

# Reduction of Intraocular Pressure and Glaucoma Progression

## Results From the Early Manifest Glaucoma Trial

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**Objective:** To provide the results of the Early Manifest Glaucoma Trial, which compared the effect of immediately lowering the intraocular pressure (IOP), vs no treatment or later treatment, on the progression of newly detected open-angle glaucoma.

**Design:** Randomized clinical trial.

**Participants:** Two hundred fifty-five patients aged 50 to 80 years (median, 68 years) with early glaucoma, visual field defects (median mean deviation, -4 dB), and a median IOP of 20 mm Hg, mainly identified through a population screening. Patients with an IOP greater than 30 mm Hg or advanced visual field loss were ineligible.

**Interventions:** Patients were randomized to either laser trabeculoplasty plus topical betaxolol hydrochloride (n=129) or no initial treatment (n=126). Study visits included Humphrey Full Threshold 30-2 visual field tests and tonometry every 3 months, and optic disc photography every 6 months. Decisions regarding treatment were made jointly with the patient when progression occurred and thereafter.

**Main Outcome Measures:** Glaucoma progression was defined by specific visual field and optic disc outcomes. Criteria for perimetric progression were computer based and defined as the same 3 or more test point locations showing significant deterioration from baseline in glaucoma change probability maps from 3 consecutive tests. Optic disc progression was determined by masked grad-

ers using flicker chronoscopy plus side-by-side photograds.

**Results:** After a median follow-up period of 6 years (range, 51-102 months), retention was excellent, with only 6 patients lost to follow-up for reasons other than death. On average, treatment reduced the IOP by 5.1 mm Hg or 25%, a reduction maintained throughout follow-up. Progression was less frequent in the treatment group (58/129; 45%) than in controls (78/126; 62%) ( $P=.007$ ) and occurred significantly later in treated patients. Treatment effects were also evident when stratifying patients by median IOP, mean deviation, and age as well as exfoliation status. Although patients reported few systemic or ocular conditions, increases in clinical nuclear lens opacity gradings were associated with treatment ( $P=.002$ ).

**Conclusions:** The Early Manifest Glaucoma Trial is the first adequately powered randomized trial with an untreated control arm to evaluate the effects of IOP reduction in patients with open-angle glaucoma who have elevated and normal IOP. Its intent-to-treat analysis showed considerable beneficial effects of treatment that significantly delayed progression. Whereas progression varied across patient categories, treatment effects were present in both older and younger patients, high- and normal-tension glaucoma, and eyes with less and greater visual field loss.

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**S**TARTING IN THE 1960s, epidemiological studies demonstrated that normal-tension glaucoma was much more common than previously thought and that ocular hypertension, or elevated intraocular pressure (IOP) without glaucomatous visual field defects or optic disc cupping, was more common than glaucoma.<sup>1-3</sup> Subsequent studies showed that relatively few patients with ocular hypertension developed signs of glaucomatous damage during follow-up periods of up to 20 years, even if the condition was left un-

treated.<sup>4-8</sup> The earlier concept that basically equated elevated IOP with glaucoma became obsolete, resulting in uncertainty of the effects of glaucoma treatment.

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Given this background, several randomized trials were initiated in the early 1980s to evaluate the relationship between glaucoma and the reduction of IOP.<sup>9-12</sup> The relationship was studied some-

what indirectly by investigating whether IOP reduction could reduce the incidence of glaucoma damage in patients with ocular hypertension. At that time, conducting a study to address the subject more unequivocally (ie, a carefully designed randomized trial of patients with glaucoma that included an untreated control arm) would probably have been considered unethical.

Controversy continued regarding when, how aggressively, and whether or not to treat,<sup>13</sup> and the uncertainty of treatment effects was outlined in a report presented to the National Leadership Commission on Health Care.<sup>14</sup> The development and widespread use of computerized perimetry and the improved understanding of early optic disc changes in glaucoma had demonstrated a complex relationship between IOP and glaucoma damage. Researchers and professional organizations emphasized a new glaucoma concept in which the disease was described as an optic neuropathy, with IOP as only one of several risk factors.<sup>15,16</sup> This view has now become the standard, and modern glaucoma definitions often do not even mention IOP.<sup>17,18</sup>

When our trial was planned in the early 1990s, several controlled studies using timolol maleate in patients with ocular hypertension had been in progress for many years but had not shown that such treatment effectively prevented glaucoma damage. Given the relatively low incidence of this damage in patients with ocular hypertension, the sample sizes and statistical power of these trials were probably insufficient. Only 1 controlled trial involving treated and untreated patients with glaucoma had been published, and with negative results.<sup>19</sup> The Collaborative Normal-Tension Glaucoma Study (CNTGS) was under way at that time.<sup>20,21</sup> In 1993, Rossetti et al<sup>22</sup> concluded in a systematic literature review that “[p]racticizing ophthalmologists should be aware that the effectiveness of pressure-lowering agents in the treatment of primary open angle glaucoma is still to be determined,” and that controlled trials with functional endpoints and sufficient duration were urgently needed.

Because the effectiveness of such treatment had never been shown in a randomized clinical trial, several clinical implications influenced glaucoma management: What price in terms of adverse effects, inconvenience, and cost could be considered acceptable when treatment effects were uncertain? Efforts to detect cases of glaucoma that remained undetected (approximately 50%)<sup>2,3,23-25</sup> could hardly be advocated because an effective treatment for a particular disease is considered a prerequisite for screening.<sup>26-28</sup> The need for knowledge in this area was clear. The development of improved methods for computerized visual field testing and recognition of mild glaucoma progression enhanced the feasibility of such trials. Hence, a randomized study with a control arm, in which patients underwent follow-up without treatment as long as progression did not occur, would not expose study patients to unacceptable risks.

The Early Manifest Glaucoma Trial (EMGT) began in 1992. It is a controlled clinical trial evaluating the effectiveness of reducing IOP in patients with newly detected, previously untreated glaucoma. The study design and baseline data were reported in 1999.<sup>29</sup>

The purpose of our article is to report the EMGT results pertaining to the primary aim of the trial, namely to compare the effect of immediate therapy to lower the

IOP, vs no treatment or later treatment, on the progression of newly detected open-angle glaucoma as measured by increasing visual field loss or optic disc changes.

## METHODS

Our previously published article<sup>29</sup> contains a detailed description of the study methods. The following is a condensed description, which should enable the reader to understand and interpret the results.

### INCLUSION AND EXCLUSION CRITERIA

Study patients had newly detected, previously untreated open-angle glaucoma. All patients fulfilled the following eligibility criteria:

- A diagnosis of early manifest open-angle glaucoma, including primary open-angle glaucoma, normal-tension glaucoma, or exfoliation glaucoma.
- Reproducible glaucomatous visual field defects in at least one eye.
- Age between 50 and 80 years.

To determine eligibility, glaucomatous visual field defects were documented with computerized static perimetry using the Full Threshold 24-2 program of the Humphrey perimeter. Eligibility required a classification of “outside normal limits” involving the same visual field area at 2 initial postscreening visits using the glaucoma hemifield test<sup>30,31</sup> of the Statpac II program for computer-assisted visual field interpretation.<sup>32</sup> A “borderline” classification was acceptable only if obvious localized glaucomatous optic disc cupping was present in an area corresponding to the visual field defect.

Exclusion criteria were as follows:

- Advanced visual field defects (mean deviation [MD] worse than -16 dB)<sup>33</sup> or a threat to fixation, defined as differential light sensitivity of 10 dB or worse at either or both test points closest to the point of fixation in both the upper and lower hemifields. If both eyes were eligible, the MD had to be better than -10 dB in at least one eye.
- Visual acuity less than 0.5 (Monoyer-Granström), corresponding to 20/40, in any eye.
- Mean IOP greater than 30 mm Hg or any IOP greater than 35 mm Hg in at least one eye.
- Any condition precluding reliable results of perimetry or optic disc photography, the use of study interventions, or 4 years of follow-up.
- Cataractous lens changes exceeding gradings of N1, C2, or P1 according to the Lens Opacities Classification System (LOCS) II.<sup>34</sup>

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

### RANDOMIZATION, TREATMENT, AND MASKING

Eligibility was independently confirmed at the data center. Eligible patients were randomized evenly between treatment and nontreatment groups according to a permuted block randomization scheme stratified by the clinical and satellite centers. All eyes randomized to treatment received a full 360° trabeculectomy plus betaxolol hydrochloride eye drops at a dose of 5 mg/mL (Betoptic; Alcon, Fort Worth, Tex) twice daily. Eyes

stayed in their allocation arms unless significant progression occurred. If, however, the IOP in treated eyes exceeded 25 mm Hg at 2 consecutive follow-up visits or 35 mm Hg in control eyes, latanoprost eye drops at a dose of 50 µg/mL (Xalatan; Pharmacia, Uppsala, Sweden) were given once daily. When definite progression occurred, patients were informed and options were discussed; decisions on subsequent clinical management were made with their cooperation and following the usual patterns of glaucoma treatment.

As part of the quality control protocol for the trial, all study personnel completed a training period according to the manual of procedures prior to data collection, which was followed by a formal certification process implemented by the data center. Regular site visits and data audits were conducted. Study outcomes were determined either through numerical, predetermined objective criteria (visual field tests) or by masked graders at the disc photography reading center. Study personnel measuring visual acuity, IOP, and visual fields were masked to patients' study group, but patients and treating physicians were not masked. An independent Data Safety and Monitoring Committee (DSMC), which includes members from both Sweden and the United States, has been responsible for monitoring all aspects of the trial since its inception. The DSMC meets yearly to review patient safety, evaluate data quality and the results of interim analyses, and supervise the overall conduct of the study.

### PATIENT VISITS

The protocol required 2 postscreening visits preceding the 2 baseline visits. These early visits were used to substantiate the diagnosis, ascertain eligibility, minimize the effects of perimetric learning, and provide information about the trial. Both baseline examinations included visual field testing and the measurement of IOP (Goldmann applanation tonometry). After eligibility was confirmed at the second baseline visit, informed consent was obtained and patients were randomized. Patients received follow-up at 3-month intervals. A recent medical and ophthalmologic history, including adverse events and compliance, was obtained at each visit. Examinations included visual acuity testing with Monoyer-Granström standard decimal charts following subjective refraction, Goldmann applanation tonometry, computerized visual field testing (Humphrey 30-2 Full-Threshold program), ophthalmoscopy, and slitlamp examination with lens classification using the LOCS II system.<sup>34</sup> Optic disc photographs were obtained every 6 months.

### ADDITIONS TO THE STUDY PROTOCOL

To further assess differences in nuclear clinical LOCS II gradings<sup>34</sup> between study groups, the DSMC approved a proposal to obtain nuclear lens photographs with slitlamp cameras specifically adapted for this purpose. After standardization and certification of the photographers, lens photographs were obtained twice: (1) between December 1999 and March 2000, and (2) between March 2001 and July 2001. The 2 sets of slitlamp photographs were evaluated concurrently, following a random order, at a reading center at the Department of Ophthalmology, University of Wisconsin–Madison. The graders were masked and applied a standardized system.<sup>35</sup>

Further additions to the protocol once the study began included visual function-related quality-of-life assessment with the National Eye Institute's Visual Function Questionnaire<sup>36</sup> and corneal pachymetry measurements.<sup>37</sup>

### OUTCOMES

The study outcome was progression of either glaucomatous visual field defects or optic disc cupping, each according to pre-

determined objective criteria. For each patient, one or both eyes could be included in the study, based on eligibility at baseline. A patient was considered to have progression when the first eligible eye met progression criteria.

To determine visual field progression, all follow-up results of visual field tests were compared with an average of those from the 2 baseline tests from the same eye using glaucoma change probability maps (GCPMs). These maps differentiate between significant progression at  $P < .05$  and random test-retest fluctuations at each of 74 test point locations in the visual field. The EMGT used pattern deviation GCPMs based on pointwise pattern deviations from the age-corrected normal threshold values<sup>38</sup> rather than the standard total deviation GCPMs. Pattern deviation maps limit the effects of increasing homogeneous loss of differential light sensitivity, such as the loss caused by progressive cataract. Definite EMGT visual field progression was defined as at least 3 test points showing significant progression, as compared with baseline, at the same locations on 3 consecutive GCPMs. These criteria have been shown to be highly sensitive indicators of early visual field progression (A.H., M.C.L., B.B., B.B., and M.H., for the EMGT Group, unpublished data, 2002).

To determine optic disc progression, baseline and follow-up photographs were compared at the disc photography reading center using flicker chronoscopy.<sup>39,40</sup> The protocol was designed to yield highly specific outcomes. Two graders masked to study group and photograph order independently judged each pair of photographs. If a suspected or definite change was found, a second set of photographs was judged. If a consensus was reached that flicker chronoscopy indicated change (sometimes after adjudication), a nonflicker side-by-side comparison by a third independent grader decided if definite optic disc progression was present. A previously described quality control system evaluated the validity and reproducibility of the gradings, as well as grading drift, based on a standard set of photographs.<sup>29</sup>

### STATISTICAL ANALYSIS

The sample size calculations were based on assuming 4-year progression rates of 40% in the treatment group and 60% in the control group, a significance level of 5%, 2-tailed tests, and an attrition rate of 15%, thus providing at least 80% statistical power to detect differences in progression between trial arms. The statistical analysis plan has previously been described in detail.<sup>29</sup> This article includes comparisons of the primary outcome of glaucoma progression between the treatment and control groups. We followed an intent-to-treat analytic strategy, with all patients analyzed according to their original group assigned by randomization. Comparisons of glaucoma progression were based on assessing visual field or optic disc changes that met the prespecified EMGT criteria while accounting for follow-up times. Analyses were patient based; for those with 2 eligible eyes, the event time to progression was defined by the first progression in either eye. Survival analysis and life-table methods<sup>41</sup> were used to (1) estimate the proportion of progressions by study group, and (2) test for a significant difference in these rates between groups using the log-rank test. The estimated difference in 4-year progression rates between groups and 95% confidence intervals were derived from the life-table analyses and calculated as binomial events. Survival curves were also plotted for all patients, stratified according to the prespecified covariates of IOP ( $< 21$  mm Hg or  $\geq 21$  mm Hg) and exfoliation ("yes" or "no") as well as MD and age (less than median values or equal to or greater than median values).

Univariate comparisons between treatment and control groups (eg, in baseline characteristics or numbers progressing) were based on *t* tests for continuous variables if normality as-

sumptions were justified (otherwise, nonparametric methods were used), and on the  $\chi^2$  test or Fisher exact test for categorical variables. In addition, progression across time by study group was compared while stratifying according to the prespecified covariates mentioned previously. The generalized estimating equations method<sup>42</sup> was used to adjust for the correlation of lens status among different follow-up visits for the same eyes. We also compared visual field changes between the 2 study arms using linear regression analyses of both MD and number of highly significantly depressed test point locations ( $P < 0.5\%$ ) according to the pattern deviation probability maps. As reported in detail elsewhere, additional multivariate statistical analyses using Cox proportional hazards models<sup>43,44</sup> were performed to evaluate factors related to glaucoma progression, including treatment. These analyses estimated the magnitude of treatment effects (for each millimeter of mercury of IOP reduction) and explored possible non-IOP-related effects of treatment while controlling for other significant variables (M.C.L., A.H., M.H., B.B., L.H., and E. Komaroff, PhD, unpublished data, 2002).

## RESULTS

### RECRUITMENT AND RETENTION

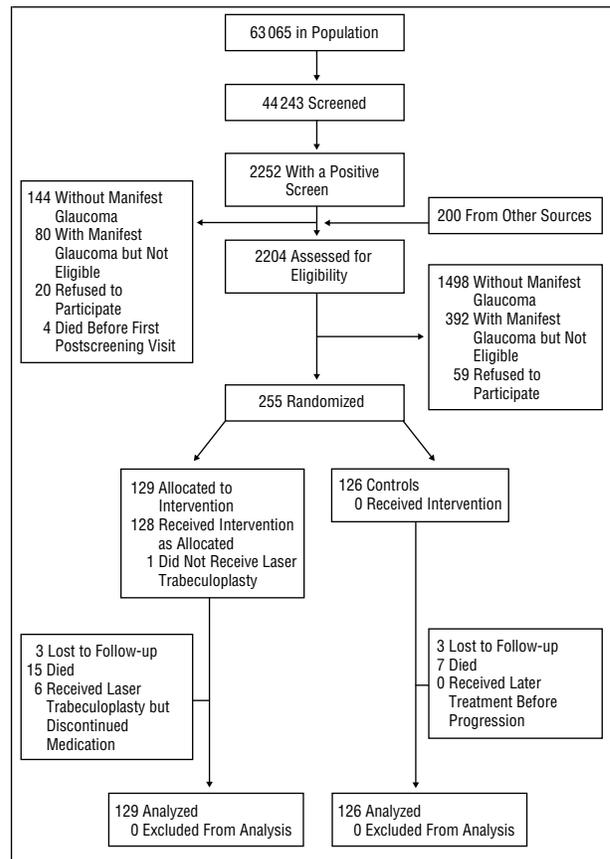
Recruitment has previously been described in detail.<sup>29</sup> A large population screening of 44 243 residents aged 57 to 76 years was conducted between October 1992 and January 1997 in the cities of Malmö, Sweden, and Helsingborg, Sweden, to recruit for the trial. Most trial participants (84.7%) came from this screening, whereas a smaller number were referred from other ophthalmologists. A flowchart is shown in **Figure 1**. The randomization period began in January 1993 and ended in April 1997. Of the 255 patients randomized, 129 were allocated to treatment and 126 were controls. Only 3 patients in each group were lost to follow-up for reasons other than death ( $n = 22$ ); that is, 6 living patients no longer received follow-up as of September 1, 2001, the time of database closure for this study. The remaining 227 patients exceeded the originally selected minimum follow-up period of 4 years, with follow-up times comparable between study groups and ranging from 51 to 102 months (for the treatment group, mean  $\pm$  SD = 67.0  $\pm$  20.4 months; median = 66 months; for the control group, mean  $\pm$  SD = 69.7  $\pm$  20.8 months; median = 69 months). The number of patient study years was similar in the 2 groups: 720 in the treatment group and 732 in the control group.

### BASELINE CHARACTERISTICS

The mean age of the patients was 68 years; 66% were women, almost all patients were white,<sup>29</sup> and 132 (52%) had a baseline IOP less than 21 mm Hg. The baseline characteristics of the 2 study groups (**Table 1**) were comparable, and none of the observed parameters differed significantly between groups.

### IOP CHANGES AFTER BASELINE

The mean IOP in the treatment group decreased from 20.6 mm Hg at baseline (Table 1) to 15.5 mm Hg at the 3-month follow-up visit, for a reduction of 25% that was maintained throughout the follow-up period; the me-



**Figure 1.** Patient flowchart. Most study patients were recruited from a population-based mass screening. Attrition rates were low, and follow-up is indicated as of September 2001.

dian change was 0.2% from 3 months until progression or the last visit (for nonprogressed eyes). The reduction was larger (29%) in eyes with a baseline IOP of 21 mm Hg or greater than in eyes with a baseline IOP less than 21 mm Hg (18%). Results were similar when considering changes in IOP from baseline to each visit until progression or the last visit. The mean  $\pm$  SD difference from baseline to all visits was  $-4.5 \pm 3.4$  mm Hg in treated eyes; the corresponding values were  $-6.8 \pm 3.0$  mm Hg for eyes with a baseline IOP of 21 mm Hg or greater and  $-2.7 \pm 2.4$  mm Hg in eyes with a baseline IOP less than 21 mm Hg. By self-report, treated patients indicated using treatment “most of the time” at 96.8% of visits. The mean IOP reduction in the treatment group from the baseline readings (average of 2 visits) to the reading obtained just before laser trabeculoplasty a few weeks later, when patients were receiving betaxolol, was 2.7 mm Hg; the IOP reduction from that reading to the 3-month visit was 2.4 mm Hg. The protocol-defined cut-off point for extra treatment in the treated patients ( $>25$  mm Hg) occurred infrequently (4 patients, or 3%), whereas no untreated patients reached the 35 mm Hg limit requiring topical medication before progression.

In the control group, IOP values were unchanged (20.9 and 20.8 mm Hg at baseline and the 3-month visit, respectively), with small changes thereafter (median change = 0.0% from 3 months until progression or the last visit). The mean  $\pm$  SD difference from baseline to all visits, censored for progression, was  $0.0 \pm 1.9$  mm Hg.

**Table 1. Baseline Characteristics of All Study Patients by Study Group\***

Characteristic	Treatment Group (n = 129)	Control Group (n = 126)
Both eyes eligible	34 (26)	27 (21)
One eye eligible	95 (74)	99 (79)
Age		
Mean ± SD	68.2 ± 4.8	68.0 ± 5.0
Median (range)	68.0 (58.0-78.0)	68.0 (50.0-79.0)
M	47 (36)	39 (31)
F	82 (64)	87 (69)
Baseline IOP, mm Hg		
Mean ± SD	20.6 ± 4.1	20.9 (4.1)
Median (range)	20.0 (13.0-30.5)	20.5 (12.0-31.0)
IOP <21 mm Hg	69	63
Visual acuity†		
Mean ± SD	0.9 ± 0.1	1.0 ± 0.1
Median (range)	1.0 (0.6-1.0)	1.0 (0.6-1.0)
Perimetric mean deviation, dB		
Mean ± SD	-5.0 ± 3.7	-4.4 ± 3.3
Median (range)	-4.3 (1.3 to -14.7)	-3.9 (2.4 to -13.6)
Any optic disc abnormality (notching saucerization, cupping, or hemorrhages)	147 (90)	138 (90)
Exfoliation syndrome	9 (6)	16 (10)
Refraction <-1 diopter	19 (12)	23 (15)
Hypertension‡	46 (36)	52 (41)
Disease history		
Family history of glaucoma	26 (20)	24 (19)
Cardiac disease	19 (15)	14 (11)
Stroke, low blood pressure, orthostatism	12 (9)	5 (4)
General arteriosclerosis	4 (3)	5 (4)
Peripheral vasospasm and migraine	21 (16)	26 (21)
Pulmonary disease	3 (2)	0 (0)
Diabetes mellitus	3 (2)	6 (5)
Medication use		
Antihypertensives	31 (24)	31 (25)
Corticosteroids	0 (0)	4 (3)
Other (eg, insulin or estrogen)	57 (44)	55 (44)

\*Data are presented as number (percentage) unless otherwise indicated. IOP indicates intraocular pressure.  
 †Determined according to the Monoyer-Granström system.  
 ‡Defined as systolic pressure greater than 160 mm Hg, diastolic pressure greater than 95 mm Hg, or a history of antihypertensive treatment.

**MAIN OUTCOMES**

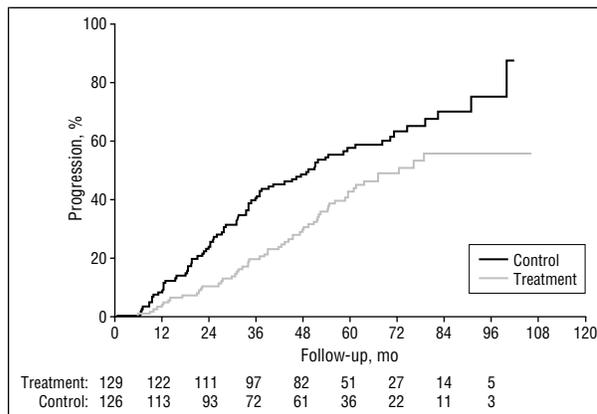
By September 1, 2001, the proportion of patients who showed definite visual field and optic disc progression was larger in the control group than the treatment group: 78 (62%) of 126 vs 58 (45%) of 129, respectively ( $P = .007$ ) (Table 2). All patients with progression met the visual field outcome criteria with 1 exception, who met the optic disc criterion only. In accordance with the specific EMGT criteria to define optic disc progression, few of these outcomes were observed.

Life-table analyses show that the separation between study groups appeared early and was maintained during the entire follow-up period; they also show that progression increased considerably with time, in the treatment group as well as the control group (Figure 2). Progression was more common in the control group at any

**Table 2. Progression by Study Group\***

	Treatment Group	Control Group
Progression	58 (45)	78 (62)
Based on visual field outcome only	53 (41)	64 (51)
Based on optic disc outcome only	1 (1)	0 (0)
Based on visual field and optic disc outcomes	4 (3)	14 (11)

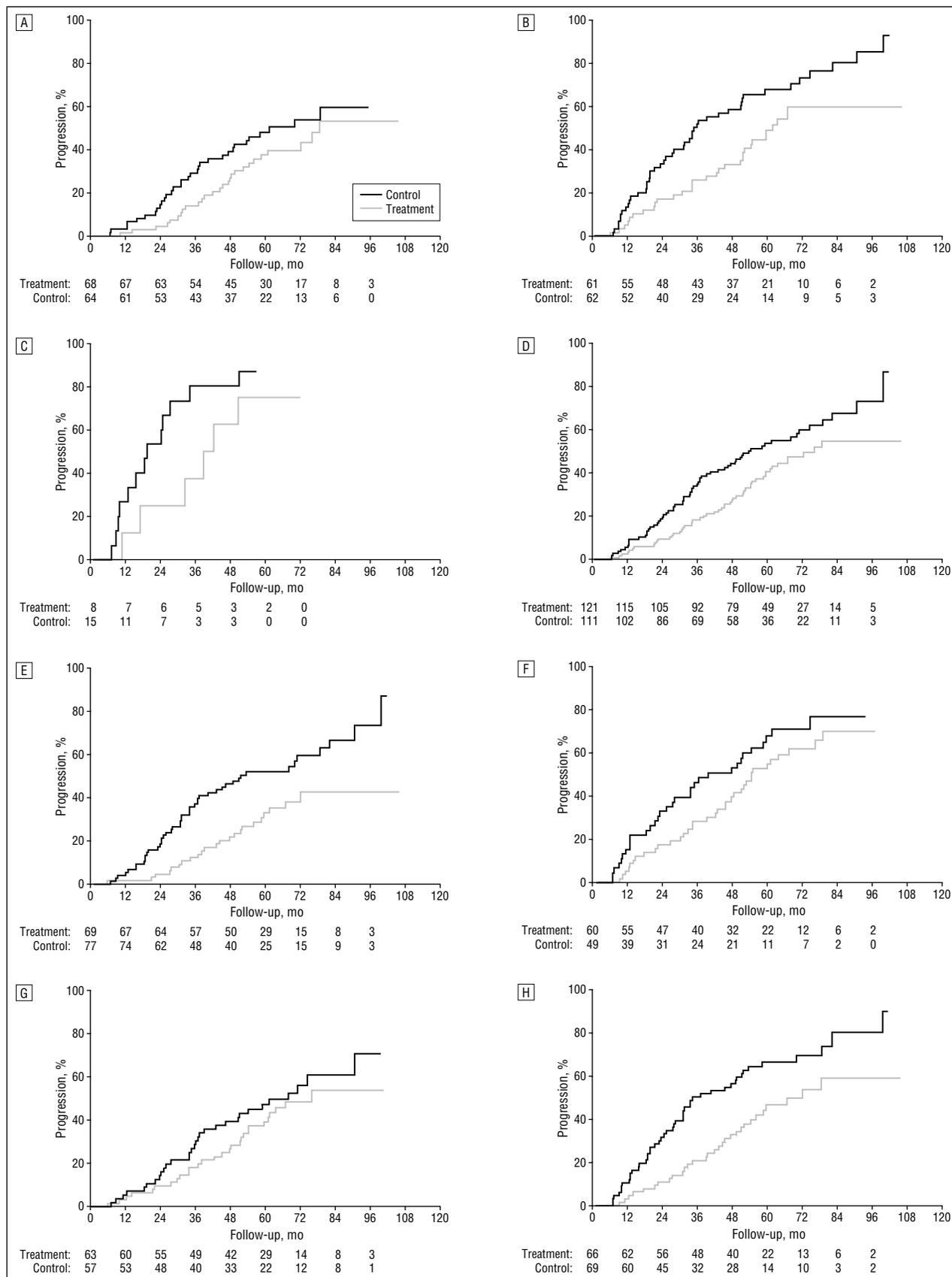
\*Data are presented as number (percentage).



**Figure 2.** Progression across time of all patients by study group. The cumulative probability of patients with progression was larger in the control group than the treatment group ( $P = .007$ ). The number of patients at risk for glaucoma progression in the treatment group and control group are shown below the x-axis.

point during follow-up; in other words, progression occurred earlier in controls than in the treatment group. Whereas the median time to progression (using the Kaplan-Meier cumulative survival function) was 48 months in controls, it was 66 months in treated patients, indicating a delay in progression caused by treatment. According to the life-table results at 48 months, 62 controls (49%) had progressed compared with 39 (30%) in the treatment group (difference = 19%; 95% confidence interval, 7%-23%;  $P = .004$ ). The differences between study groups and apparent treatment effects were also observed when stratifying according to the baseline covariates (Figure 3). All of these curves show a clear and persistent separation between treatment and control groups, and the covariates were significantly related to progression in multivariate analyses (M.C.L., A.H., M.H., B.B., L.H., and E. Komaroff, PhD, unpublished data, 2002). In these analyses, each millimeter of mercury of decreased IOP was related to an approximately 10% lowering of risk, and the results showed no significant treatment effects beyond those related to IOP reduction.

The regression analyses of MD and number of highly significantly depressed test point locations ( $P < .5\%$ ) in pattern deviation probability maps yielded differences between study groups similar to those based on EMGT-defined progression criteria. Although the regression analyses may underestimate true progression because of sustained, low-grade perimetric learning, these results show significantly slower visual field deterioration in patients allocated to treatment than in control patients



**Figure 3.** Progression across time stratified according to baseline covariates: patients with an intraocular pressure less than 21 mm Hg (A) and 21 mm Hg or greater (B), with exfoliation (C) and without (D), with mean deviation values better than  $-4.5$  dB (E) and worse (F), and who are younger than 68 years (G) and 68 years or older (H). The numbers of patients at risk for glaucoma progression in the treatment group and control group are shown below the x-axes. These numbers decrease significantly with length of follow-up and were small from the beginning in the exfoliation group.

**Table 3. Change of Mean Deviation Values and Number of Highly Significant Test Point Locations Until Time of Progression in Progressed Eyes or Until Last Visit in Nonprogressed Eyes, by Study Group\***

	Treatment Group (n = 125)	Control Group (n = 122)	P Value
Mean deviation change, dB per month	-0.03 ± 0.05	-0.05 ± 0.07	.008
Median	-0.02	-0.04	...
Change in number of significant† test point locations per month	0.06 ± 0.10	0.10 ± 0.13	.006
Median	0.03	0.06	...

\*Data excludes 7 treated and 4 control patients who developed nonglaucomatous damage or had insufficient follow-up. Data are presented as mean ± SD unless otherwise indicated.

†Significance was defined as  $P < 0.5\%$ .

**Table 4. Adverse Events and Self-reported Conditions by Study Group\***

	Treatment Group	Control Group
Systemic		
Asthma	2	0
Bradycardia	1	0
Cardiac insufficiency	0	0
Depression	3	1
Impotence	0	0
Ocular		
Thrombosis	1	1
Cataract surgery	6	2
Trabeculectomy	1	0
Other (eg, reduction of visual acuity, floaters, or conjunctivitis)	21	16

\*Data are presented as number of patients.

(**Table 3**). The mean change in visual field loss from baseline to the end of follow-up, as expressed by the MD, was a worsening by 2.24 dB in the treatment group and 3.90 dB in the control group. A separate analysis has shown that the amount of visual field deterioration needed to reach EMGT-defined visual field progression is associated with a worsening in MD by 2.26 dB (A.H., M.C.L., B.B., B.B., and M.H., for the EMGT Group, unpublished data, 2002).

#### ADVERSE EVENTS AND SELF-REPORTED ADVERSE EFFECTS

As seen in **Table 4**, few systemic and ocular conditions were identified; however, both occurred more commonly in the treatment group. Cataract surgery was performed in 8 patients, 6 of whom were in the treatment group. Ocular adverse effects of treatment were generally mild, with redness, dryness, and erythema reported by 11 patients, blurred vision by 8 patients, and other symptoms, mainly transient discomfort, by 12 patients. Visual acuity decreased with time and was not significantly different between study groups (visual acuity at 4 years of follow-up

[Monoyer-Granström]: mean ± SD = 0.87 ± 0.18 in the treatment group vs 0.90 ± 0.16 in the control group;  $P = .82$ ).

Data-monitoring analyses indicated an unexpected increased incidence of nuclear opacities evident in the LOCS II clinical gradings. The percentages of LOCS II gradings of 2 or higher by study group during the initially planned 4-year follow-up period are shown in **Figure 4**. There was a clear and significantly more rapid development of nuclear opacities in the treatment group, without similar changes observed for cortical and posterior subcapsular lens gradings. The results of analysis using generalized estimating equations indicated a significant increase in clinical nuclear opacities with time ( $P = .02$ ) and treatment ( $P = .002$ ).

Lens photographs were taken to further evaluate these clinical findings, but a high percentage of controls had received treatment by that time: 34.5% (41/119) at the first round of photographs and 45.9% (50/109) at the second round. The intent-to-treat analyses of these lens photogradings were inconclusive, although more eyes in the treatment group (8) were ungradable because of cataract or cataract surgery than in controls (2). In multivariate analyses including these eyes and evaluating associations with treatment (independent of study group and controlling for age, sex, and follow-up time), lens photograding scores were related to treatment ( $P = .004$ ).

More patients died in the treatment group than in the control group: 15 of 22 (Figure 1). This difference, although not statistically significant ( $P = .08$ ), was observed within the first few years of follow-up. The patterns of cause-specific mortality were not unusual, with most deaths due to cardiovascular diseases (eg, myocardial infarction or stroke) or malignancies (eg, liver cancer or stomach cancer) in both trial arms; most deaths occurred in men.

#### DATA QUALITY

The rate of missed visits was 5.9% and was similar between study groups. Protocol deviations at follow-up were infrequent and were mainly due to the noncompletion of data items (29, or 0.5% of visits) and nonscheduling or noncompletion of additional visits according to protocol (33, or 0.6% of visits). Only 0.2% of data entries on study forms required editing. Unmasking of the technicians to study group occurred in 81 visits (1.5%) involving 31 treated patients and 17 controls. The evaluations of optic disc gradings confirmed the high specificity of the protocol, with no false-positive gradings in 12 cycles of masked readings of a quality control set of photographs. Reproducibility of flicker gradings varied throughout the quality control cycles and among graders, with most  $\kappa$  statistics in the "fair" to "good" range for both intragrader agreement (medians ranged from  $\kappa = 0.50$ –0.73 among graders) and intergrader agreement (median of all comparisons of grader pairs:  $\kappa = 0.63$ ).

#### REVIEW BY THE DSMC

No patient safety issues were identified by the DSMC, and the trial has continued as planned. In May 2000, the results suggested favorable subclinical treatment effects, and

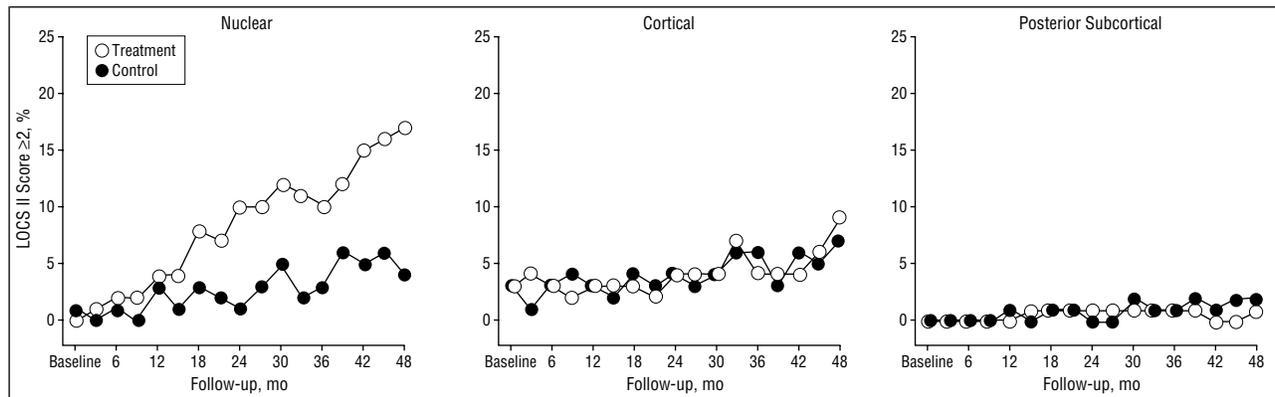


Figure 4. Lens Opacities Classification System (LOCS) II scores of 2 and higher by study group during the first 48 months of follow-up.

the DSMC recommended that the investigators share this information with enrolled patients and continue the study according to protocol until all patients had completed at least 4 years of follow-up. After receiving such information and discussing clinical management options, all patients continued follow-up in their assigned study groups.

#### COMMENT

Modern evidence-based medicine recognizes that the best proof of treatment effectiveness comes from randomized controlled trials that are not only well designed and executed but also thoroughly and accurately reported. Beginning in 1996, a series of statements were published by the Consolidated Standards of Reporting Trials (CONSORT) Group to increase and ensure the quality of such reports.<sup>45</sup> Our article follows the recently updated CONSORT guidelines.<sup>46</sup>

#### EFFECTS OF TREATMENT ON GLAUCOMA PROGRESSION

The EMGT showed clear beneficial effects of treatment on delaying the onset of progression, with lower rates of progression in the treatment group than the control group (Tables 2 and 3; Figure 2). Differences between treated and untreated patients also remained when results were further stratified according to various baseline characteristics: IOP level, degree of visual field damage, patient age, or presence of exfoliation (Figure 3). Despite these clear treatment effects, a large percentage of treated eyes showed progression during the follow-up period.

The median time to progression was 18 months longer in the treatment group than the control group. This observation should not be interpreted to mean that the only benefit of treatment (as used in the EMGT) is to delay glaucoma progression by 18 months. Instead, the finding means that the amount of disease worsening necessary to trigger the EMGT-defined progression criteria took an average of 18 months longer in treated patients than controls. This article provides data just up to the time of the initial EMGT outcome, but it is likely that the difference in glaucoma progression between study groups would have increased if the initial allocation to treat-

ment or no treatment had remained unchanged even after this outcome.

The IOP reduction achieved by the EMGT treatment was substantial and was not associated with adverse effects as significant as those typically encountered after filtering surgery and documented in the CNTGS.<sup>20,21</sup> There was no difference in visual acuity loss across time between the 2 study groups, despite the fact that treatment was associated with an increased incidence of cataract in the EMGT.

Time to progression varied greatly among treated patients as well as untreated ones and was sometimes rather short. This indicates that the standardized treatment was insufficient in many rapidly progressing patients. On the other hand, many patients, even untreated ones, showed no progression after 6 or more years of follow-up. Because the EMGT visual field progression criterion is a sensitive indicator of deterioration, careful follow-up may allow treatment to be deferred in some patients, as suggested by Drance et al<sup>47</sup>: “[I]t might be prudent not to treat most patients with normal-tension glaucoma until the rate of the disease in the particular individual had been established over a period of observation.” The EMGT thus supports today’s emphasis on individualized treatment, and we expect that after further analyses, EMGT data will be found useful for tailoring follow-up and treatment to individual patients.

#### ADVERSE EVENTS

In our opinion, only 2 types of adverse events deserve comment: cataract and mortality. During recruitment, the EMGT used a standardized system of lens classification to ascertain lens status so that patients with cataractous changes were excluded from the trial. This design feature and the absence of glaucoma surgery in the treatment protocol resulted in a low frequency of cataract surgery at follow-up ( $n=8$ , or 3%) compared with the rates reported in other glaucoma trials. Continued monitoring of clinical lens gradings in the EMGT led to the detection of an increase in nuclear opacities in the treatment group (Figure 4), which was paralleled by a higher frequency of cataract surgery in that group (Table 4).

Analysis of nuclear photograding scores also showed associations with treatment, but the difference in scores

between groups was not confirmed in intent-to-treat analyses. The latter result is difficult to interpret because many of the controls were receiving treatment at the time the lens photographs were taken.

It is well known that glaucoma filtering surgery is associated with a marked rise in cataract incidence and that topical irreversible cholinesterase inhibitors caused cataract. The reports of the CNTGS have emphasized the frequent occurrence of cataract surgery in its treated group<sup>20,21</sup>; cataracts were also common in the Advanced Glaucoma Intervention Study (AGIS).<sup>48,49</sup> The CNTGS is the only other glaucoma study besides ours that permits a comparison in cataract rates between treated and untreated arms. Although it did not show a significant difference in cataract rates between the medically treated patients and untreated controls, numbers were small; the mean time to cataract development was actually lower in the medical treatment group. The use of topical IOP-lowering medications was strongly related to an increased incidence of nuclear lens opacities in the Barbados Eye Studies.<sup>50</sup> The Ocular Hypertension Treatment Study<sup>51</sup> (OHTS) reported "a slight excess of cataract surgery" in the medication group: 6.4% (52/806) vs 4.3% (35/813) in the observation group ( $P=.06$ ), a result consistent with EMGT observations.<sup>52</sup>

Everything considered, we deem it likely that therapeutic IOP reduction can be linked with cataract formation.

The difference in death rate between groups is worth attention. The rate observed in the treated patients was as expected according to the population statistics of Sweden,<sup>53</sup> whereas the control group had a considerably lower value. Furthermore, there was no difference in cause-of-death patterns between the 2 groups. The OHTS reports similar death rates in treated and untreated patients: 3.2% and 3.5%, respectively.<sup>52</sup> For these reasons, it is likely that the observed mortality differences in the EMGT were caused by chance.

#### POSSIBLE MECHANISMS

In the EMGT, all patients received standardized treatment, and no effort was made to meet specific target IOPs. This design allowed an unbiased quantification of treatment effects related to IOP reduction, which was strongly related to glaucoma progression. The magnitude of this dependence on IOP change was impressive: an estimated 10% decrease in risk of progression with each millimeter of mercury of IOP reduction. Our results do not suggest that the outcome differences between study groups were due to non-IOP reduction effects; for example, to possible intrinsic vasoactive or neuroprotective properties of the topical medications used in this study.

Even though the EMGT clearly supports the beneficial effect of IOP reduction on open-angle glaucoma, these results do not prove that elevated IOP is the primary cause of glaucoma. The true causes of the disease may be a set of more fundamental malfunctions, some of which may lead to elevated IOP (defined as either a statistically high pressure level or a level that is not tolerated by the individual patient while falling within the normal range). However, the fact that IOP reduction slows

progression indicates that IOP levels are important in the course of the disease.

#### COMPARISON WITH OTHER TRIALS

Since the start of the EMGT, data have become available that are of value when examining the overall evidence for the effect of IOP reduction on open-angle glaucoma.<sup>20,21,48,51,54</sup> In general, available results have been interpreted to indicate that all modalities of IOP reduction slow the progression of glaucomatous optic atrophy, but to an unknown extent.<sup>20,21,52,55,56</sup> Even recent evidence remains conflicting. A nonrandomized analysis of data from the AGIS provided evidence that effective IOP reduction is of great importance for disease progression.<sup>55</sup> In the Collaborative Initial Glaucoma Treatment Study<sup>56</sup> (CIGTS), however, aggressive medical therapy and initial surgery resulted in indistinguishable rates of visual field progression despite differences in IOP reduction, and the intent-to-treat analysis of the CNTGS showed no difference between treated and untreated arms.<sup>21</sup> Thus, up to now, uncertainty has remained regarding the effect of IOP reduction on glaucoma progression. Recently, researchers have agreed that conclusive evidence should come from trials specifically designed to address this issue.<sup>55</sup>

Most important is the CNTGS, in which 140 patients with normal-tension glaucoma were randomized either to nontreatment as controls or to have the IOP lowered by 30% from baseline. The clinical course and visual field and optic disc outcomes of both groups were then compared. Although the intent-to-treat analyses of the CNTGS found no significant differences between treated and untreated arms,<sup>21</sup> these negative results have largely been ignored in the ophthalmic community. Our results show that the conclusion of the CNTGS (that IOP reduction decreases glaucoma progression in normal-tension glaucoma<sup>20</sup>) is correct but that treatment effects can be achieved without a rigid IOP goal or serious adverse effects.

Although trials involving patients with ocular hypertension address a somewhat different subject, they deal with the same fundamental question of the relationship between IOP and glaucoma damage. It is therefore appropriate to include the results from such studies in the discussion of overall evidence. Earlier controlled studies of patients with ocular hypertension had diverging results<sup>9-12</sup> and together failed to demonstrate a statistically significant beneficial effect,<sup>22</sup> but their study power was usually low. The OHTS currently provides conclusive data showing positive effects of IOP reduction in decreasing the frequency of glaucoma damage in patients with ocular hypertension. The incidence of glaucoma damage differed significantly between treated patients and untreated controls, amounting to 4.4% and 9.5%, respectively, after 60 months of follow-up.<sup>52</sup> The overall evidence that lowering the IOP reduces the risk of further visual field progression in glaucoma must now be regarded as very strong.

#### STRENGTHS AND LIMITATIONS

Interpretation of the EMGT results must consider several methodologic strengths of the trial. That only 2.4%

of patients were lost to follow-up for reasons other than death indicates a very high motivation among patients and personnel to conduct the study according to protocol. Consequently, we are able to report the study results with few missing data items.

Data on both visual field and optic disc outcomes were obtained by masked observers following standardized and unbiased methods. Visual field criteria were defined using modern statistical programs for visual field analysis and were therefore numerical and objective. Glaucoma change probability maps provided early yet specific detection of visual field progression. These maps were based on pattern deviation rather than total deviation, strongly reducing any confounding effects of progressing lens opacities on visual field outcomes.<sup>38</sup> The number of significantly progressing test point locations and the reproducibility of such progressed locations required to reach a visual field endpoint were specified prior to the EMGT, based on retrospective studies of a large number of clinical visual field series. These visual field progression criteria were not changed during the study; they permitted immediate objective recognition of tentative and definite perimetric progression based on printouts that could be judged while the patient was still in the clinic. This feature allowed immediate scheduling of extra visits when tentative progression was found, as well as discussions of visual field progression and treatment alternatives with the patient when definite progression occurred and thereafter. The computer-assisted visual field analysis also obviated the need for a visual field reading center.

Because glaucoma cases were newly detected and previously untreated, no residual effects of previous drug therapy or surgery were possible. Most patients were identified through a screening of a large population group of relevant age in a designated geographical area, and the screening examination included a majority of invited citizens. This knowledge is valuable when deriving conclusions on glaucoma management from the results of this study and particularly when assessing the implications of the EMGT results on glaucoma screening.

Interpretation of the EMGT results must also consider potential limitations of the study. One such limitation is that the study involved a specific, homogeneous patient population: almost all patients were white. This certainly limits the generalizability of the study results to other populations. Patients also had relatively early glaucoma, so our study results cannot provide quantitative data pertaining to patients with high IOP levels (>30 mm Hg) or advanced visual field loss. Another necessary limitation was that the initial randomization to treatment or no treatment was maintained only as long as progression did not occur; this shortened the ascertainment period of the glaucoma's natural history, which was a secondary EMGT aim. The study, therefore, does not include long-term follow-up of untreated patients beyond EMGT progression.

The EMGT used a new criterion to define visual field progression, which was unchanged throughout the entire study. The EMGT definition allowed the detection of small amounts of progression, an important safety aspect of the trial. This criterion was based on knowledge gathered during the 1980s on the nature of random vari-

ability in glaucomatous visual fields<sup>57</sup> and permitted an earlier separation between treatment arms than more conventional criteria (eg, linear regression of MD values or changes in numbers of test point locations developing significant or absolute visual field loss). However, the EMGT visual field criterion is not as intuitively comprehensible as other simpler criteria. To address this issue and to provide a basis for a later article that will present clinically useful conclusions from the study results, we have compared the EMGT criterion with other criteria in a separate report (A.H., M.C.L., B.B., B.B., and M.H., for the EMGT Group, unpublished data, 2002).

The EMGT's visual field progression criterion showed excellent sensitivity and specificity in a comparison of the performance of such criteria used in the EMGT, AGIS, and CIGTS. In this pilot study, the EMGT criteria detected progression in 20 of 20 series of visual fields from EMGT patients who had been deemed to have definite progression by 2 independent glaucoma experts. Progression was sustained in 90.8% of visits following the visit when definite progression was first found. Specificity was determined from another 20 series of visual fields that had been classified as stable by the same experts. It was found to be high; none of the 20 stable visual fields were falsely labeled as progressing with the EMGT's criterion (A.H., M.C.L., B.B., B.B., and M.H., for the EMGT Group, unpublished data, 2002).

## IMPLICATIONS OF STUDY RESULTS

The EMGT is the first randomized study providing a long-term comparison of progression between treated and untreated patients with primary open-angle glaucoma, normal-tension glaucoma, and exfoliation glaucoma that shows a definite positive effect of IOP reduction. This information is valuable because treatment effects in chronic open-angle glaucoma have been largely unknown, and there is very little information about the natural history of glaucoma.

Although these results provide quantitative data directly applicable to most patients with glaucoma, our eligibility criteria led to a study population with earlier disease than a typical clinical glaucoma population.<sup>58</sup> At the population screening, 19% of patients with newly detected early manifest glaucoma were ineligible for the EMGT because their IOP exceeded the inclusion criteria (mean IOP >30 mm Hg or any IOP >35 mm Hg), and an additional 10% could not participate because the visual field damage exceeded our limits for inclusion. The EMGT results provide little information directly pertaining to patients with advanced glaucoma and high IOP levels; however, as mentioned earlier, future analyses will likely show that the current results are indeed applicable to such patients.

The EMGT data have important clinical implications. The results not only confirm previous beliefs that IOP reduction is beneficial but also provide new knowledge on rates of disease progression, with and without treatment, in patients with various characteristics. Our results therefore strengthen the rationale for current standard clinical management. In addition, they afford a basis for increased efforts to achieve earlier detection of the

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disease and for tailoring the clinical management of glaucoma to the needs of the individual patient. The latter issues are worth special consideration and will be addressed separately.

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