The Ocular Hypertension Treatment Study

A Randomized Trial Determines That Topical Ocular Hypotensive Medication Delays or Prevents the Onset of Primary Open-Angle Glaucoma

Michael A. Kass, MD; Dale K. Heuer, MD; Eve J. Higginbotham, MD; Chris A. Johnson, PhD; John L. Keltner, MD; J. Philip Miller, AB; Richard K. Parrish II, MD; M. Roy Wilson, MD; Mae O. Gordon, PhD; for the Ocular Hypertension Treatment Study Group

Background: Primary open-angle glaucoma (POAG) is one of the leading causes of blindness in the United States and worldwide. Three to 6 million people in the United States are at increased risk for developing POAG because of elevated intraocular pressure (IOP), or ocular hypertension. There is no consensus on the efficacy of medical treatment in delaying or preventing the onset of POAG in individuals with elevated IOP. Therefore, we designed a randomized clinical trial, the Ocular Hypertension Treatment Study.

Objective: To determine the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of POAG.

Methods: A total of 1636 participants with no evidence of glaucomatous damage, aged 40 to 80 years, and with an IOP between 24 mm Hg and 32 mm Hg in one eye and between 21 mm Hg and 32 mm Hg in the other eye were randomized to either observation or treatment with commercially available topical ocular hypotensive medication. The goal in the medication group was to reduce the IOP by 20% or more and to reach an IOP of 24 mm Hg or less.

Main Outcome Measures: The primary outcome was the development of reproducible visual field abnormality or reproducible optic disc deterioration attributed to POAG. Abnormalities were determined by masked certified readers at the reading centers, and attribution to POAG was decided by the masked Endpoint Committee.

Results: During the course of the study, the mean ± SD reduction in IOP in the medication group was 22.5% ± 9.9%. The IOP declined by 4.0% ± 11.6% in the observation group. At 60 months, the cumulative probability of developing POAG was 4.4% in the medication group and 9.5% in the observation group (hazard ratio, 0.40; 95% confidence interval, 0.27-0.59; P < .0001). There was little evidence of increased systemic or ocular risk associated with ocular hypotensive medication.

Conclusions: Topical ocular hypotensive medication was effective in delaying or preventing the onset of POAG in individuals with elevated IOP. Although this does not imply that all patients with borderline or elevated IOP should receive medication, clinicians should consider initiating treatment for individuals with ocular hypertension who are at moderate or high risk for developing POAG.

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Surveys show that glaucoma is among the leading causes of blindness in the United States and worldwide.1-5 It is estimated that more than 2.5 million people in the United States have glaucoma and that more than 130,000 people are legally blind from the disease.7 Population surveys indicate that less than 50% of those with glaucomatous visual field loss have received an appropriate diagnosis or treatment.8-9

Glaucoma is the leading cause of blindness in individuals of West African origin.2-9-11 In the Baltimore Eye Survey, the age-adjusted prevalence rates of primary open-angle glaucoma (POAG) were 4 to 5 times higher in African Americans than in white individuals. The prevalence ranged from 1.2% in African Americans between the ages of 40 and 49 years to 11.3% in those 80 years and older.11 Furthermore, the Barbados Eye Study7,12 found a high prevalence and incidence of glaucoma among black individuals in an Afro-Caribbean population.

See also pages 714 and 829

It is estimated that 3 to 6 million people in the United States, including 4% to 7% of those older than 40 years, have elevated intraocular pressure (IOP) without detectable glaucomatous damage on standard clinical tests.13 These individuals are at increased risk for developing POAG and are sometimes referred to as ocular hypertensives or glaucoma suspects.13-15 Kerrigan-Baumrind et al16 re-
PARTICIPANTS AND METHODS

The design and methods of the OHTS were described previously,11-13 and can be found on the World Wide Web at www.trc.wustl.edu, and are briefly summarized as follows.

PARTICIPANTS

Eligibility criteria included age between 40 and 80 years, a qualifying IOP between 24 mm Hg and 32 mm Hg in one eye and between 21 mm Hg and 32 mm Hg in the other eye, gonioscopically open angles, 2 normal and reliable visual field tests per eye as determined by the Visual Field Reading Center, and normal optic discs seen at clinical examination and on stereoscopic photographs as determined by the Optic Disc Reading Center. Exclusion criteria included a visual acuity worse than 20/40 in either eye, previous intraocular surgery (other than uncomplicated cataract extraction with posterior chamber lens implantation), and diabetic retinopathy or other diseases capable of causing visual field loss or optic disc deterioration. Both eyes of each participant had to meet eye-specific eligibility criteria. Participants signed a statement of informed consent approved by the institutional review board of each participating clinic.

STUDY DESIGN

This study was conducted at 22 clinical centers; eligible individuals were randomized in equal proportion to either the medication group or observation group. Randomization assignments were released by the Coordinating Center during the participant’s baseline visit. The randomization unit was the individual, and randomization was performed using a permuted block design stratified by clinic and race. Neither the participant nor the clinician was masked to the randomization assignment during follow-up.

Participants randomized to medication began treatment to achieve a target IOP of 24 mm Hg or less and a minimum 20% reduction in IOP from the average of the qualifying IOP and IOP at the baseline randomization visit, except that an IOP of less than 18 mm Hg was not required. Topical medication was changed and/or added until both of these goals were met or the participant was receiving maximum-tolerated topical medical therapy. Medications were added and changed in one-eyed therapeutic trials. Drugs were distributed to clinics from the study’s central pharmacy, which included all topical ocular hypotensive medications commercially available in the United States. As new medications became commercially available, they were added to the study formulary.

Follow-up visits were scheduled every 6 months from the date of randomization. Each semiannual examination included an ocular and medical history, refraction, best-corrected visual acuity, full-threshold Humphrey white-on-white 30-2 visual field tests, slitlamp examination, IOP measurement, and direct ophthalmoscopy. Additional evaluations at annual visits included a dilated fundus examination and stereoscopic optic disc photographs.

Information on adverse effects was collected using diverse sources of information. Prior to each examination, the participants completed the Glaucoma Symptom Scale,36 a checklist of 13 ocular symptoms and 15 systemic symptoms. They rated the “bothersomeness” of symptoms on a scale of 1 to 4: from 1, “not at all,” to 4, “a lot.” At annual visits, participants completed the Medical Outcomes Study Short Form (SF-36),37 a survey of 36 questions designed to measure health-related quality of life. At each visit, clinic staff recorded medical and ocular history and completed an adverse-event form when a new health problem was diagnosed, an existing medical condition worsened, an incident hospitalization had occurred, or surgery had been required. Clinic staff recorded the organ system affected and determined the severity of the condition. Clinicians judged whether the event was related to the study medication. Serious adverse events were defined as death, cancer or other life-threatening conditions, inpatient hospitalization, prolongation of hospitalization, or outpatient hospitalization for an incapacitating condition. Clinic personnel obtained hospital discharge summaries and death certificates. In January 1997, the OHTS protocol for reporting adverse events was made more rigorous because of large clinic-to-clinic variation in the completion of the adverse-event forms. Therefore, data from the adverse-event forms are reported from January 1997 to the present.

PRIMARY OUTCOME AND MONITORING

The primary outcome was the development of POAG in one or both eyes. This was defined as reproducible visual field abnormality or reproducible clinically significant optic disc deterioration attributed to POAG by the masked Endpoint Committee.

Development of visual field abnormality was determined by masked certified readers at the Visual Field Reading Center. A technically acceptable visual field was considered abnormal if P < .05 for the corrected pattern standard deviation or if the glucoma hemifield test result was

PARTICIPANTS

Recruitment and baseline characteristics of participants

Recruitment was extended from 24 months to 30 months to achieve an enrollment of 400 African American participants. Between February 28, 1994, and October 31, 1996,
3328 individuals were considered for study enrollment, and 1636 individuals with documented informed consent were randomized as follows: 817 were assigned to receive topical ocular hypotensive medication, and 819 were assigned to observation. A total of 1692 people were not eligible for randomization for a variety of reasons including an IOP outside the specified range, abnormal or unreliable visual field test results, poor visual acuity, optic disc abnormalities, the inability to obtain clear photographs, and refusal to participate. A flowchart shows the progress of participants during the study (Figure 1).

No statistically significant differences in demographic or clinical factors were found between the 2 randomized groups at baseline (for all comparisons, P > .05) (Table 1). Additional details on the randomized participants were provided in a previously published article.33

FOLLOW-UP

The median duration of follow-up was 72 months for African American participants and 78 months for other participants. Of the expected follow-up visits, 90% were completed during the study, and the visit completion rate did not differ by randomization group. The visit completion rate was 86.6% for African Americans and 91.4% for other participants (P < .001). Technically acceptable statistical analysis was performed with SAS statistical software, version 8.1 (SAS Institute Inc, Cary, NC). P values were 2-tailed. To adjust for multiple interim tests of the primary hypothesis, we calculated symmetric O'Brien-Fleming sequential log-rank boundaries using the α-spending function of Lan and DeMets.39,40

The Data and Safety Monitoring Committee approved the termination of the trial when the last randomized participant reached 5 years of follow-up, as specified in the original protocol. This article includes data through November 8, 2001.
The IOP goal was met in both eyes at 87% (7515 of 8621) of the medication and observation groups is shown in Figure 2.

The distribution of IOP at baseline and follow-up for the medication group than in the observation group (hazard ratio, 0.58; 95% CI, 0.44-0.76; Mantel-Haenszel log-rank test; P = .00008). There was a trend for treatment to be less protective among self-identified African American participants (hazard ratio, 0.54; 95% CI, 0.28-1.03) compared with the other participants in the trial (hazard ratio, 0.34; 95% CI, 0.21-0.56), although this difference was not statistically significant (P = .26). Primary open-angle glaucoma developed in 14 (6.9%) of 203 African American participants in the medication group and 26 (12.7%) of 205 African Americans in the observation group, compared with 22 (3.6%) of 614 other medication participants and 63 (10.2%) of 614 other observation participants.

A total of 218 participants (137 participants in the observation group and 81 participants in the medication group) developed reproducible visual field abnormality or reproducible optic disc deterioration due to POAG or a variety of other causes including trauma, stroke, branch retinal vein occlusion, macular degeneration, and testing artifact. The cumulative probability of developing a reproducible abnormality from any cause was statistically significantly lower in the medication group than in the observation group (hazard ratio, 0.38; 95% CI, 0.44-0.76; P = .00008).

SAFETY

To ascertain the safety of treatment, the medication and observation groups were compared for participant self-report of symptoms (Glaucoma Symptom Scale and SF-36) and for medical and ocular history (new conditions, worsening of existing conditions, hospitalization, prolongation of hospitalization, or death) as collected by clinic staff during the course of the study. The following P values are unadjusted for multiple comparisons between

IOP REDUCTION AND MEDICATION

The baseline and follow-up IOP for the medication group and observation group are reported by race in Table 2. The distribution of IOP at baseline and follow-up for the medication and observation groups is shown in Figure 2. The IOP goal was met in both eyes at 87% (7515 of 8621) and in one eye at 7% (613 of 8621) of the scheduled follow-up visits completed by medication participants. Figure 3 shows the percentage of participants who were prescribed each class of topical ocular hypotensive medication at each follow-up visit. At 60 months, 2 or more topical medications were prescribed for 39.7% (259 of 653) of the medication participants, and 3 or more medications were prescribed for 9.3% (61 of 653) of participants in this group. At 60 months, 44.5% (65 of 146) of African American participants in the medication group were prescribed multiple medications, compared with 38.3% (194 of 507) of the other medication participants.

PRIMARY OPEN-ANGLE GLAUCOMA

Table 3 reports the progress and outcome of randomized participants, unadjusted for follow-up time. In the medication group, 36 of the 817 randomized participants developed POAG compared with 89 of 819 randomized participants in the observation group. The first POAG endpoint for each participant is reported in Table 4. At 60 months, the cumulative probability of developing POAG was 4.4% in the medication group and 9.3% in the observation group. During the course of the entire study, the cumulative probability of developing POAG was significantly lower in the medication group compared with the observation group (hazard ratio, 0.40; 95% CI, 0.27-0.59; Mantel-Haenszel log-rank test; P < .0001). The estimate of the effect of treatment was not substantially altered after adjusting for baseline age, visual field pattern standard deviation, vertical cup-disc ratio, IOP, and corneal thickness, which was measured after randomization (hazard ratio, 0.34; 95% CI, 0.23-0.51). A treatment benefit was observed for reproducible visual field abnormality attributed to POAG (hazard ratio, 0.45; 95% CI, 0.27-0.76; P = .002) and for reproducible optic disc deterioration attributed to POAG (hazard ratio, 0.36; 95% CI, 0.23-0.56; P < .0001).

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visual field test results and stereoscopic optic disc photographs were obtained at 99% and 96%, respectively, of the specified completed follow-up visits and did not differ by randomization group. The numbers of participants completing each follow-up visit are shown at the bottom of Figure 2.

ADHERENCE TO RANDOMIZATION

Forty participants in the medication group (4.9%) were withdrawn from medication or chose to stop medication for 6 months or more during the study. Fifteen of these individuals eventually resumed treatment. Forty-two participants in the observation group (5.1%) received topical ocular hypotensive medication for 6 months or more during the study. In most cases, treatment was initiated by the OHTS clinician because of concern about the participant’s high IOP. Three of these individuals eventually stopped treatment.

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groups. In the self-administered surveys, there was no evidence that the medication group had increased ocular or systemic symptoms compared with the observation group (Figure 5). In the medical and ocular histories collected by clinic staff, a higher percentage of participants in the medication group, compared with the observation group, reported ocular symptoms (57% vs 47%; \( P < .001 \)) or symptoms affecting the skin, hair, or nails (23% vs 18%; \( P < .001 \)). The most common symptoms affecting the eyes were dryness, tearing, and itching. Changes in iris color, darkening of the eyelids, and growth of eyelashes occurred in 17% of the 44 serious genitourinary adverse events in the medication group. Clinic staff recorded serious genitourinary adverse events in 5.5% (44 of 800) of the medication participants compared with 3.4% (27 of 802) of the observation participants (\( P = .04 \)). Clinicians judged none of the 44 serious genitourinary adverse events in the medication group to be “probably” or “definitely” related to the study medication. Clinical staff recorded serious genitourinary adverse events in 5.5% (44 of 800) of the medication participants compared with 3.4% (27 of 802) of the observation participants (\( P = .04 \)). Clinicians judged none of the 44 serious genitourinary adverse events in the medication group to be “probably” or “definitely” related to the study medication. These differences were not statistically significant when corrected for multiple comparisons. No differences between randomization groups were found in the rates of serious adverse events for the 11 other organ systems inventoried, including ocular events or those related to the skin, hair, or nails (\( P > .05 \)).

The OHTS has shown that topical ocular hypotensive medication is effective in reducing the incidence of glaucomatous visual field loss and/or optic nerve deterioration in individuals with elevated IOP between 24 mm Hg and 32 mm Hg. The mean ± SD baseline IOP of all participants was 24.9 ± 2.7 mm Hg with no difference be-

**Table 1. Baseline Characteristics by Randomization Group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medication (n = 817)</th>
<th>Observation (n = 819)</th>
<th>Overall (N = 1636)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>359 (43.9)</td>
<td>346 (42.2)</td>
<td>705 (43.1)</td>
</tr>
<tr>
<td>F</td>
<td>458 (56.1)</td>
<td>473 (57.8)</td>
<td>931 (56.9)</td>
</tr>
<tr>
<td>Age, No. (%), y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 to 50</td>
<td>291 (35.6)</td>
<td>287 (35.0)</td>
<td>578 (35.3)</td>
</tr>
<tr>
<td>&gt;50 to &lt;60</td>
<td>270 (33.0)</td>
<td>259 (31.6)</td>
<td>529 (32.3)</td>
</tr>
<tr>
<td>&gt;60 to &lt;70</td>
<td>202 (24.7)</td>
<td>210 (26.6)</td>
<td>412 (25.6)</td>
</tr>
<tr>
<td>&gt;70 to 80</td>
<td>54 (6.6)</td>
<td>63 (7.7)</td>
<td>117 (7.2)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>1 (0.1)</td>
<td>3 (0.4)</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (0.5)</td>
<td>10 (1.2)</td>
<td>14 (0.9)</td>
</tr>
<tr>
<td>African American</td>
<td>203 (25.0)</td>
<td>205 (25.0)</td>
<td>408 (25.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>24 (2.9)</td>
<td>35 (4.3)</td>
<td>59 (3.6)</td>
</tr>
<tr>
<td>White</td>
<td>577 (70.6)</td>
<td>560 (68.4)</td>
<td>1137 (69.5)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (1.0)</td>
<td>6 (0.7)</td>
<td>14 (0.9)</td>
</tr>
<tr>
<td>Intraocular pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.9 (2.6)</td>
<td>24.9 (2.7)</td>
<td>24.9 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Horizontal cup-disc ratio, mean (SD)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0.36 (0.19)</td>
<td>0.36 (0.18)</td>
<td>0.36 (0.18)</td>
<td></td>
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<tr>
<td>Vertical cup-disc ratio, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.39 (0.20)</td>
<td>0.39 (0.19)</td>
<td>0.39 (0.19)</td>
<td></td>
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<tr>
<td>Visual field mean deviation, mean (SD), dB</td>
<td>+0.27 (1.07)</td>
<td>+0.21 (1.03)</td>
<td>+0.24 (1.05)</td>
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<tr>
<td>Visual field pattern standard deviation, mean (SD), dB</td>
<td>1.92 (0.21)</td>
<td>1.90 (0.21)</td>
<td>1.91 (0.21)</td>
</tr>
<tr>
<td>Visual field corrected pattern standard deviation, mean (SD), dB</td>
<td>1.12 (0.34)</td>
<td>1.12 (0.36)</td>
<td>1.12 (0.35)</td>
</tr>
<tr>
<td>Central corneal thickness, mean (SD), µm*</td>
<td>570.5 (38.9)</td>
<td>574.5 (37.7)</td>
<td>572.5 (38.4)</td>
</tr>
<tr>
<td>Previous use of ocular hypotensive medication, %</td>
<td>35.0</td>
<td>39.3</td>
<td>37.2</td>
</tr>
<tr>
<td>First-degree family history of glaucoma, %</td>
<td>34.0</td>
<td>35.6</td>
<td>34.8</td>
</tr>
<tr>
<td>Myopia ≥1 diopter spherical equivalent, %</td>
<td>34.4</td>
<td>33.7</td>
<td>34.1</td>
</tr>
<tr>
<td>Oral β-adrenergic antagonist, %</td>
<td>5.4</td>
<td>4.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Oral calcium channel blocker, %</td>
<td>12.8</td>
<td>14.0</td>
<td>13.4</td>
</tr>
<tr>
<td>History of migraine, %</td>
<td>10.4</td>
<td>11.7</td>
<td>11.1</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>11.5</td>
<td>12.1</td>
<td>11.8</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>37.5</td>
<td>38.1</td>
<td>37.8</td>
</tr>
<tr>
<td>History of low blood pressure, %</td>
<td>4.8</td>
<td>4.0</td>
<td>4.4</td>
</tr>
<tr>
<td>History of cardiovascular disease, %</td>
<td>5.8</td>
<td>6.5</td>
<td>6.1</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>0.9</td>
<td>1.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*For central corneal thickness, \( n = 699 \) for medication, \( n = 699 \) for observation, and \( n = 1398 \) overall. Measurements were conducted after 1999, about 2 years after randomization of the last participant.
Randomization groups. Individuals were randomized either to observation or to receive topical ocular hypotensive medication. The goal of treatment was to reduce the IOP by 20% or more and to reach an IOP of 24 mm Hg or less. In the medication group, the mean ± SD reduction in IOP during the follow-up period was 22.5% ± 9.9%. The IOP declined by 4.0% ± 11.6% in the observation group. Randomization groups had similar baseline demographic and clinical characteristics as well as similar rates of visit completion and outcome ascertainment throughout follow-up. The rate of adherence to randomization assignment was high and did not differ by group.

To our knowledge, the OHTS is the largest randomized trial to date of the safety and efficacy of ocular hypotensive medication in delaying or preventing the onset of POAG in individuals with ocular hypertension. At 60 months, the cumulative probability of developing POAG was 4.4% in the medication group and 9.5% in the observation group. It is difficult to compare the incidence of POAG in this study with that in many previous publications because the incidence rate reflects both study-specific eligibility criteria and endpoint criteria. The OHTS used strict entry criteria and included generally healthy volunteers. In addition, stringent endpoint criteria included only reproducible visual field abnormality and optic disc deterioration attributable to POAG. The OHTS used quality control criteria for certifying and monitoring visual field technicians and photographers. Criteria for POAG were made more stringent during the course of the study. The number of consecutive abnormal visual field test results required to confirm an abnormality was increased from 2 to 3. In addition, the criterion for optic disc deterioration was increased from a “barely detectable difference” to a “clinically significant change” in the optic disc neuroretinal rim.

Table 2. Intraocular Pressure at Baseline and Follow-up in the Medication Group and Observation Group Reported by Race*

<table>
<thead>
<tr>
<th></th>
<th>Medication Group</th>
<th>Observation Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>African American</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>(n = 203)</td>
<td>(n = 614)</td>
</tr>
<tr>
<td>IOP at baseline</td>
<td>25.1 ± 2.9</td>
<td>24.9 ± 2.6</td>
</tr>
<tr>
<td>IOP averaged across scheduled follow-up visits</td>
<td>19.3 ± 2.3</td>
<td>19.3 ± 2.3</td>
</tr>
<tr>
<td>Reduction from baseline, %</td>
<td>-22.9 ± 9.9</td>
<td>-22.4 ± 9.9</td>
</tr>
</tbody>
</table>

*Intraocular pressure measurements (in millimeters of mercury) are excluded after the date participants developed primary open-angle glaucoma. Data are presented as mean ± SD. IOP indicates intraocular pressure; sample size, number of randomized participants.
hypotensive medication for 6 months or more prior to reaching the POAG but did not die or reach the POAG endpoint. With longer follow-up, we will be able to report how many of the individuals with optic disc deterioration eventually develop visual field loss.

Because glaucoma is the leading cause of blindness in African Americans, recruitment was extended to ensure that 25% of the sample was of African American origin. Although there was a trend for the treatment benefit to be lower in African Americans than for other participants, the median follow-up time for African American participants was 6 months shorter. It is therefore possible that the treatment response would be more similar with additional follow-up, particularly because the baseline and follow-up IOP in the observation and medication groups did not differ by race.

Topical ocular hypotensive medication reduced the incidence of both glaucomatous visual field abnormality and optic disc deterioration. Approximately 55% (69 of 125) of the initial POAG endpoints involved optic disc deterioration in the absence of visual field abnormalities meeting study criteria for a visual field endpoint. With longer follow-up, we will be able to report how many of the participants randomized to medication who were withdrawn from medication for 6 months or more to participants randomized to observation who were prescribed topical hypotensive medication for 6 months or more prior to reaching the POAG endpoint.

**Table 3. Progress and Outcome of Study Participants**

<table>
<thead>
<tr>
<th>Medication Group, No. (%)</th>
<th>Observation Group, No. (%)</th>
<th>Overall, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>817 (100.0)</td>
<td>819 (100.0)</td>
</tr>
<tr>
<td>Died</td>
<td>26 (3.2)</td>
<td>29 (3.5)</td>
</tr>
<tr>
<td>Inactive†</td>
<td>89 (10.9)</td>
<td>84 (10.2)</td>
</tr>
<tr>
<td>Nonadherence to randomization‡</td>
<td>40 (4.9)</td>
<td>42 (5.1)</td>
</tr>
<tr>
<td>Developed reproducible visual field abnormality or optic disc deterioration due to any cause</td>
<td>81 (9.9)</td>
<td>137 (16.7)</td>
</tr>
<tr>
<td>Developed reproducible visual field abnormality or optic disc deterioration due to POAG</td>
<td>36 (4.4)</td>
<td>89 (10.9)</td>
</tr>
</tbody>
</table>

*POAG indicates primary open-angle glaucoma. †Inactive status refers to participants who missed their last 2 follow-up visits but did not die or reach the POAG endpoint. ‡Nonadherence to randomization refers to participants randomized to medication who were withdrawn from medication for 6 months or more and to participants randomized to observation who were prescribed topical hypotensive medication for 6 months or more prior to reaching the POAG endpoint.

**Table 4. First POAG Endpoint for Each Participant**

<table>
<thead>
<tr>
<th>Medication Group, No. (%)</th>
<th>Observation Group, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual field</td>
<td>15 (41.7)</td>
</tr>
<tr>
<td>Optic disc</td>
<td>18 (50.0)</td>
</tr>
<tr>
<td>Concurrent visual field and optic disc</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Total</td>
<td>36 (100.0)</td>
</tr>
</tbody>
</table>

*POAG indicates primary open-angle glaucoma. Other POAG endpoints may have occurred in these eyes or the other eyes at a later time.

**Figure 3. Percentage of medication participants prescribed each class of medication at each follow-up visit. Percentages sum to greater than 100% because more than 1 class of medication may be prescribed. Combination drugs are counted twice.**

**Figure 4. Kaplan-Meier plot of the cumulative probability of developing primary open-angle glaucoma (POAG) by randomization group. The number of participants at risk are those who had not developed POAG at the beginning of each 6-month period. The number of participants classified as developing POAG is given for each interval. Participants who did not develop POAG and withdrew before the end of the study or who died are censored from the interval of their last completed visit.**
necessary a reduction to less than 18 mm Hg. These treatment objectives reflect common clinical practice, but no assumption was made that these IOP levels were ideal for each participant. During the course of the trial, 87% of the medication participants achieved this IOP target reduction in both eyes, and an additional 7% did so in one eye. The use of all commercially available topical ocular hypotensive medications prescribed singly or in combination allowed a high proportion of participants to reach their IOP target.

We monitored the safety of treatment through diverse sources of information. Throughout the study, there was no evidence of excess risk in the medication group for participant-reported symptoms according to the Glaucoma Symptom Scale or SF-36. The medication group had a similar mean visual acuity to the observation group throughout the study. There was no evidence of excess risk in the medication group for the overall number of occurrences made between the randomization groups. Although the differences between randomization groups were not statistically significant after correcting for multiple comparisons, these findings warrant further study. The use of ocular hypotensive medication may cause more adverse effects in routine practice than reported in this article because the OHTS sample consists of relatively healthy volunteers, with a mean age younger than 60 years, who may be less susceptible to the adverse effects of topical hypotensive medication. The safety experience reported in the OHTS implies the safety of the treatment protocol, not of particular medications. The recent availability of many different types of ocular hypotensive medications should allow clinicians to choose a safe regimen for most patients.

The results of the OHTS do not imply that all individuals with elevated IOP should be treated with ocular hypotensive medication. The decision to recommend treatment should involve many factors, such as (1) the low overall incidence of POAG among individuals with ocular hypertension in population-based studies and this study; (2) the burden of long-term treatment, including possible adverse effects, cost, and inconvenience; (3) the individual's risk of developing POAG; (4) the individual's likelihood of being helped by treatment; and (5) the individual's health status and life expectancy. In our companion article,41 we report baseline factors that predict which participants in the OHTS developed POAG. These factors may be useful to a clinician caring for a patient with ocular hypertension.

Figure 5. Percentage of participants in the medication group and observation group who rated that they were bothered “a lot” by ocular or systemic symptoms at 1 or more follow-up visits.
Participating Clinics, Committees, and Resource Centers

in the Ocular Hypertension Treatment Study

The following participants were certified on or before November 11, 2001. Principal investigators are listed in italics. Names marked with an asterisk are no longer part of the study.

Clinical Centers

Bascom Palmer Eye Institute, University of Miami, Miami, Fla
Investigators: Donald L. Budenz, MD; Francisco E. Fantes, MD; Steven J. Gedde, MD; Richard K. Parrish II, MD. Coordinators and Staff: Madeline L. Del Calvo, BS; James R. Davis,*; Elena Ferrer.*

Eye Consultants of Atlanta (formerly M. Angela Vela, MD, PC), Atlanta, Ga
Investigators: Thomas S. Harbin, Jr, MD; Paul McManus, MD; Charles J. Patorgis, OD; Ron Tilford, MD*; M. Angela Vela, MD*; Randall R. Ozment, MD.* Coordinators and Staff: Laura Brannon, COMT; Montanna L. Hooper, COT; Stacey S. Goldstein, COMT; June M. LaSalle Garril, COA; Debbie L. Lee, COT; Michelle D. Mondschein; Marianne L. Perry, COT; Julie M. Wright, COT; Linda Butler, COT*; Carla F. Crissey*; Mary Pat Hubert*; Marsha B. Liner*; Teresa Long, COT*; Alma Newkirk*; Emily J. Reese, COA*; Shelly R. Smith, COA*; Vanora Weeden.*

Cullen Eye Institute, Baylor College of Medicine, Houston, Tex
Investigators: Ronald L. Gross, MD; Silvia Orenco-Nania, MD. Coordinators and Staff: Pamela M. Frady, COMT, CCRC; Benita D. Slight, COT, EMT-P, CCRC; Sandy A. Ellis, COA.*

Devers Eye Institute, Portland, Ore
Investigators: George A. (Jack) Cluff, MD; Elizabeth Donohue, MD; Steven Mansberger, MD; E. Michael Van Buskirk, MD; Julia Whiteside-Michel, MD.* Coordinators and Staff: Kathryn Sherman; Jo-Anne M. Fraser, COT; Linda Diehl Boly, RN*; Vanora Volk.*

Emory University Eye Center, Atlanta, Ga
Investigators: Allen D. Beck, MD; Anastasias Costarides, MD, PhD; Reay H. Brown, MD*; Mary Lynch, MD*; John Rieser, MD.* Coordinators and Staff: Donna Leef, MMSc, COMT; Jatinder Bansal, COT*; David Jones, COT*; Lillie Reyes, COT.*

Henry Ford Medical Center, Detroit, Mich
Investigators: G. Robert Lesser, MD; Deborah Darnley-Fisch, MD; Nauman R. Imami, MD; James Klein, MD*; Talya Kupin, MD*; Rhett Schifman, MD.* Coordinators and Staff: Melanie Guitkowsk, COMT, CO; Jim Bryant, COT; Ingrid Crystal Fugmann, COMT; Monica R. Gibson, COT; Wendy Gilroy, COMT; Monica Lacoursiere; Sue Loomis, COT; Lauren S. Turner; Amandal Cole-Brown*; Amy Daghisceanu, COMT*; Jeannine M. Gartner*; Norma Hollins, COT, RN*; Melina Mazurk, COT*; Colleen Wojtala.*

Johns Hopkins University School of Medicine, Baltimore, Md
Investigators: Donald J. Zach, MD; Donald A. Abrams, MD; Nathan G. Congdon, MD, MPH; Robert A. Copeland, MD; David S. Friedman, MD, MPH; Ramzi Hemady, MD; Eve J. Higginbotham, MD; Henry D. Jampel, MD, MHS; Irvin P. Pollack, MD; Harry A. Quigley, MD; Alan L. Robin, MD; Agnes S. Huang, MD*; Omomofasade B. Kosoko, MD, MSPH*; Scott LaBorwit, MD*; Stuart J. McKinnon, MD, PhD*; Sreedhar V. Patarazu, MD*; Scott Drew Smith, MD*; Nancy E. Williams, MD. Coordinators and Staff: Rachel Scott, BS, COA; Rani Kalsi; Felicia Keel, COT; Lisa Levin; Robyn Priest-Reed, MMSc; Mary Ellen Flaks*; Kathy A. Hoffman*; Claudia Johns*; Nicole K. Lavinieri*; Patricia Zawaska.*

Charles R. Drew University, Jules Stein Eye Institute, University of California, Los Angeles
Investigators: Anne L. Coleman, MD, PhD; Richard S. Baker, MD; Michelle C. Banks, MD; Y. P. Dang, MD; Simon K. Law, MD; Dana P. Tannenbaum, MD; Baber H. Ali, MD*; Luca O. Brigatti, MD*; Mary R. Chang, MD*; Hyong S. Choe, MD*; Nichola X. Hamush, MD*; Ricky S. Huo, MD*; Leonidas A. Johnson, OD*; Michael S. Kook, MD*; Francis A. La Rosa, MD*; Hung H. Le, MD*; David A. Lee, MD*; John C. Marsh, MD*; Mamdouh L. Nakla, MD*; Irene Fong Sasaki, MD*; Robert K. Stevens, MD*; M. Roy Wilson, MD.* Coordinators and Staff: Jackie R. Sanguinet, BS, COT; Bobbie Ballenberg, COMT; Salvador Murillo; Manju Sharma; Rodolfo X. Garcia*; Rebecca A. Rudenko.*

W. K. Kellogg Eye Center, Ann Arbor, Mich
Investigators: Terry J. Bergstrom, MD; Sayoko E. Moroi, MD, PhD; Andrew N. Bainmoss, MD*; Bruce D. Cameron, MD*; Maria S. Gottfreds, MD*; Pam R. Henderson, MD*; Eve J. Higginbotham, MD*; A. Tim Johnson, MD*; Kurt K. Lark, MD*; Mariannette Miller-Meeks, MD*; Robert M. Schertzer, MD.* Coordinators and Staff: Carol J. Pollack-Rundle, BS, COMT; Salvador Murillo; Manju Sharma; Rodolfo X. Garcia*; Rebecca A. Rudenko.*

Kresge Eye Institute, Wayne State University, Detroit
Investigators: Bret A. Hughes, MD; Monica Y. Allen, MD; Mark S. Juzych, MD; Mark L. McDermott, MD; John M. O’Grady, MD; John M. Ramocki, MD; Dian Shi, MD; Dong H. Shin, MD, PhD; Robert V. Finlay, OD*; Stephen Y. Reed, MD.* Coordinators and Staff: Juan Allen; Laura L. Schulz, CNA; Linda A. Van Conett, COT; Mary B. Hall; Beverly McCarty, LPN,*; Chris R. Foster.*

(continued)
Participating Clinics, Committees, and Resource Centers

in the Ocular Hypertension Treatment Study (cont)

University of Louisville, Louisville, Ky
Investigators: Joern B. Soltau, MD; Gustavo E. Gamero, MD; Judit Mohay, MD; Gokhan Ozdemir, MD; Robb R. Shrader, MD; Richard M. Fenton, MD*; Robert D. Fechtner, MD*; Nicholas Karunaratne, MD*; Albert S. Khoury, MD*; Mahnud A. Naser, MD*; Tony Realini, MD*; Jianming Ren, MD*; Michelle Robison, MD*; George V. Shafranov, MD*; Gilbert Sussman, MD*; Mike Roy Willman, MD*; Thomas W. Uihlein, MD*; Thom J. Zimmerman, MD, PhD.* Coordinators and Staff: Sandy Lear, RN; Kathleen Loons, COT; Jane H. Fenton, COT*; Nancy Mahoney*; Linda Upton, COA.*

Mayo Clinic/Foundation, Rochester, Minn
Investigators: David C. Herman, MD; Douglas H. Johnson, MD; Paul H. Kalina, MD; Matthew Hattenhauer, MD*; Erik O. Schoff, MD.* Coordinators and Staff: Becky A. Nielsen, LPN; Nancy J. Tvedt.

New York Eye & Ear Infirmary, New York
Investigators: Jeffrey M. Liebmann, MD; Robert Ritch, MD; Celso A. Tello, MD; Ronald M.Caronia, MD*; David S. Greenfield, MD*; Alyson L. Hall, MD*; Elisa N. Mortelini, MD*; Robert F. Rothman, MD.* Coordinators and Staff: Jean L. Walker, BS, COA; Deborah L. Simon, COA; Kim A. Barget*; Debra Beck, BA, COA*; Jean E. Denaro, MA*; E. Eugenie Hartmann, PhD*; Anna N. Norris*; Melissa R. Perez*; David A. Steinberger.*

Ohio State University, Columbus
Investigators: Paul Weber, MD; N. Douglas Baker, MD; Robert J. Derick, MD; David Lehmard, MD; Omar Mobin-Uddin, MD. Coordinators and Staff: Kathryn McKinney, COMT; Cynthia Hutchinson; Diane Moore, COA; Cynthia A. Williams; Lori Black, COA*; Becky Gloccecker, COT*; Crystal Y. Hendrix Coleman, COT*; Tammy Lauderbaugh*; Billie J. Romans.*

Pennsylvania College of Optometry/MCP Hahnemann University School of Medicine, Philadelphia
Investigators: G. Richard Bennett, MS, OD; Elliot Werner, MD; Myron Yanoff, MD; Sara Foster, OD.* Coordinators and Staff: Lindsay C. Bennett, BA; Mary Jameson, Opt, TR; Maria Massini*; Kim Y. Moak, BS.*

Scheie Eye Institute, University of Pennsylvania, Philadelphia
Investigators: Jody R. Piltz-Seymour, MD; Robert Ritch, MD; Celso A. Tello, MD; Ronald M.Caronia, MD*; David S. Greenfield, MD*; Alyson L. Hall, MD*; Elisa N. Mortelini, MD*; Robert F. Rothman, MD.* Coordinators and Staff: Kathryn McKinney, COMT; Cynthia Hutchinson; Diane Moore, COA; Cynthia A. Williams; Lori Black, COA*; Becky Gloccecker, COT*; Crystal Y. Hendrix Coleman, COT*; Tammy Lauderbaugh*; Billie J. Romans.*

University of California–Davis, Sacramento
Investigators: James D. Brandt, MD; Jeffrey J. Casper, MD; John T. Dragicevich, MD; Thomas R. Johansen, MD; Esther S. Kim, MD; Michele C. Lim, MD; Michael B. Mizoguchi, MD; Alan M. Roth, MD; Ivan R. Schwab, MD; Richard Bernheimer, MD*; Marcia V. Beveridge, MD*; Craig Bindi, MD*; Marina Checchelnskys, MD*; Janet K. Han, MD*; Edward V. Hernandez, MD*; Andrea V. Gray, MD*; Denise Kaysor, MD*; Soohying Kim, MD*; Richard L. Nguyen*; Loan Tran, MD.* Coordinators and Staff: Ingrid J. Clark, COA; Vachiraporn X. Jaicheun, COA*; Denise M. Owensby, BS, COA; Marilyn A. Sponzo, COA.

University of California–San Diego, La Jolla
Investigators: Robert N. Weinreb, MD; J. Righy Slight, MD. Coordinators and Staff: Eva Kroneker, COA; Barbara Brunet*; Marizta K. Antunez*; Dawn Frasier, COT*; Rivak Hoffman, COT*; Kimberly Kebabjian*; Jennifer Kraker*; Marina Madrid*; Julia M. Williams.*

University of California–San Francisco
Investigators: Michael V. Drake, MD; Allan J. Flach, MD; Robert Stamper, MD. Coordinators and Staff: Fermin P. Balleseros, Jr; Marjan Karimabadi; Valerie Margol; Peggy Yamada, COT; Lou Anne Aber, COA*; Ilya Saltkov,*

University Suburban Health Center, South Peoria, IL
Investigators: Kathleen A. Lampmg, MD; Gregory A. Eippert, MD; Beverly C. Forcier, MD*; Laurence D. Kaye, MD.* Coordinators and Staff: Angela K. McKeau; Bettina J. Modica; Tonya Sims; Susan Van Huss*; Cheryl L. Vitelli; Laura Brevard*; Sheri Burked Porter, COT*; Elizabeth Laux*; Carla R. DeLaRosa Valenti*; Dina DeLisio*; Kimberly Purkey.*

Washington OHTS Center, Washington DC
Investigators: Douglas E. Gaasterland, MD; Frank S. Ashburn, MD; Arthur L. Schwartz, MD; Howard S. Weiss, MD; Sherri L. Berman, MD*; Alice T. Gash, MD*; Jane Hughes, MD*; John D. Mitchell, MD*; Guy S. Mullin, MD*; Pedro M. Rivera, MD*; Soo Y. Shin, MD*; Thomas H. Yau, MD.* Coordinators and Staff: Robin L. Montgomery, COA; Donna M. Caggert; Karen D. Schacht, COT; Anne M. Bocckl, MS; Ellen T. Coyle, COMT*; Christopher T. Garvin, COA*; Jennifer A. Gloor*; Melissa M. Kellogg, COA*; Jocelyn Kotev*; Diane Latham*; Vikki L. Monks*; Suzanne M. Flavnieks, COA*; Dina E. Rothlin*; Lynne S. Vayer, BS, COT*; Cindy V. Witol,CO*; Jing Cheng Zhao.*

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From the Department of Ophthalmology and Visual Sciences (Drs Kass and Gordon) and the Division of Biostatistics (Mr Miller), Washington University School of Medicine, St Louis, Mo; Department of Ophthalmology, Medical College of Wisconsin, Milwaukee (Dr Heuer); Maryland Center for Eye Care Associates and the Department of Ophthalmology, University of Maryland, Baltimore (Dr Higginbotham); Devers Eye Institute, Portland Ore (Dr Johnson);
Participating Clinics, Committees, and Resource Centers (cont)

Washington University School of Medicine, St Louis, Mo

Investigators: Martin B. Wax, MD; Edward M. Barnett, MD; Bernard Becker, MD; Michael A. Kass, MD; Allan E. Kolker, MD; Carla J. Siegfried, MD; Regina M. Smolyak, MD; Dipali V. Apte, MD*; David C. Ball, MD*; John C. Burchfield, MD*; Deepak P. Edward, MD*; Rebecca S. Heaps, MD*; Pierre G. Mardelli, MD*; J. Eric Pepperl, MD*; Jonathan Silbert, MD*; Marshall W. Stafford, MD*; Paul M. Tesser, MD*; James W. Umas, MD.*

Coordinators and Staff: Arnold D. Jones, COA; Lori A. Clark, COT*; Fortunata Darmody, COT*; Diana L. Moellering, COT.

Committees

Executive/Steering Committee: Ingrid Adamsons, MD (nonvoting); Douglas R. Anderson, MD; James D. Brandt, MD; Anne L. Coleman, MD, PhD; Michael Drake, MD; Donald F. Everett, MA; Robert Fechtner, MD*; Douglas Gaasterland, MD; Mac D. Gordon, PhD; Dale K. Heuer, MD; Eve J. Higginbotham, MD; Chris A. Johnson, PhD; Michael A. Kass, MD (chair); John L. Keltner, MD; Richard K. Parrish II, MD; Jody R. Pilz-Seymour, MD; M. Roy Wilson, MD; Arthur Shedden, MD* (nonvoting); Roger Vogel, MD* (nonvoting); Jane L. Anderson, MS, CCRC; Debra Beck, BA, COA*; Ingrid Clark, COA*; Donna Leef, MMS, COMT*; Patricia A. Morris (nonvoting); Carol J. Pollack-Rundle, COMT; Ann K. Wilder, RN, BSN (nonvoting).

Data and Safety Monitoring Committee: Ingrid Adamsons, MD (nonvoting; open session); Roy Beck, MD, PhD; John Connett, PhD; Claude Cowan, MD; Barry Davis, MD, PhD (chair); Donald F. Everett, MA (nonvoting); Mac O. Gordon, PhD (nonvoting); Michael A. Kass, MD (nonvoting; open session, 11/4/93 to 4/30/98; closed session, 3/1/98 to present); Ronald Munson, PhD; Mark Sherwood, MD; Gregory L. Skuta, MD; Keven O’Rourke, OP, JCL, STEM.*

Endpoint Committee: Dale K. Heuer, MD; Eve J. Higginbotham, MD; Richard K. Parrish II, MD; Mac O. Gordon, PhD.

Resource Centers

Coordinating Center: Washington University School of Medicine, St Louis

Investigators: Mac O. Gordon, PhD; J. Philip Miller, AB; Kenneth Schechtman, PhD.*

Coordinators and Staff: Joel Achtenberg, MSW; Mary Bednarski, MAS; Julia Beiser, MS; Karen Clark, BS; Christopher Ewing, BA; Elizabeth Hornbeck, BS; Ellen Long, CCRA; Carolyn R. Miles, MA; Patricia Morris; Denise Morrison; Ann K. Wilder, RN, BSN, CCRP.

Chairman’s Office: Washington University School of Medicine, St Louis

Investigator: Michael A. Kass, MD. Coordinators and Staff: Deborah Dunn; Debra Browning*; Dawn Tourville.*

Project Office: National Eye Institute, Rockville, Md

Donald F. Everett, MA; Richard Mowery, PhD.*

Optic Disc Reading Center: Bascom Palmer Eye Institute, University of Miami, Miami, Fla

Investigators: Richard K. Parrish II, MD; Douglas R. Anderson, MD; Donald L. Budenz, MD. Coordinators and Staff: Maria-Cristina Wells-Albornoz, MPH; William Feuer, MS; Ditte Hess, CRA; Heather Johnson; Joyce Schiffman, MS; Ruth Vandenbroucke.

Visual Field Reading Centers: University of California–Davis, Sacramento; Discoveries in Sight, Devers Eye Institute, Portland, Ore

Investigators: John L. Keltner, MD (Sacramento); Chris A. Johnson, PhD (Portland). Coordinators and Staff: Kimberly E. Cello, BS; Shannan E. Bandermann, MA; Bhupinder S. Dhillon, BS; Daniel Redline, BS; David Claunch*; Mary A. Edwards, BS*; Peter Gunther*; Jacqueline Quigg*; John Spurr.*

Ancillary Study Reading Centers

Confocal Scanning Laser Ophthalmoscopy Reading Center: University of California–San Diego, La Jolla

Investigators: Robert N. Weinreb, MD; Linda Zangwill, PhD. Coordinators and Staff: Keri Dirkes, MPH; Amanda R. Smith, BS.

Short Wavelength Automated Perimetry Reading Center: Devers Eye Institute, Legacy Portland Hospitals, Portland, Ore

Investigator: Chris A. Johnson, PhD. Coordinator: Erna Hibbits.

Corneal Endothelial Cell Density Reading Center: Mayo Clinic/Foundation, Rochester, Minn

Investigator: William M. Bourne, MD. Coordinators and Staff: Becky A. Nielsen, LPN; Thomas P. Link, CRA, BA; Jay A. Rostvold.

Department of Ophthalmology, University of California, Davis (Dr Keltner); Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Fla (Dr Parrish); and Creighton University School of Medicine, Omaha, Neb (Dr Wilson).

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The following investigators have disclosed a proprietary or financial interest in companies providing medications and/or equipment to the Ocular Hypertension Treatment Study. This information is for 2000-2001, the most current reporting period.

Ingrid Adamsom, MD: Merck, full-time employee. Frank Ashburn, MD: Merck, stock. Roy Beck, MD: Allergan, consultant. Terry Bergstrom, MD: Merck, stock. James D. Brandt, MD: Merck, study principal investigator, honoraria; Allergan, study principal investigator, honoraria. G. A. Cioffi, MD: Alcon, grant support, honoraria; Merck, honoraria; Bausch and Lomb, honoraria; CIBA Vision, honoraria, consultant; Allergan, consultant, grant support, honoraria; Otsuka American Pharmaceutical, grant support; Pharmacia/Upjohn, consultant, grant support, honoraria. Anne Coleman, MD: Merck, stock, honoraria. Anastasios Costarides, MD: Merck, stock; Medi-Pro, consultant. Barry Davis, MD, PhD: Merck, consultant; Pharmacia/Upjohn, consultant. Ronald Gross, MD: Alcon, consultant, grant support, speakers bureau; Allergan, consultant, grant support, speakers bureau; Novartis, grant support, speakers bureau. Dale Heuer, MD: Merck, honoraria, consultant; Pharmacia, honoraria, consultant; Allergan, grant support, honoraria. Eve Higginbotham, MD: Pharmacia/Upjohn, consultant; CIBA Vision, consultant; Merck, grant support, honoraria. Nauman Imam, MD: Merck, honoraria; Pharmacia, speakers bureau. Chris Johnson, MD: Humphrey Systems, consultant, grant support; Allergan, consultant; Merck, honoraria; Pharmacia, honoraria. Douglas Johnson, MD: Allergan, grant support. Paul Kalina, MD: Merck, stock. Michael Kass, MD: Merck, consultant; Pharmacia, consultant; Allergan, grant support. John Keltner, MD: Merck, stock. Jody Piltz-Seymour, MD: Merck, consultant; Allergan, grant support. Alan Robin, MD: Alcon, consultant; Pharmacia/Upjohn, honoraria; Humphrey Zeiss, consultant. Arthur Schwartz, MD: Merck, stock; Allergan, consultant; Alcon, consultant; Pharmacia, consultant. Mark Sherwood, MD: Allergan, consultant; CIBA Vision, consultant; Merck, consultant; Pharmacia/Upjohn, consultant. Gregory Skuta, MD: Pharmacia/Upjohn, consultant; Allergan, honoraria; Pharmacia/Upjohn, honoraria. Robert L. Stamper, MD: Allergan, consultant, speakers bureau; Pharmacia, speakers bureau; Alcon, speakers bureau; Merck, speakers bureau. Martin Wax, MD: Pharmacia, consultant. Paul Weber, MD, PhD, stock. Robert N. Weinreb, MD: Allergan, consultant, grant support; Merck, stock, consultant, grant support; Humphrey, grant support; Heidelberg, grant support; Pharmacia/Upjohn, consultant, grant support.

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Drs Kass and Gordon take responsibility for authorship, financial disclosure, and copyright transfer for the group.

Corresponding author and reprints: Mae O. Gordon, PhD, OHTS Coordinating Center, Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, Box 8203, 660 South Euclid, St Louis, MO 63110 (e-mail: mae@vrcc.wustl.edu).

REFERENCES

29. Kass MA, Gordon MO, Hoff MR, et al. Topical timolol administration reduces the


Archives Web Quiz Winner

Congratulations to the winner of our March quiz, Christina Canakis, MD, Vitreoretinal Fellow at the Department of Ophthalmology, Tulane University Medical Center, New Orleans, La. The correct answer to our March challenge was idiopathic polypoidal choroidal vasculopathy. For a complete discussion of this case, see the Clinicopathologic Reports, Case Reports, and Small Case Series section in the April ARCHIVES (Rosa RH, Davis JL, Eifrig CWG. Clinicopathologic correlation of idiopathic polypoidal choroidal vasculopathy. Arch Ophthalmol. 2002;120:502-508).

Be sure to visit the Archives of Ophthalmology World Wide Web site (http://www.archophthalmol.com) and try your hand at our Clinical Challenge Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of the book One Hundred Years of JAMA Landmark Articles.