparing visual field progression in patients randomized to treatment versus no treatment. In the "intent-to-treat" analysis, which is the accepted method to evaluate treatment effects of clinical trials, no differences were observed between study groups.[11] Significantly less progression in the treated group was only found in subsequent analyses, which followed treated patients after IOP reduction was achieved and censored data from those considered to have cataract.[12] No study analyses found a relationship between a change in the IOP and visual field progression,[11,12] highlighting methodologic issues in interpreting the findings,[13,14] and the need to answer this question using the established clinical trial design.

The uncertainties about the role of IOP reduction on glaucoma progression have led to controversies in glaucoma management and difficulties in defining indications for treatment, especially in early disease and in patients with moderately increased IOP. They also cast doubts on the value of glaucoma screening.[15,16] Resolution of these issues is important, since glaucoma treatment is lifelong, causes various side effects and complications, and has considerable economic impact.

The Early Manifest Glaucoma Trial (EMGT) is the first large randomized, controlled clinical trial to evaluate the efficacy of IOP-lowering treatment on the progression of OAG with moderately elevated and low IOP values. The trial will allow an evaluation of whether immediate IOP reduction by conventional methods influences the natural history of early OAG at such pressures (i.e., whether immediate treatment is beneficial in controlling visual field loss as compared to no treatment or later treatment). Finally, the EMGT aims to clarify treatment effects in subgroups of patients and to provide much-needed data on the natural history of newly diagnosed glaucoma without treatment. This article describes the design of EMGT and presents baseline data on the 255 patients enrolled in the trial.

Methods

A synopsis of major EMGT design features is presented in Table 1; the procedures performed at each visit are summarized in Table 2. The specific aims are identified below as follows.

Primary Aim

To compare the effect of immediate therapy to lower the IOP versus later treatment or no treatment on the progression of newly detected open-angle glaucoma as measured by increasing visual field loss or optic disc changes. This aim is being achieved by conducting a randomized, clinical trial that compares glaucoma progression in initially treated versus initially untreated (control) patients with newly detected OAG. The null hypothesis being tested is that no differences in progression will occur between patients randomized to initial IOP reduction versus no initial reduction.

Secondary Aims

To determine the extent of IOP reduction attained by treatment. This aim will be achieved by comparing IOP levels over time in the treated and control groups. Knowledge of the extent of

Table 2. Procedures Performed at Each EMGT Visit

Visit	Pulse/ Blood Pressure	Medical History	Ocul. History	Refract. and Visual Acuity	IOP	Slit-lamp Examination	Gonioscopy	Ophthalmoscopy	Comp. Perimetry	Disc Photo	Random Assignment	Laser Treatment
Post screening 1				X	X	X		X	X			
Post screening 2		X	X	X	X	X		X*	X			
Baseline 1					X	X		X*	X	X		
Baseline 2	X	X		X	X	X	X		X		X	
Laser treatment visit 1					X							X
Laser treatment visit 2 (for second eye if both eligible)					X							X
Post laser 1												
Post laser 2 (for second eye if both eligible)					X							
Follow-up visits	Every year	X	X	X	X	X		X	X	Every 6 mos		

IOP = intraocular pressure; OAG = open-angle glaucoma; VA = visual acuity; GHT = Glaucoma Hemifield Test; DSMC = Data Safety and Monitoring Committee.

* Dilated examination.

IOP reduction that is actually attained by treatment will complement evaluations of the primary aim.

To explore factors that may influence progression. This aim will be achieved by multivariate analyses of predictor variables for progression in both groups.

To describe the natural history of newly detected glaucoma. This aim will be achieved by analyses limited to untreated patients, which will provide previously unavailable longitudinal data on optic disc damage, visual field loss, and IOP in these patients.

Study Organization

The EMGT organization consists of several centers. The Clinical Center is located at the Department of Ophthalmology of Malmö University Hospital, Sweden, which initially designed and began the study with approval from the Ethics Committee of the University of Lund. Its responsibilities have included a large population-based screening to identify eligible patients, as well as recruitment, treatment, and follow-up. A satellite center is located at the Department of Ophthalmology at Helsingborg Hospital, Helsingborg, Sweden. A Data Center is located at the Department of Preventive Medicine, University Medical Center at Stony Brook, New York, which is responsible for epidemiologic and biostatistical input, eligibility confirmation, randomization, quality assurance, data processing, management and analysis, and report preparation. A Disc Photography Reading Center, located at the Department of Ophthalmology of Lund University Hospital, Sweden, is responsible for evaluating and grading the fundus photographs. The National Eye Institute and the Swedish Medical Research Council support the study. An Executive Committee, which includes members from the Clinical Center, the Data Center, and the National Eye Institute, provides leadership for the study and reviews its progress continually. An independent Data Safety and Monitoring Committee (DSMC) includes members from Sweden and the United States and is responsible for monitoring all aspects of the trial. This committee is the only group provided with evidence of treatment effects during the course of the study.

Eligibility Criteria

The eligibility criteria were selected to ensure a high degree of patient safety, minimize losses to follow-up, and ensure completion of the major outcome measures. Eligibility was evaluated at postscreening visits 1 and 2 and confirmed at baseline visits 1 and 2 before randomization.

Inclusion Criteria. Inclusion criteria are as follows:

1. Men and women, 50 to 80 years of age, with newly diagnosed, previously untreated chronic OAG.
2. The diagnosis of early manifest chronic OAG required repeatable visual field defects in at least one eye. Defects had to be compatible with glaucoma and not explained by other causes. This definition included chronic simple glaucoma, normal-tension glaucoma, and exfoliative glaucoma. Glaucoma visual field defects were documented by static computerized perimetry, initially using the Humphrey 24-2 Full-Threshold program at Post screening visits 1 and 2. The Humphrey Full-Threshold algorithm is used extensively, reproducible, and well-documented, yielding visual field data that can be analyzed with the Statpac I and II software.[17,18] This computer-based approach met the EMGT requirement to have objective and immediate visual field criteria to determine EMGT eligibility and progression, thus obviating the need for a visual field reading center.

Eligibility was based on results of the Glaucoma Hemifield Test (GHT) of the Statpac II program,[19,20] a diagnostic program able to identify glaucomatous visual field loss with high sensitivity and specificity.[20,21] The GHT is based on empirically determined statistical significance limits at 44 points located in 5 zones of the superior hemifield and 5 mirror-image zones in the inferior hemifield. The EMGT definition of a definite visual field defect required at least two reliable tests that met one of the following criteria:

1. A classification of Outside Normal Limits affecting the same GHT sector (or sector 1 or 2) on two consecutive tests performed on different days.
2. A classification of Borderline affecting the same GHT sector of the visual field on two consecutive tests performed on

different days, and obvious localized glaucomatous changes of the optic disc in an area corresponding to the field defect.

Exclusion Criteria. Exclusion criteria are as follows:

1. Advanced visual field defects (mean deviation worse than −16 dB)[17] or threat to fixation (sensitivity 10 dB or worse affecting either or both test points closest to the point of fixation in the upper hemifield and at either or both of the corresponding test points in the lower hemifield).
2. Visual acuity less than 0.5.
3. Mean IOP greater than 30 mmHg, or any IOP greater than 35 mmHg in at least one eye.
4. Any condition precluding reliable visual fields or disc photography, use of study treatments, or 4-year follow-up. Eyes with lens opacities exceeding standard photographs N1, C2, or P1 in the Lens Opacities Classification System II (LOCS II)[22] were ineligible.
5. If both eyes had glaucomatous visual field defects, the patient was eligible only if mean deviation was −10 dB or better in one eye and −16 dB or better in the other eye.

Main Outcome Measures

The study outcome is glaucoma progression, which is measured by: (1) objective, quantitative visual field criteria requiring at least three consecutive fields, at least 1 week apart, and (2) optic disc changes identified by flicker chronoscopy[23,24] and confirmed in side-by-side comparisons of fundus photographs by masked graders at the Disc Photography Reading Center. Outcome criteria were selected to provide valid, reproducible, and objective measures of changes in visual field loss and optic disc damage between baseline and follow-up.

Description of Perimetric Outcomes and Their Rationale. Glaucomatous visual fields are subject to large and complex variation of threshold values and to learning effects.[25–27] Random test/retest variability in glaucomatous fields depends on the initial defect depth, location of the test point, and general visual field status.[26] Increasing media opacities result in increasing diffuse visual loss, which is added to any worsening of the differential light sensitivity caused by glaucoma damage. Glaucoma Change Probability Maps[18] can be used to compare successive fields while considering these factors. The maps identify each test point of a follow-up field as nonchanging, significantly deteriorating, or improving, as compared with the average from two baseline fields. The standard Glaucoma Change Probability Maps of Statpac II[18] were modified and improved to enhance visual field follow-up for EMGT. Although standard Glaucoma Change Probability Maps are based on total deviation from age-corrected values, these new EMGT maps analyze change based on pattern deviation, thus largely eliminating the distorting effects of increasing media opacities.[28] Such opacities would considerably influence the results of traditional Glaucoma Change Probability Maps and be detrimental for linear regression analyses, whether based on global sensitivity indices, such as mean deviation, or on threshold values at individual test point locations.

In EMGT, tentative visual field progression is defined by the presence of at least three test points that are flagged as significantly ($P < 0.05$) progressing at the same location in the EMGT Pattern Change Probability Maps of two consecutive tests. The EMGT perimetric outcome is definite visual field progression, which is defined by at least three significantly progressing points at the same locations in three consecutive tests. The validity of these EMGT criteria was evaluated by retrospective analyses of existing series of fields at the Clinical Center (Early Manifest Glaucoma Trial [EMGT], Manual of Procedures, 1998). Because the EMGT perimetric criteria are based on specific results from computer-generated maps, possible biases due to subjective assessment are eliminated. Furthermore, they allow immediate and early determination of progression (i.e., tentative progression may be detected as early as the second visit, that is, at the 6-month visit). When tentative progression occurs, an additional visual field test is performed within 1 month to confirm or exclude definite progression.

Description of Optic Disc Outcomes and Their Rationale. In EMGT, baseline and follow-up disc photographs are compared by flicker chronoscopy, which is a sensitive indicator of changes in optic disc anatomy.[23,24] Flicker chronoscopy has the unique property of highlighting areas of change, which can be confirmed later in traditional side-by-side comparisons. It is inherently a very sensitive technique, and false-positive results may occur, such as those caused by parallax. Therefore, an extensive, repeated grading protocol was designed to ensure a rather high specificity. First, two masked graders independently compare the best of two follow-up slides versus a baseline slide. Second, if a grader classifies the result as "clear change" or "suspect change," the second follow-up slide is judged in the same way. Third, any disagreements between graders are resolved by consensus or, if needed, by adjudication by a third grader. Fourth, if consensus exists on the presence of a clear and progressive change in both sets of photographs, a side-by-side comparison is performed by yet another independent grader.

An optic disc progression outcome is reached only: (1) if the side-by-side grader confirms the clear and progressive change located at the same optic disc clock-hour, and (2) the same finding persists in the photographs obtained 6 months later. Quality control of this protocol is monitored by assessing intraobserver and interobserver reproducibility, as well as drift in gradings. The quality control scheme involves continuous masked evaluations of a standard set of photographs.

Sample Size and Power Considerations

The sample size will provide sufficient statistical power (at least 80%) to detect differences in outcomes between the study groups based on the following premises:

- Four-year progression rates of 40% in the treated group and 60% in the control group.
- Significance level of 5%; two-tailed test.
- Attrition of 15%.

Recruitment

Early manifest glaucoma is asymptomatic, and patients usually are identified and immediately treated at later stages of the disease. Therefore, EMGT required special efforts to recruit previously untreated glaucoma patients who were detected in four ways:

1. At a large-scale population-based screening of specific age cohorts.
2. Among patients followed from the screening.
3. Among patients followed at the clinical centers.
4. Among patients referred from eye specialists in clinical practice.

In Malmö, the screening started in October 1992 (after pilot studies in December 1991 and April 1992) and ended in January 1997. In Helsingborg, the screening started in November 1994 and ended in February 1997. Randomization started in January 1993 (in Malmö) and June 1995 (in Helsingborg) and ended in April 1997. The screening was intended to identify most persons with manifest glaucoma, as well as those who would probably develop the disease in the near future. The methods and criteria to determine positive screening results, which follow, combined a high sensitivity and high specificity.[29]

Table 3. Distribution of Open-angle Glaucoma and EMGT Randomized Patients, by Age, among the Population Screened

Age (yrs)	Screened (n)	Glaucoma		Randomized	
		n	%	*n*	%
≤60	3615	20	0.55	17	0.47
61–65	10,150	94	0.93	34	0.33
66–70	16,684	295	1.77	84	0.50
71–75	12,558	238	1.90	73	0.58
>75	1236	32	2.59	8	0.65
Total	44,243	679	1.53	216	0.49

1. Applanation tonometry: Persons with IOP greater than 25 mmHg in at least one eye were asked to return for a postscreening examination.
2. Fundus photography: One single picture of each optic disc was taken after pupil dilatation using a nonmydriatic camera, and photographs were evaluated by the same experienced examiner. Persons with suspicious glaucomatous changes, retinal nerve fiber defects, or optic disc hemorrhages were asked to return for a postscreening examination.
3. Slit-lamp examination: After pupil dilatation, eyes with IOP greater than 20 mmHg were examined at the slit lamp. Persons found to have pseudoexfoliations were seen by an ophthalmologist. If other findings were negative for glaucoma, a visit to a physician in private practice was recommended after approximately 1 year.
4. History: Persons reporting manifest glaucoma in at least one first-degree relative were seen by an ophthalmologist. If findings were negative for glaucoma, a visit to a physician in private practice was recommended after approximately 5 years.

A total of 44,243 residents of Malmö and Helsingborg were screened, representing 70% of the population in these age cohorts. Of these, 2252 (5%) had positive screening results. At postscreening, 679 persons (1.5%) were found to have a manifest glaucoma, but most did not meet the EMGT eligibility criteria. Reasons for ineligibility included a higher IOP than specified by the EMGT criteria, visual field damage exceeding maximum criteria, lens opacities, unreliable fields, and medical or surgical history. Of those confirmed eligible, 6 did not participate and 216 (0.5%) were randomized (Table 3). Thus, only 39 (15%) of the 255 EMGT patients were recruited from sources other than the screening (Table 4).

Patient Visits

The EMGT protocol includes four pretreatment visits (i.e., two postscreening visits and two baseline visits), laser treatment visits, and follow-up visits (Table 2).

Postscreening Visits. The two postscreening visits were intended to ascertain eligibility and exclude persons without manifest glaucoma or who were otherwise ineligible, as well as to minimize the untoward effects of perimetric learning and of regression to the mean. Eligibility was ascertained after a careful history, repeated perimetry and tonometry, funduscopy, and dilated slit-lamp examination. Due consideration was given to the size and repeatability of any visual field defects, as well as to their compatibility with a diagnosis of glaucoma and the possibility of alternative explanations. The ability of the patients to comply with EMGT interventions was assessed, as well as the feasibility of prolonged follow-up. Potential study participants were given written information about the trial at the second postscreening visit.

Baseline Visits and Randomization. At the first baseline examination, perimetry (Humphrey 30-2 Full-Threshold program), fundus photography, and applanation tonometry were performed in a standardized manner. The patient was also given the opportunity to ask questions, supplementing the written information received at the previous visit. If patients remained eligible and willing to participate, they were scheduled for a second baseline visit; additionally, both postscreening forms and the first baseline form were sent by facsimile machine to the Data Center for independent eligibility confirmation.

The second baseline examination included medical history, measurements of pulse, blood pressure, visual acuity, refraction, visual fields, intraocular pressure, and gonioscopy. After eligibility confirmation and informed consent, the patient was randomized. The Clinic Coordinator issued randomization assignments using a set of sequentially numbered, opaque, sealed envelopes provided by the Data Center. Assignments were stratified by center (Malmö or Helsingborg) and based on a blocked randomization scheme. Patients randomized to treatment were instructed to instill one drop of betaxolol 5 mg/ml twice daily in eligible eyes and given oral and written information about argon laser trabeculoplasty, which was scheduled approximately 1 week later.

Laser Treatment Visits. A full 360° laser treatment was administered to eligible eyes.

Table 4. Distribution of EMGT Patients by Recruitment Source and Center

Recruitment Source	Malmö		Helsingborg		Total	
	n	%	*n*	%	*n*	%
Positive screening	136	71.6	58	89.2	194	76.1
Followed from screening	19	10.0	3	3.3	22	8.6
From clinical centers	13	6.8	4	4.4	17	6.6
Referrals from practitioners	22	11.6	0	0	22	8.6
Total	190	100	65	100	255	100

Follow-up Visits. Examinations every 3 months include interim history, best-corrected visual acuity, using Monoyer–Gran-ström standard decimal charts after subjective refraction, perimetry (Humphrey 30-2 Full-Threshold program), applanation tonometry, slit-lamp examination, and funduscopy and lens classification to assess cataract using Lens Opacities Classification System II standards.[22] Blood pressure is measured once a year, and fundus photographs are obtained at the 3- and 6-month visits and every sixth month thereafter. Information about masking, adverse effects, compliance, and eligibility of second eyes is sought at all follow-up visits. Additional visits are scheduled in patients with tentative visual field progression, IOP of 26 to 35 mmHg in any treated eye, or a confirmed IOP over 35 mmHg in any eye.

Early Manifest Glaucoma Trial Treatment Protocol

The treated group receives betaxolol 5 mg/ml (Betoptic; Alcon, Ft. Worth, TX) twice daily and argon laser trabeculoplasty in eligible eyes. Betaxolol was initially given at the second baseline visit and continued throughout the follow-up period. The protocol specifies the addition of latanoprost 50 μg/ml (Xalatan; Pharmacia, Piscataway, NJ; Upjohn, Kalamazoo, MI) if the IOP exceeds 25 mmHg in treated eyes or 35 mmHg in control eyes. If EMGT progression is reached, further clinical management is decided in collaboration with the patient and usually follows customary patterns of glaucoma treatment.

Masking

Patients and physicians are not masked as to the treatment assignment, since physicians need this information for clinical management. The main study outcomes, however, are based on computerized visual field criteria and on fundus photographs, which are read by masked graders at the Disc Photography Reading Center. Other important variables, such as visual acuity and IOP, are also obtained by masked ophthalmic technicians according to standard protocols. The masking status of the technicians collecting data is recorded at each study visit.

Quality Assurance

All the data collection protocols are standardized through study documentation (*Manual of Procedures and Handbook*), uniform study protocols, and forms. All personnel were certified before study data were collected. Eligibility and progression are independently assessed at the Data Center, which also determines treatment allocations and monitors data quality and adherence to protocol. There is centralized, concurrent processing of data; forms are reviewed for missing, invalid, and questionable responses; and data issues are resolved by edit queries to the other centers. A data audit is performed yearly by comparing information available at the Data Center and the clinical sites based on a representative sample of study visits. Photograph gradings are evaluated periodically for reproducibility and drift based on a set of quality control photographs.

A double data entry system, with two independent certified persons, is used and a sequence of logic checking and frequencies of all variables are examined periodically. The accuracy of the data is monitored regularly by selecting a random sample of participant numbers and comparing the data entered into the computerized system with the original forms.

The study is reviewed regularly by the DSMC, which monitors: (1) any significant adverse reactions or side effects of the treatments; (2) the need for additional treatment in the treated group or for treatment of the control group; and (3) the overall study performance. The DSMC periodically reviews interim reports to determine possible differences between study groups that would warrant stopping the study and making the results known to patients and the scientific community. Extensive data are provided to the DSMC on all aspects of recruitment, patient follow-up, protocol adherence, and data quality.

Statistical Analyses

Interim Analyses and Stopping Guidelines. Interim analyses are being conducted to test for differences in progression rates between the groups, as well as to examine the distributions of study data and monitor possible adverse effects. The timing for these analyses depends on reaching a specific ratio of cumulative progressions, relative to the total number expected by the end of the trial. These ratios define the spending function for the overall 5% significance level set for this study. The Lan and DeMets[30] procedure is used, which allows interim testing without prespecification of the number of times or calendar times for such analyses. The DSMC is regularly provided with interim analyses to evaluate differences between study arms; their recommendations are forwarded to the Director of the National Eye Institute, who decides whether results warrant stopping the trial.

Baseline Comparisons. The comparability of study groups at baseline was evaluated by the Mann–Whitney test, Student's *t* test, chi-square, and Fisher's exact tests.

Analysis of Progression

Unit of Observation

Patient-based analyses: The main analytic strategy involves patients as the unit of analysis. Sample size estimation, randomization plan, and study design are based on the patient as the statistical unit of observation. Comparisons between study groups include: (1) whether progression in an eligible eye has occurred, and (2) the time since baseline that progression was first observed. Survival analysis will be used, as well as actuarial life-table methods to compute and compare progression at specific timepoints. Cox proportional hazards regression models will test for differences while controlling for effects of covariables.

Eye-based analyses: Eligible treated and control eyes comprise the units of observation for these analyses. For most patients, only one eye was eligible at baseline. If the second eye becomes eligible during the trial, that eye will also be considered for analyses. The strategy to control for intraclass correlation while assessing effects of eye-specific predictor variables, such as treatment, is based on the methods of Liang and Zeger[31,32] for estimating regression coefficients. Methods for estimating logistic and Cox proportional hazard regression parameters, while accounting for correlation between fellow eyes,[33,34] will also be considered.

Intent to treat analyses: Patients will be analyzed as part of their originally assigned groups (i.e., treatment or control). As noted earlier, for patient safety concerns, treatment changes within groups occur if:

1. Confirmed IOP exceeds 25 mmHg in the treated group, which requires addition of latanoprost.

2. Confirmed IOP exceeds 35 mmHg in either group, which requires addition of latanoprost or individualized treatment as needed.

3. Clinical findings, in the judgment of the ophthalmologist, require treatment.

Giving treatment to an eligible control eye is defined as *later treatment.* Follow-up on that eye as a *later treated eye* commences when treatment is begun.

Main Outcome Measures

Primary Outcomes

Progression of glaucoma is the primary outcome and will be assessed on the basis of visual field changes or optic disc changes, accounting for follow-up times. Several methods will be used. The study groups will be compared as to the frequency of EMGT-predefined perimetric and optic disc outcomes, which are binary variables. By this approach, analyses will provide the probability of progression, expressed as a function of treatment status and other factors. Other approaches will involve continuous variables, such as rates of visual field change summarized by measurable slopes. Plans for subgroup analyses, while accounting for multiple comparisons, include those based on glaucoma subtypes, such as normal tension and pseudoexfoliation glaucoma. Sample size permitting, these analyses will include testing for interaction between these baseline covariates and the study group. If necessary, exact tests will be used to compare progression frequencies between the groups.

Secondary Outcomes

Prognostic Factors. To explore the factors that may influence progression, multivariate analyses of predictor variables will be used, including treatment as one of the covariates.

Natural History. Information on the natural history of early, newly detected glaucoma will be obtained by analyses of follow-up data on untreated patients in the control group, when no medication was given.

Changes in IOP Over Time. Distributions of change, percent change, and slope of IOP in the two groups will be evaluated to quantify the effect of IOP reduction, and results will be compared by Student's *t* test or the Mann–Whitney *U* test. To control for other factors, linear regression will be used to test for differences between groups, in which analysis is based on the followed single eye of the person. For analyses based on eyes, the methods described earlier will be used, treating IOP as a continuous variable.

Baseline Data

Baseline characteristics were evaluated by patient (Table 5) and by eye (Table 6). The 255 participants had a mean age of 68.1 years (Fig 1) and were predominantly female (66%). One fifth had a family history of glaucoma. Health status was generally good; 98 (38%) had hypertension, defined as systolic pressure greater than 160 mmHg or diastolic pressure greater than 95 mmHg or antihypertensive treatment history; 15 (6%) had myocardial infarction history; 9 (4%) had diabetes mellitus; 22 (9%) had peripheral vasospasm or Raynaud's syndrome; and 25 (10%) had migraine.

Sixty-one (24%) patients had both eyes eligible for the trial at baseline. Patients had good visual acuity (mean of 0.9) as expected from the eligibility criteria. Abnormal visual fields (i.e., GHT results "outside normal limits") were found in 97% of participants. The remaining nine patients had abnormal field results when eligibility was determined during the postscreening examinations. Median mean deviation was −4.1 dB. The average IOP was 20.6 mmHg, and 80% of eligible eyes had a baseline IOP less than 25 mmHg (Fig 2). Pseudoexfoliations were present in 25 (10%) patients. Ninety percent of participants had disc pathology, mainly notching, as well as saucerization, large cupping reaching the optic disc margin, or optic disc hemorrhage. Eye pathology other than glaucoma was minimal.

Table 5. General Baseline Characteristics of all EMGT Patients (n = 255 patients)

Characteristic	n (%)	Mean ± SD [median (range)]
Age (yrs)		68.1 ± 4.9 68.0 (50.0–79.0)
50–59	12 (5)	
60–64	46 (18)	
65–69	92 (36)	
70–74	80 (31)	
75–80	25 (10)	
Gender		
Male	86 (34)	
Female	169 (66)	
Family history of glaucoma		
No family history	205 (80)	
Sibling only	17 (7)	
Parents only	26 (10)	
Parents and siblings	7 (3)	
Systolic pressure (casual)		148.0 ± 18.8 145.0 (100.0–210.0)
>160 mmHg	42 (16)	
Diastolic pressure (casual)		85.7 ± 10.3 85.0 (60.0–120.0)
>95 mmHg	34 (13)	
Hypertension*	98 (38)	

Characteristic	n (%)
History of	
Cardiac incompensation	3 (1)
Myocardial infarction	15 (6)
Arrhythmia, bradycardia	15 (6)
Stroke	2 (1)
Low blood pressure	8 (3)
Orthostatism	7 (3)
General arteriosclerosis	9 (4)
Peripheral vasospasm, Raynaud disease	22 (9)
Migraine	25 (10)
Obstructive pulmonary disease	3 (1)
Diabetes mellitus	9 (4)
Medication use	
Antihypertensives	62 (24)
Corticosteroids	4 (2)
Other (e.g., insulin, estrogen)	112 (44)

* Defined as systolic pressure >160 mmHg or diastolic pressure >95 mmHg or a history of antihypertensive treatment.

Discussion

The primary aim of EMGT is to address a classic and central question in ophthalmology, namely the effect of pressure-lowering therapy on primary OAG. This is a very important issue to resolve because large numbers of patients are involved, glaucoma damage is irreversible, and treatment is associated with side effects and cost. Although other glaucoma clinical trials, such as the Advanced Glaucoma Intervention Study[35] and the Collaborative Initial Glaucoma Treatment Study (Musch et al. Invest Ophthalmol Vis Sci 1998;39[Suppl]:4072), are comparing various treatments to

Table 6. Baseline Ocular Characteristics in Eligible Eyes of All EMGT Patients (n = 316 eyes/255 Patients)

Characteristic	n (%)	Mean ± SD [median (range)]
Eyes eligible for trial		
Both eyes	61 (24)	
One eye only	194 (76)	
OD	87	
OS	107	
IOP (mmHg)–average of two baseline visits		20.7 ± 4.1 20.5 (12.0–31.0)
<15	21 (7)	
15–19	124 (39)	
20–24	108 (34)	
25–29	60 (19)	
≥30	3 (1)	
Refractive error (D)		
<−1	42 (13)	
−1 to 1	95 (30)	
>1	179 (57)	
		0.9 ± 0.1
Best-corrected visual acuity		1.0 (0.6–1.0)
0.6	4 (1)	
0.7–0.9	95 (30)	
1.0	217 (69)	
Perimetry		
Within normal limits	3 (1)	
Borderline	6 (2)	
Outside normal limits	307 (97)	
Mean deviation (dB)		−4.7 ± 3.5 −4.1 (−14.7–2.4)

Characteristic	n	(%)
Fundus examination	Upper	Lower
Optic disc	n(%)	n(%)
Saucerization	24 (8)	36 (11)
Notch	128 (41)	138 (44)
Marginal cupping	2 (1)	15 (5)
Disc hemorrhage	22 (7)	21 (7)
Any of the above	156 (49)	193 (61)
Any disc pathology	285 (90)	
Other findings		
Macular degeneration	14 (4)	
Other	17 (5)	
Slit-lamp examination findings		
Exfoliation	25 (8)	
Corneal clouding	4 (1)	
Pigment dispersion	2 (1)	
Lens opacities (nuclear)	1 (0)	
Gonioscopy (angle width)		
0–1	3 (1)	
2	54 (17)	
3	148 (47)	
4	111 (35)	
Trabecular pigmentation grade		
0–1	156 (49)	
2	142 (45)	
3	18 (6)	
Anterior synechiae	7 (2)	

IOP = intraocular pressure; OD = right eye; OS = left eye.

lower IOP, EMGT is the first large trial to compare immediate IOP reduction versus no reduction or later reduction in newly diagnosed OAG. The Collaborative Normal-Tension Glaucoma Study, also including an untreated control arm, was based on patients with IOP less than 24 mmHg who

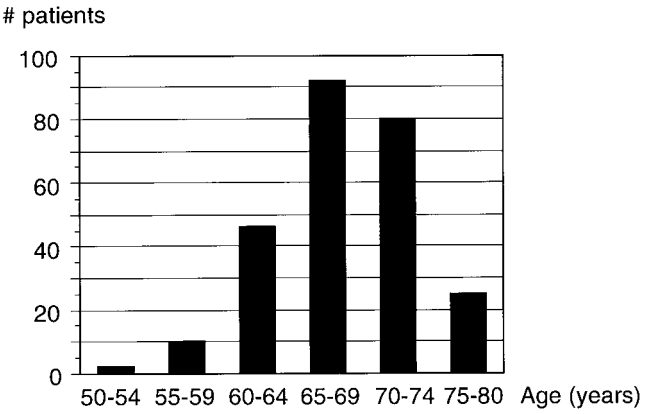

Figure 1. Age distribution of randomized patients at baseline.

were randomized only after showing progressive disease or threat to fixation.[11,12] The results of the "intent-to-treat" analyses found no differences in visual field progression between groups,[11] a result that was attributed to the higher frequency of cataract in the treated group. In additional analyses including treated eyes only after achieving a 30% reduction of IOP,[12] a step that may result in bias (refer to next paragraph), less progression was seen in the treated group. Similar results were found when observations were censored after the occurrence of visual acuity reduction attributed to cataract.[11] There was no relationship between IOP changes and visual field progression, even when analyses attempted to control the effect of cataract. Although these results contribute to our knowledge, they highlight the need for further research.

The goal of treatment in EMGT is to lower the IOP as much as possible without causing major side effects. Such a goal is important to achieve in trials with treated and untreated arms, in which treatment side effects and treatment crossovers are a potential problem. A related design feature of EMGT is that no target IOP is set for treatment (e.g., to reach a specific IOP value such as <21 mmHg or a specific percent reduction from baseline). For various reasons, EMGT avoided setting such a numeric criterion to define treatment success or failure in terms of "controlled" IOP. It

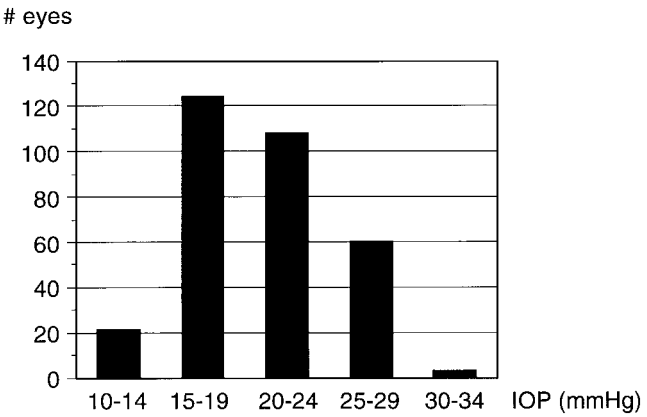

Figure 2. Baseline intraocular pressure in all study eyes (average of two baseline visits).

is possible that patients who achieve sufficient IOP reductions to meet a treatment goal have milder disease (and thus inherently better outcome) than patients who respond to treatment with smaller reductions in IOP. As such, comparisons based on this controlled IOP group could show a beneficial effect of treatment, even if none existed. Another reason is the lack of firm data on which to base target values for effective IOP reduction. Potentially, the EMGT goal of maximum possible reduction could lead to a more substantial lowering of IOP than a specific numeric goal. It also avoids the distinction between "controlled" and "not controlled" IOP.

Clinical observations indicate that very high IOP (>40 mmHg) frequently is followed by progression of glaucomatous optic disc cupping and field deterioration within relatively short time. There is also consensus among clinicians that eyes with such pressure levels need vigorous treatment. Experimental glaucoma with cupping and visual field defects can also be created in monkeys when high IOP levels are produced by extensive laser treatment of the trabecular meshwork.[36] Large fluctuations of IOP are common in this monkey model,[37] however, and it is difficult to produce experimental glaucoma with only moderately elevated IOP. In fact, although glaucoma damage often is considered to be pressure-induced, the relationship between such damage and IOP is much less clear at moderately elevated or low pressure levels. When glaucoma occurs at these lower IOP levels, its presence could be explained by other factors.[3,4] Most persons with glaucoma have moderately elevated or "normal" pressures. At the EMGT population-based screening, 82.3% of patients with newly detected glaucoma had IOP values of 30 mmHg or less, thus meeting the IOP eligibility criterion for the study. The results of EMGT may, therefore, not be directly applicable to patients with glaucoma with very high IOP, but they will provide information on the effectiveness of conventional treatment in most patients with glaucoma.

Ocular hypertension is another example of the unclear relationship between IOP and glaucoma damage. This condition is common and usually associated with a good prognosis, since most people with moderately elevated IOP do not develop glaucoma damage, even after very long follow-up without treatment.[2] As emphasized by Rossetti et al,[5] several trials have given variable results and failed to show a clearly decreased incidence of glaucoma damage in patients with treated versus untreated ocular hypertension. This has motivated the large, currently ongoing Ocular Hypertension Treatment Study (Invest Ophthalmol Vis Sci 1998;39 [Suppl]:878), a clinical trial again addressing whether glaucoma risk in subjects with ocular hypertension is decreased by pressure-lowering treatment.

We expect that EMGT results will have considerable importance for ophthalmologic care in similar populations. If progression is significantly and substantially lower in initially treated patients, as compared to untreated or subsequently treated patients, the rationale for current standard clinical management of glaucoma will be strengthened. Such results would also motivate screening efforts to identify the large percentage of patients with glaucoma, approximately 50%, who currently are undetected. At present, the scientific rationale for glaucoma screening is weakened by the lack of firm evidence to show that early detection and treatment favorably influence the natural history of the disease.[15,16]

If lowering IOP is found to be effective at all pressure levels, screening must use methods that can detect structural or functional glaucoma damage, thus identifying the large proportion of undetected cases with normal-tension glaucoma. If pressure reduction effectively reduces progression only if the IOP is "elevated," screening for glaucoma with tonometry can again be advocated, as long as those screening positive have further tests to identify the subgroup with glaucoma damage. Conversely, if EMGT results fail to show statistically and clinically significant effects of treatment, the basis of our clinical management of glaucoma would be seriously weakened. It would then be important to search for new treatment methods.

The results of analyses to address the secondary EMGT aim of identifying markers or risk factors for progression will be important to plan strategies for glaucoma screening. These results may also enhance our currently quite-deficient understanding of glaucoma pathogenesis. Other results on secondary EMGT aims also should provide much-needed information on the natural history of early and moderately advanced glaucoma and how the risks of progression may depend on factors such as the IOP level, the amount of damage, and other possibly important (modifying) factors. This knowledge, in itself, is clinically important, since it may allow an assessment of the value of rapid treatment or early detection or both. In summary, EMGT results will be relevant for clinical practice, for evaluating the role of glaucoma screening, and for understanding the natural history of the disease. Future articles will present forthcoming data from the study.

Appendix

EMGT Group

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