

The Ocular Hypertension Treatment Study

Topical Medication Delays or Prevents Primary Open-angle Glaucoma in African American Individuals

Eve J. Higginbotham, MD; Mae O. Gordon, PhD; Julia A. Beiser, MS; Michael V. Drake, MD; G. Richard Bennett, OD; M. Roy Wilson, MD; Michael A. Kass, MD; for the Ocular Hypertension Treatment Study Group

Background: The prevalence of glaucoma is higher in African American individuals than in white individuals.

Objective: To report the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of primary open-angle glaucoma (POAG) among African American participants in the Ocular Hypertension Treatment Study.

Methods: Eligibility criteria included age between 40 and 80 years, intraocular pressure between 24 and 32 mm Hg in one eye and between 21 and 32 mm Hg in the other eye, and no evidence of glaucomatous structural or functional damage by standard clinical measures. Participants were randomized to either the observation group or medication group. Of the 1636 participants randomized, 408 were self-identified as African American.

Main Outcome Measure: The primary outcome was the development of reproducible visual field abnormality and/or reproducible optic disc deterioration attributed to POAG.

Results: Among African American participants, 17 (8.4%) of 203 in the medication group developed POAG during the study (median follow-up, 78 months) compared with 33 (16.1%) of 205 participants in the observation group (hazard ratio, 0.50; 95% confidence interval, 0.28-0.90; $P = .02$).

Conclusion: Topical ocular hypotensive therapy is effective in delaying or preventing the onset of POAG in African American individuals who have ocular hypertension.

Arch Ophthalmol. 2004;122:813-820

From the Department of Ophthalmology, Maryland Center for Eye Care Associates, Baltimore (Dr Higginbotham); the Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St Louis, Mo (Drs Gordon, Beiser, and Kass); the University of California San Francisco, Oakland (Dr Drake); Pennsylvania College of Optometry, Philadelphia (Dr Bennett); and Texas Tech University Health Sciences Center, Lubbock (Dr Wilson). A complete list of members of the Ocular Hypertension Treatment Study is available at <https://vrcc.wustl.edu>. The authors have no relevant financial interest in this article.

THE OCULAR HYPERTENSION Treatment Study (OHTS) reported that reducing intraocular pressure (IOP) with topical antiglaucoma medication delayed or prevented the onset of primary open-angle glaucoma (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.¹ Prior studies comparing treated and untreated eyes with ocular hypertension generally had small sample sizes, used various definitions of glaucoma, used single agents to reduce pressure, and included fairly homogeneous populations of patients.²⁻⁵ These factors contributed to a lack of consensus regarding the benefits of early therapy. The OHTS is the first randomized treatment study of ocular hypertension to recruit sufficient numbers of African American participants to examine the therapeutic benefit of ocular hypotensive medication in this group.

Glaucoma is the leading cause of blindness among African American individuals. In the Baltimore Eye Survey, the age-adjusted prevalence rates of POAG were 4 to 5 times higher in African American individuals than among white individuals.⁶ At the time of publication of the OHTS primary outcome article, there was a trend for treatment to be protective in

For editorial comment see page 909

African American individuals, but the results did not attain statistical significance.¹ There may be several reasons why the protective trend did not achieve statistical significance, including the shorter length of follow-up of the African American participants. The purpose of this article is to present longer follow-up data on the cohort of African American participants enrolled in the OHTS, which, in fact, demonstrate that topical ocular hypotensive medication delays or prevents the onset of POAG in this group as well.

METHODS

PARTICIPANTS

Eligibility criteria included: age, 40 to 80 years; an IOP of 24 mm Hg or higher and 32 mm Hg or lower in one eye and 21 mm Hg or higher and 32 mm Hg or lower in the fellow eye; normal and reliable visual fields as determined by the University of California Davis Visual Field Reading Center, Sacramento; and normal optic discs on clinical examination and on stereoscopic photographs as determined by the Bascom Palmer Eye Institute Optic Disc Reading Center, Miami, Fla. The qualifying IOP was the mean of 4 to 6 IOP measurements per eye taken on 2 separate visits. Individuals were excluded if they had a visual acuity worse than 20/40 in either eye, previous intraocular surgery other than uncomplicated cataract extraction, or background diabetic retinopathy or other diseases capable of causing visual field loss or optic disc abnormalities. Individuals signed an informed consent form approved by the institutional review board of each clinic.

STUDY DESIGN

Eligible individuals were randomized in equal proportions to either the medication group or the observation group. Participants who were randomized to the medication group began using topical ocular hypotensive medication to achieve a target IOP reduction of (1) an IOP 24 mm Hg or lower and (2) a 20% reduction in IOP from the average of the qualifying IOP and baseline IOP but not necessarily lower than 18 mm Hg. All commercially available topical ocular hypotensive medications were included. Participants completed follow-up visits every 6 months. Semiannual visits included ocular and medical history; measurements of refraction, best-corrected visual acuity, and Humphrey 30-2 visual fields; slitlamp examination; direct ophthalmoscopy; and IOP measurement. In addition, dilated fundus examination and stereoscopic optic disc photography were performed at annual visits. Information on adverse effects was collected at each visit using a patient-completed checklist of ocular and systemic symptoms (Glaucoma Symptom Checklist and the Medical Outcomes Study Short Form with 36 questions [SF-36]) and ocular and medical history as elicited by clinic personnel. The study design has been described elsewhere.^{7,8}

PRIMARY OUTCOME AND MONITORING

The primary outcome was development of POAG in one or both eyes. This was defined as a reproducible visual field abnormality or as a clinically significant reproducible optic disc deterioration attributed to POAG by the masked endpoint committee. Development of a visual field abnormality was determined by masked certified readers at the Visual Field Reading Center. A technically acceptable visual field was considered abnormal if the corrected pattern standard deviation had a $P < .05$ or if the glaucoma hemifield test results were outside normal limits by STATPAC 2 criteria.⁸ Because most abnormal visual fields were found to be normal on retest, the protocol was changed effective June 1, 1997, so that confirmation of abnormality required 3 consecutive abnormal visual fields with the same type, location, and index of abnormality.⁹ If 3 consecutive visual fields met criteria for abnormality, the Visual Field Reading Center initiated the endpoint review process. Additional details about the process of reviewing visual fields were given in a previously published report.^{7,8}

Optic disc deterioration was determined by masked certified readers at the Optic Disc Reading Center. Optic disc deterioration was defined as a generalized or localized thinning of the optic disc neuroretinal rim compared with baseline ste-

reoscopic optic disc photographs in side-by-side comparisons. If optic disc deterioration was confirmed by 2 consecutive sets of stereoscopic optic disc photographs in independent masked reviews, the Optic Disc Reading Center initiated the endpoint review process. Additional details about the process of reviewing optic disc photographs were given in a previously published report.^{7,8,10}

The Data and Safety Monitoring Committee approved the termination of the overall trial when the last randomized participant reached 5 years of follow-up, as specified in the original protocol. The primary outcome article, which was published in June 2002, included data through November 8, 2001, on 125 participants who had developed POAG of the 1636 participants randomized.¹ This article reports on 148 participants who developed POAG whose first abnormality was detected by June 1, 2002, with additional data collected through September 11, 2003, to confirm reproducibility of abnormalities. The protocol as described in the baseline article and the primary outcome article continued through June 1, 2002.

STATISTICAL ANALYSES

The overall target sample size of 1500 participants (750 per randomization group) was selected assuming a 40% reduction in the 5-year incidence of POAG in the medication group, a 2-sided α error of .05, and statistical power of 0.90. Our goal at study onset was to recruit 400 African American participants, approximately 25% of the overall sample, to provide a valid estimate of the treatment effect in this group.⁸

All comparisons of randomization groups were made on an intention-to-treat basis. For the purposes of the primary efficacy analysis, the time to develop POAG was determined by the date of the first abnormal finding that was subsequently confirmed and attributed to POAG. The primary hypothesis was tested using the Mantel log rank test to compare the cumulative risk of developing POAG among African American participants randomized to the medication or to the observation group. Cox proportional hazards analysis was used to estimate the hazard ratio of POAG in the medication group compared with the observation group, adjusting for the influence of baseline factors.

The potential for differential treatment protection on the risk of POAG by race was estimated using Cox proportional hazards models that adjusted for baseline IOP and heart disease as well as those baseline factors that differed by race, age, sex, vertical cup-disc ratio, corneal thickness, mean deviation, systemic hypertension, and diabetes mellitus. The final Cox proportional hazards model that we report included pattern standard deviation rather than mean deviation to reduce potential confounding due to lens opacification. Analyses were performed with SAS software (version 8.2; SAS Institute, Cary, NC). P values were 2 sided.

RESULTS

RECRUITMENT AND BASELINE CHARACTERISTICS OF PARTICIPANTS

Recruitment was extended by 6 months, from 24 months to 30 months, to achieve enrollment of 400 African American participants. Between February 28, 1994, and October 31, 1996, 1636 individuals with documented informed consent were randomized. Two hundred three (25%) of the 817 participants randomized to receive topical medication were self-identified as African American. Two hundred five (25%) of the 819 participants random-

ized to the observation group were self-identified as African American.

For purposes of this article, OHTS participants were classified as either self-identified African American (not of Hispanic origin) or "other," which includes white (n=1137), Hispanic (n=59), Asian (n=14), American Indian or Alaskan Native (n=4), and unknown (n=14). Detailed description of clinical and demographic characteristics of participants have been reported.⁸

Among African American participants enrolled in the OHTS, no statistically significant differences in baseline demographic or clinical factors were found between groups (all comparisons, $P > .05$) (**Table 1**).

FOLLOW-UP

The median follow-up was 78 months for African American participants and 84 months for other participants. The visit completion rate was 76.3% for African American participants and 81.2% for other participants ($P < .001$). Among African American participants, the visit completion rate was essentially identical for the observation and medication groups ($P = .98$). Technically acceptable visual fields and stereoscopic optic disc photographs were obtained at 99% and 96%, respectively, of the specified completed follow-up visits for African American participants.

ADHERENCE TO RANDOMIZATION

In the medication group, 3 (1.5%) of 203 African American participants and 34 (5.5%) of 614 other participants were withdrawn from medication or chose to stop using medication for 6 months or more during the study ($P = .02$). In the observation group, 11 (5.4%) of 205 African American participants and 30 (4.9%) of 614 other participants received topical ocular hypotensive medication for 6 months or longer during the study ($P = .78$). In most cases, treatment was initiated by the OHTS clinician out of concern for the participant's high IOP.

IOP REDUCTION AND MEDICATION

The baseline and follow-up IOP for the medication and observation groups are reported by race in **Table 2**. The distribution of IOP at baseline and across the course of follow-up visits for the African American participants is plotted in **Figure 1**. Among African American participants, the IOP goal was met in both eyes in 1807 (87.6%) of 2063 scheduled follow-up visits and in only 1 eye in 137 (6.6%) of 2063 scheduled follow-up visits. Among other participants, the IOP goal was met in both eyes in 6152 (84.8%) of 7251 scheduled follow-up visits and in 1 eye in 594 (8.2%) of 7251 scheduled follow-up visits. **Figure 2** shows the percentage of African American participants who were prescribed each class of topical ocular hypotensive medication during the follow-up period. At 60 months, 64 (42.7%) of 150 African American participants in the medication group were prescribed 2 or more topical ocular hypotensive medications compared with 195 (38.3%) of 509 other participants in the group ($P = .34$). At the 60-month visit, fewer African American participants were prescribed β -adrenergic antagonists compared with other par-

Table 1. Baseline Characteristics for African American Participants by Randomization Group

	Medication Group (n = 203)	Observation Group (n = 205)
Sex, No. (%)		
Men	73 (36.0)	67 (32.7)
Women	130 (64.0)	138 (67.3)
Age, y, mean \pm SD	54.9 \pm 9.2	55.4 \pm 8.8
Age, y, No. (%)		
40 to \leq 50	74 (36.5)	63 (30.7)
>50 to \leq 60	68 (33.5)	72 (35.1)
>60 to \leq 70	48 (23.6)	60 (29.3)
>70 to 80	13 (6.4)	10 (4.9)
Clinical measures, mean \pm SD		
Intraocular pressure, mm Hg	25.1 \pm 2.9	25.1 \pm 2.8
Horizontal cup-disc ratio	0.43 \pm 0.2	0.41 \pm 0.2
Vertical cup-disc ratio	0.46 \pm 0.2	0.44 \pm 0.2
Visual field mean deviation, dB	0.10 \pm 1.1	0.03 \pm 0.99
Visual field pattern standard deviation, dB	1.94 \pm 0.21	1.90 \pm 0.19
Visual field corrected pattern standard deviation, dB	1.11 \pm 0.35	1.06 \pm 0.34
Central corneal thickness, μ m*	554.8 \pm 41.1	555.0 \pm 36.3
Medical history, %		
Previous use of ocular hypotensive medication	36.0	41.0
First-degree family history of glaucoma	30.5	34.6
Myopia \geq 1 diopter spherical equivalent	26.1	22.9
Oral β -adrenergic antagonist	8.1	4.6
Oral calcium channel blocker	26.0	21.8
Migraine	11.0	11.2
Diabetes	18.7	19.0
Hypertension	55.7	56.4
Low blood pressure	5.4	2.9
Cardiovascular disease	9.9	8.3
Stroke	0.5	2.0

*Overall, n = 356 for central corneal thickness, n = 177 for the medication group, and n = 179 for the observation group. Measurements were conducted after 1999, about 2 years after randomization of the last participant.

ticipants (85 [57%] of 150 African American participants vs 351 [69%] of 509 other participants; $P = .005$) and were more likely to be prescribed prostaglandin agonists (78 [52.0%] of 150 African American participants vs 203 [39.9%] of 509 other participants; $P = .008$).

PRIMARY OPEN-ANGLE GLAUCOMA

Table 3 reports the progress and outcome of randomized participants by race unadjusted for follow-up time. **Table 4** reports whether the first POAG endpoint was ascertained by visual field abnormality, by optic disc deterioration, or both. Among African American participants, the percentage developing POAG in the medication group during the entire follow-up period (median follow-up, 78 months) was significantly lower (17 [8.4%] of 203) compared with the observation group (33 [16.1%] of 205) (hazard ratio, 0.50; 95% confidence interval [CI], 0.28-0.90; Mantel log rank $P = .02$) (**Figure 3**). Among other participants, the percentage developing POAG during the entire follow-up period (median follow-up, 84 months) was significantly lower in the medication group (27 [4.4%] of 614) compared with the observation group (71 [11.6%] of 614) (hazard ratio, 0.36; 95% CI, 0.23-

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

	African American		Other Race	
	Medication Group	Observation Group	Medication Group	Observation Group
Baseline IOP	203 (25.1 ± 2.9)	205 (25.1 ± 2.8)	614 (24.9 ± 2.6)	614 (24.9 ± 2.7)
Mean follow-up IOP	198 (19.2 ± 2.4)	202 (23.8 ± 3.2)	608 (19.1 ± 2.1)	611 (23.7 ± 2.8)
Percentage of IOP reduction	198 (-22.9 ± 10.4)	202 (-4.7 ± 13.0)	608 (-22.5 ± 10.0)	611 (-4.1 ± 11.3)

*The IOP measurements are excluded after the date that participants developed primary open-angle glaucoma. Values are expressed as number of participants (mean ± SD).

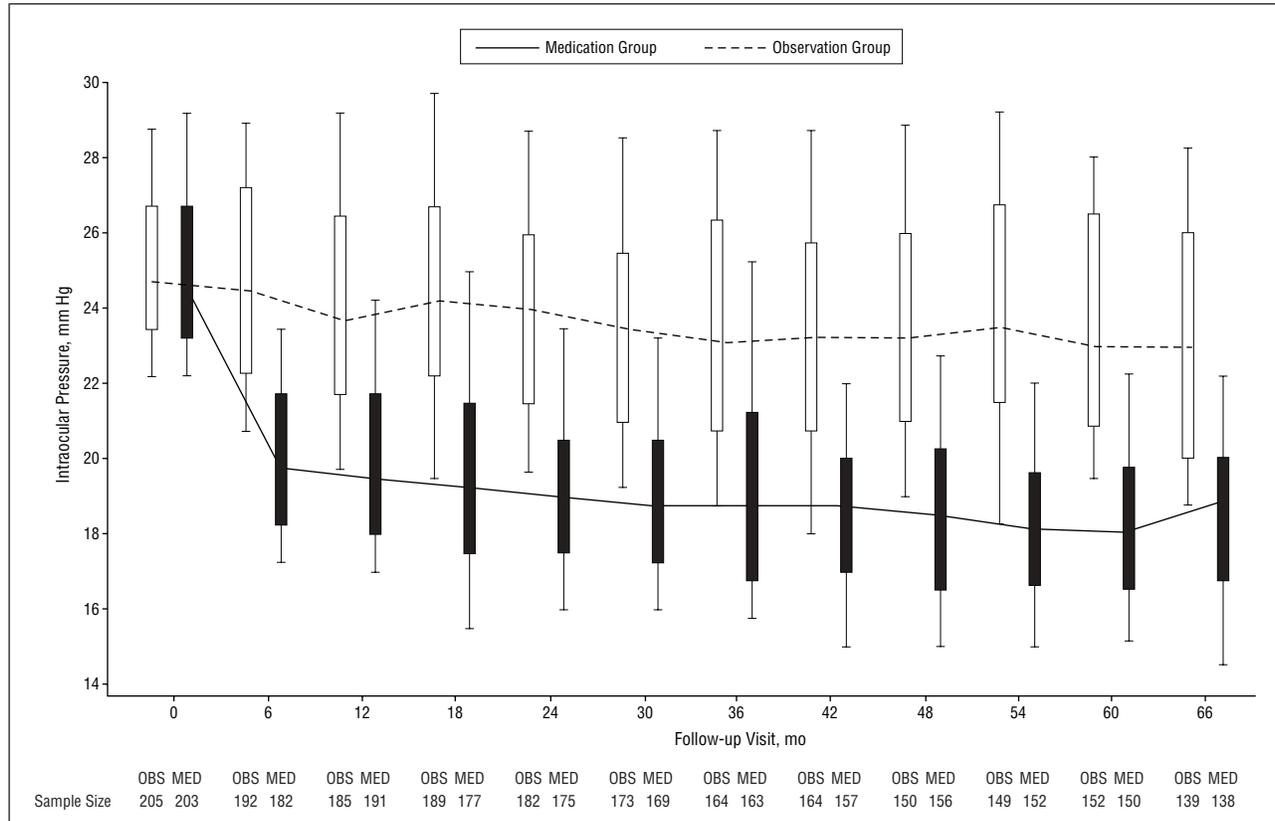


Figure 1. The distribution of intraocular pressure among African American participants at baseline and follow-up is shown for the medication (MED) and observation (OBS) groups. The median intraocular pressure for each group is joined by a line. The top and bottom of the boxes include the 75th and 25th percentiles, respectively, and the marks above and below include the 90th and 10th percentiles. Each participant's right and left eye were averaged to calculate a mean. The number of participants completing each follow-up visit is shown at the bottom.

0.57; $P < .001$). The protective effect of medication among African American participants (hazard ratio, 0.50) was not statistically different from its protective effect among other participants (hazard ratio, 0.36; $P = .40$ for race interaction).

The estimate of the effect of treatment among African American participants 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, 0.41; 95% CI, 0.22-0.75). Among African American participants, treatment appeared to be protective against both reproducible visual field abnormality attributed to POAG (hazard ratio, 0.51; 95% CI, 0.25-1.06; $P = .07$) and reproducible optic disc deterioration attributed to POAG (hazard ratio, 0.36; 95% CI, 0.17-0.78; $P = .007$).

Adjusting for time of follow-up, the risk of developing POAG was higher among African American partici-

pants compared with others in both groups. In the medication group, the risk among African American participants was 2 times higher during the course of the study compared with other participants (hazard ratio, 2.03; 95% CI, 1.10-3.73; Mantel log rank $P = .02$) (Table 3) (**Figure 4**). In the observation group, the risk among African American participants was 58% higher compared with other participants (hazard ratio, 1.58; 95% CI, 1.04-2.39; Mantel log rank $P = .03$) (Table 3) (**Figure 5**).

SAFETY

To ascertain the safety of treatment among African American participants, the medication and observation groups were compared for participant self-report of symptoms (Glaucoma Symptom Checklist and SF-36) and for medical and ocular history as collected by clinic staff during

the course of the study. All *P* values reported in the safety section are unadjusted for multiple comparisons between groups.

On the Glaucoma Symptom Checklist, there was no evidence that the medication group had more ocular or systemic symptoms compared with the observation group dur-

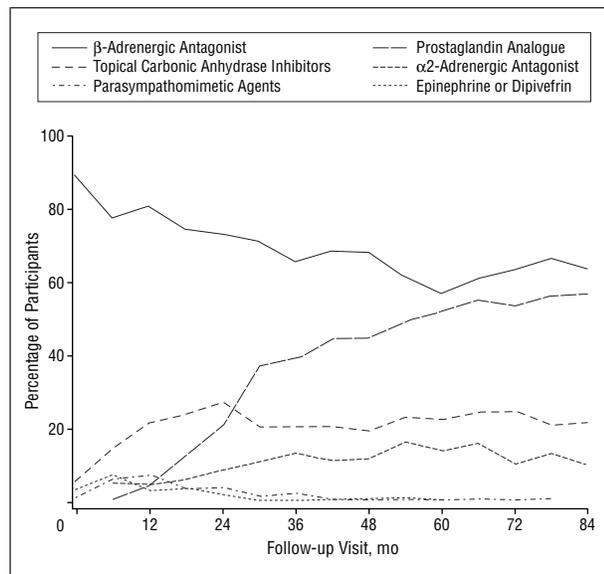


Figure 2. Percentage of African American participants in the medication group prescribed each class of medication at each follow-up visit. Percentages sum to greater than 100% because more than 1 class of medication may have been prescribed. Combination drugs are counted twice.

ing follow-up ($P > .05$), except for symptoms associated with administration of prostaglandin analogues. Changes in iris color, darkening of eyelids, and growth of eyelashes were reported by 19 (18.8%) of 101 African American participants prescribed a prostaglandin analogue for 6 months or longer compared with 20 (13.8%) of 145 African American participants in the observation group ($P = .29$). On the SF-36, there were no differences between randomization groups on the physical component or mental health component at any annual visit ($P > .05$).

In medical and ocular histories collected by clinic staff, there were no differences among African American participants in either group in total hospitalizations ($P = .24$), worsening of preexisting conditions ($P = .55$), mortality ($P = .24$), percentage reporting 1 or more adverse events ($P = .79$), and percentage reporting 1 or more serious adverse events ($P = .19$). There was a trend for a higher percentage of any cancer in the medication group (medication group, 9% vs observation group, 4.5%; $P = .08$) and a trend for prolonged hospitalizations (medication group, 2% vs observation group, 0%; $P = .06$). There were differences in some adverse events between groups. Among African American participants, clinic personnel classified a higher percentage of adverse events in the medication group as life threatening (medication group, 3.5% vs observation group, 0.5%; $P = .04$). Among African American participants, a higher percentage in the medication group compared with the observation group was reported to have psychiatric adverse events (18.4% vs 8.3%, respectively; $P < .001$). Clinic staff classified 4

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

	African American		Other Race	
	Medication Group	Observation Group	Medication Group	Observation Group
Randomized	203 (100)	205 (100)	614 (100)	614 (100)
Died	11 (5.4)	6 (2.9)	22 (3.6)	32 (5.2)
Inactive†	20 (9.8)	19 (9.3)	57 (9.3)	61 (9.9)
Nonadherence to randomization‡	3 (1.5)	11 (5.4)	34 (5.5)	30 (4.9)
Developed reproducible visual field abnormality or optic disc deterioration due to any cause	38 (18.7)	48 (23.4)	65 (10.6)	106 (17.3)
Developed reproducible visual field abnormality or optic disc deterioration due to primary open-angle glaucoma	17 (8.4)	33 (16.1)	27 (4.4)	71 (11.6)

*Values are expressed as number (percentage) of participants.

†Inactive status refers to participants who missed their last 2 follow-up visits but who have not died or reached the primary open-angle glaucoma endpoint.

‡Nonadherence to randomization refers to participants randomized to the medication group whose medication treatment was discontinued for 6 months or more and to participants randomized to the observation group who were prescribed topical hypotensive medication for 6 months or more prior to reaching the primary open-angle glaucoma endpoint.

Table 4. First Primary Open-angle Glaucoma Endpoint for Each Participant by Randomization Group and Race*

	African American			Other Race		
	Medication Group	Observation Group	All	Medication Group	Observation Group	All
Optic disc	8 (47.1)	16 (48.5)	24 (48.0)	14 (51.9)	41 (57.7)	55 (56.1)
Visual field	9 (52.9)	13 (39.4)	22 (44.0)	10 (37.0)	23 (32.4)	33 (33.7)
Concurrent visual field and optic disc	0	4 (12.1)	4 (8.0)	3 (11.1)	7 (9.9)	10 (10.2)
All	17 (100.0)	33 (100.0)	50 (100.0)	27 (100.0)	71 (100.0)	98 (100.0)

*Values are expressed as number (percentage) of participants. Other primary open-angle glaucoma endpoints may have occurred in these eyes or the fellow eyes at a later time.

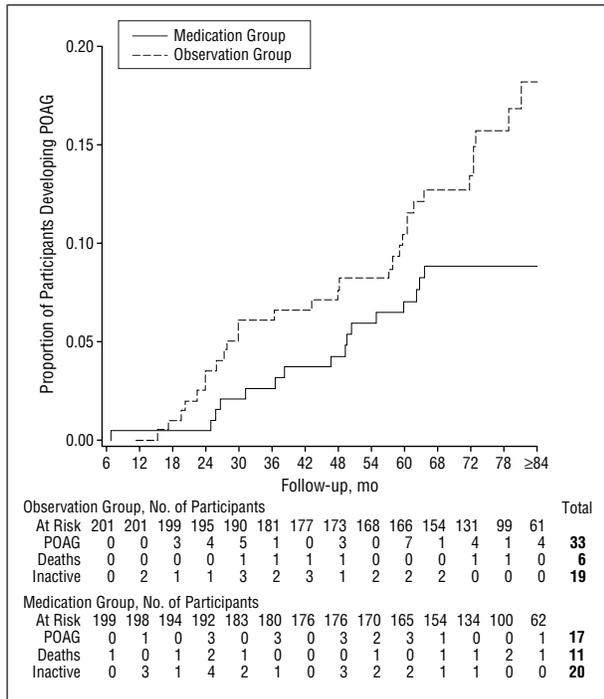


Figure 3. Kaplan-Meier plot of the cumulative probability of developing primary open-angle glaucoma (POAG) for African American participants by randomization group. The number of participants at risk are those who had not developed POAG at the beginning of each 6-month period. The number of participants classified as developing POAG is given for each interval. Participants who did not develop POAG or withdrew before the end of the study or who died are censored from the interval of their last completed visit.

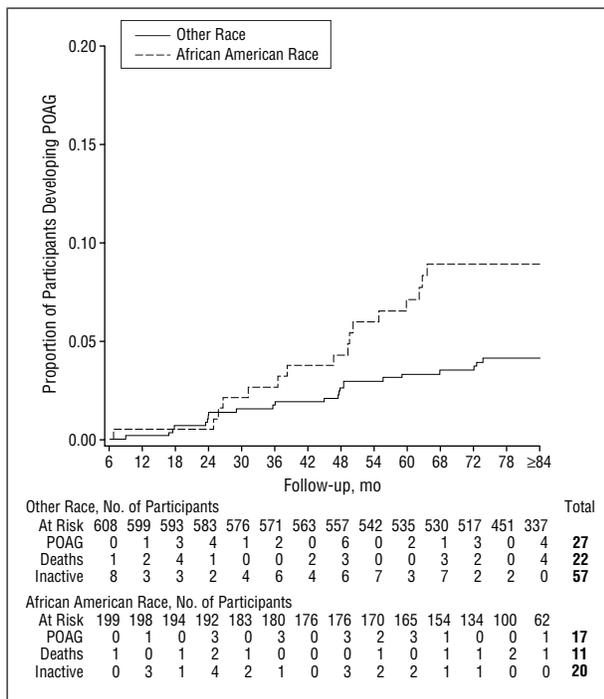


Figure 4. Medication participants' Kaplan-Meier plot of the cumulative probability of developing primary open-angle glaucoma (POAG) by race (African American vs. other).

(2.0%) of 201 psychiatric adverse events in the medication group as serious and 1 (0.5%) of 204 in the observation group as serious ($P=.21$). None of the 5 serious

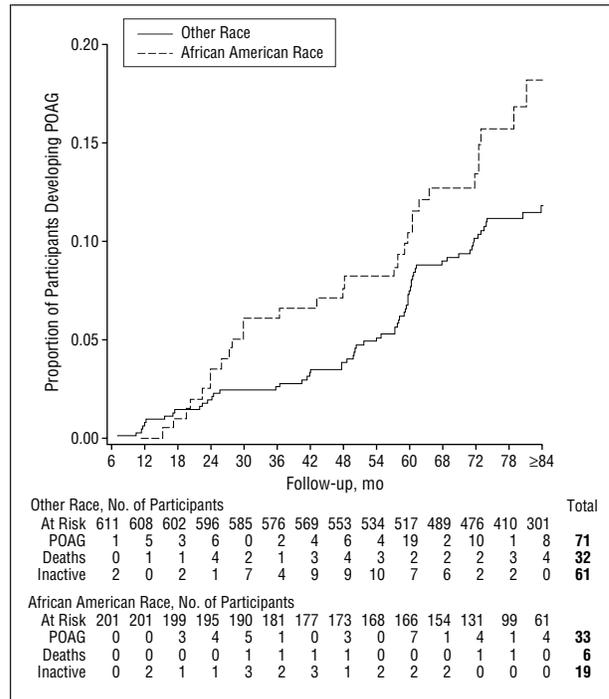


Figure 5. Observation participants' Kaplan-Meier plot of the cumulative probability of developing primary open-angle glaucoma (POAG) by race (African American vs. other).

psychiatric adverse events in the medication group were judged to be "probably" or "definitely" related to study medication by the clinicians. Among African American participants, a higher percentage in the medication group reported genitourinary symptoms compared with the observation group (16.9% vs 10.8%, respectively; $P=.08$). Clinic staff classified 12 (6.0%) of 201 genitourinary adverse events in the medication group as serious and 5 (2.5%) of 204 in the observation group as serious ($P=.09$). None of the 12 serious genitourinary adverse events in the medication group were judged to be "probably" or "definitely" related to study medication.

No difference was found between randomization groups by race in the percentage of participants reporting 1 or more adverse events (interaction test for race and randomization group, $P=.58$) or in the percentage of participants reporting 1 or more serious adverse events (interaction test for race and randomization group, $P=.16$).

Among African American participants, no differences in Early Treatment Diabetic Retinopathy Study visual acuity were found between randomization groups throughout the study ($P>.05$ at all follow-up periods except at 66 months when visual acuity in the medication group averaged 1 letter lower than in the observation group; $P=.04$). There was a slight excess in the rate of cataract surgery for African American participants in the medication group (10 [5.1%] of 198) compared with the observation group (5 [2.5%] of 202) ($P=.17$).

RACE AS A PREDICTOR FOR THE DEVELOPMENT OF POAG

The sample for predictive analyses of POAG consisted of 148 randomized participants who developed POAG (50 Af-

frican American participants and 98 other participants) and 1471 participants who did not develop POAG (350 African American participants and 1121 other participants). Inclusion in the predictive analyses required the completion of at least 1 follow-up visit (17 of 1636 participants did not complete any follow-up visits). In the univariate predictive model, self-identified African American race was associated with a 71% increase in risk of developing POAG compared with other participants (hazard ratio, 1.71; 95% CI, 1.2-2.40). However, African American participants had larger baseline vertical and horizontal cup-disc ratios (0.45 ± 0.18 SD and 0.42 ± 0.17 SD, respectively) compared with other participants (0.37 ± 0.19 SD and 0.34 ± 0.18 SD, respectively) and thinner central corneal measurements ($554.9 \mu\text{m} \pm 38.7 \mu\text{m}$ SD) compared with other participants ($578.3 \mu\text{m} \pm 36.5 \mu\text{m}$ SD). In a multivariate Cox proportional hazards model that was stratified by randomization group and adjusted for these factors as well as age, sex, history of diabetes, systematic hypertension and heart disease, IOP, and pattern standard deviation, African American race was no longer statistically significantly associated with an increased risk of developing POAG (hazard ratio, 1.1; 95% CI, 0.76-1.66).

COMMENT

The OHTS is the first randomized trial on the prevention of POAG to enroll a large number of African American participants. This is important given the high prevalence of glaucoma and glaucoma-related blindness in African American individuals.^{6,11} At the time of the publication of the primary outcome article in 2002, there was a trend for treatment to be protective in African American participants, but the results did not attain statistical significance. With additional follow-up, the OHTS demonstrates that topical ocular hypotensive medication reduces the incidence of POAG in individuals of African derivation with ocular hypertension. This finding is consistent with the overall findings of the OHTS published previously.¹ Among African American participants in the OHTS, 17 (8.4%) of 203 in the medication group and 33 (16.1%) of 205 in the observation group developed POAG. The median follow-up among African American participants was 78 months in this article compared with 72 months in the previous article.¹ There was a slight trend for treatment to be less protective in African American participants than in other participants, but this difference was small and not statistically significant.

Despite substantial treatment benefit, the incidence of POAG was still significantly higher among African American participants compared with other participants in both the medication and observation groups. In the medication group, African American participants had twice the hazard of developing POAG compared with other participants, despite similar baseline and treated follow-up IOPs. In the observation group, African American participants had a 58% higher hazard of developing POAG, despite similar baseline and follow-up IOPs. The results of the OHTS are consistent with reports of higher prevalence of glaucoma and glaucoma-related blindness in African American individuals.^{6,11-14} Among the factors that may contribute to the increased prevalence of glaucoma and glau-

coma-related blindness in individuals of African origin are the following: genetic susceptibility to POAG,¹⁵⁻¹⁹; higher prevalence of comorbidity such as cardiovascular disease²⁰; earlier onset of POAG^{15-17,19}; later detection of POAG; and economic and social barriers to treatment.^{21,22} Data from the OHTS address some of these possible explanations. In the OHTS, African American participants had a higher prevalence of risk factors for POAG than other participants.²³ In addition, a higher proportion of African American participants compared with other participants reported a history of hypertension and diabetes, factors that have been associated with an increased risk of POAG by some investigators.^{18,24-29} In the OHTS, we did not find that diabetes and hypertension were associated with increased risk of POAG.²³ However, since information on systemic conditions was collected by self-report without confirmation by medical records or testing, it is difficult to determine the true extent that hypertension or diabetes may have contributed to the risk of developing glaucoma. Furthermore, individuals with moderate to severe diabetes were excluded from the trial because of the possible effect of retinopathy on visual fields. The OHTS does not directly address the questions of age of onset of POAG or delay in detection among African American individuals. Nor does the OHTS address the question of whether a lower IOP goal would have been more protective against POAG. In the OHTS, there was no charge for medication and copayments were minimized, which should diminish but not eliminate potential barriers to treatment. In the OHTS, the study protocol was standardized so that differences in management among participants were minimized. However, adherence to medical therapy must always be considered as a potential confounding factor.

It is not surprising that the increased risk of POAG associated with participants who self-identified as African American in the OHTS appears largely attributable to differences in specific clinical factors and not race itself. Since the completion of the mapping of the human genome, the validity of race as a construct for classifying individuals has been questioned.^{30,31} Moreover, data from the 2000 US Census demonstrates that self-identification of race is problematic, given that more than 800 000 individuals self-identified as both African American and white.³² The OHTS predictive analyses underscore the importance of measuring clinical risk factors, specifically corneal thickness and cup-disc ratio, in the management of individual patients rather than relying on the perceived race of that individual.

Because the safety of topical ocular hypotensive medications was systematically assessed on all participants, OHTS data allow us to compare the safety of medication in African American participants with other participants as well as safety in African American participants in the medication and observation groups. There were no differences by race in the overall rate of adverse events or the rate of serious adverse events in the OHTS. Among African American participants, there were no overall differences by randomization group in either the ocular or systemic self-reported complaints except changes in iris color, darkening of eyelids, and growth of eyelashes, which were more frequently reported with the use of the prostaglandin analogues in the medication group. Among African Ameri-

can participants, there was a trend for cataract surgery to be more frequently performed in the medication group than in the observation group. A similar trend was noted among other participants as well. These trends are consistent with the higher incidence of lens opacities reported in patients receiving topical ocular hypotensive medication in the Barbados Eye Study and the Early Manifest Glaucoma Trial and require further study.^{33,34} Among both African American participants and other participants, clinical staff classified a higher percentage of psychiatric events and genitourinary adverse events as serious in the medication group compared with the observation group. With the large number of statistical comparisons conducted and with classification of these data by unmasked clinic personnel, it is difficult to interpret these differences. However, these findings warrant continued evaluation.

In summary, topical ocular hypotensive therapy is effective in delaying or preventing the onset of glaucoma in African American individuals with ocular hypertension. However, the therapeutic benefit of medication does not imply that every patient of African descent with ocular hypertension requires treatment. Clinicians should consider factors such as corneal thickness, cup-disc ratio, IOP, age, general health, and life expectancy in determining who should be treated rather than relying on the race of the individual as an indication for treatment. Adverse effects should be monitored closely, and patients should be encouraged to adhere to their prescribed regimens. Finally, given the protective benefit of topical therapy among African American individuals, it is important to identify those at moderate to high risk of developing POAG so they can be evaluated for possible medical treatment.

Submitted for publication November 11, 2003; final revision received January 29, 2004; accepted February 3, 2004.

This study was supported by grants EY09307 and EY09341 from the National Eye Institute and the National Center on Minority Health and Health Disparities, National Institutes of Health, Bethesda, Md; Merck Research Laboratories, White House Station, NJ; and by an unrestricted grant from Research to Prevent Blindness, New York, NY.

Drugs were donated by the following pharmaceutical companies: Alcon Laboratories Inc, Fort Worth, Tex; Allergan Therapeutics Group, Irvine, Calif; Bausch & Lomb Pharmaceutical Division, Tampa, Fla; CIBA Vision Corporation, Duluth, Ga; Merck Research Laboratories, White House Station; Novartis Ophthalmics Inc, Duluth, Minn; Otsuka America Pharmaceutical Inc, Rockville, Md; and Pharmacia & Upjohn, Peapack, NY. Pachymeters were loaned to clinical centers by DGH Technology, Exton, Pa.

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

REFERENCES

- Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701-703.
- Becker B, Morton WR. Topical epinephrine in glaucoma suspects. *Am J Ophthalmol*. 1966;62:272-277.
- Shin DH, Kölker AE, Kass MA, Kaback MB, Becker B. Long-term epinephrine therapy of ocular hypertension. *Arch Ophthalmol*. 1976;94:2059-2060.
- Epstein DL, Krug JH Jr, Hertzmark E, Remis LL, Edelstein DJ. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. *Ophthalmology*. 1989;96:1460-1467.
- Kass MA, Gordon MO, Hoff MR, et al. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals. *Arch Ophthalmol*. 1989;107:1590-1598.
- Sommer A, Tielsch JM, Katz J, et al. Racial differences in the cause-specific prevalence of blindness in East Baltimore. *N Engl J Med*. 1991;325:1412-1417.
- Gordon MO, Kass MA, and the Ocular Hypertension Study Group. *Manual of Procedures*. Washington, DC: National Technical Information Service; 1997. Publication PB 97-148308NZ.
- Gordon MO, Kass MA, and the Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol*. 1999;117:573-583.
- Keltner JL, Johnson CA, Quigg JM, Cello KE, Kass MA, Gordon MO. Confirmation of visual field abnormalities in the Ocular Hypertension Treatment Study (OHTS). *Arch Ophthalmol*. 2000;118:1187-1194.
- Feuer WJ, Parrish RK II, Schiffman JC, et al. The Ocular Hypertension Treatment Study: reproducibility of cup/disk ratio measurements over time at an optic disc reading center. *Am J Ophthalmol*. 2002;133:19-28.
- Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open angle glaucoma: The Baltimore Eye Survey. *JAMA*. 1991;266:369-374.
- Hiller R, Kahn H. Blindness from glaucoma. *Am J Ophthalmol*. 1975;80:62-69.
- Grant W, Burke J. Why do some people go blind from glaucoma? *Ophthalmology*. 1982;89:991-998.
- Wilensky JT, Gandhi N, Pan T. Racial influences in open-angle glaucoma. *Ann Ophthalmol*. 1978;10:1398-1402.
- Mason RP, Kosoko O, Wilson MR, Cowan CL, Gear JC, Ross-Degnan D. National survey of the prevalence and risk factors of glaucoma in St Lucia, West Indies. I: prevalence findings. *Ophthalmology*. 1989;96:1363-1368.
- Wilson MR. Progression of visual field loss in untreated glaucoma patients and suspects in St Lucia, West Indies. *Trans Am Ophthalmol Soc*. 2002;100:365-410.
- Leske MC, Connell AMS, Schachat AP, Hyman L, for the Barbados Eye Study Group. Prevalence of open angle glaucoma. *Arch Ophthalmol*. 1994;112:821-829.
- Leske MC, Wu S-Y, Nemesure B, Hennis A, for the Barbados Eye Study Group. Incident open-angle glaucoma and blood pressure. *Arch Ophthalmol*. 2002;120:954-959.
- Buhrmann RR, Quigley HA, Barron Y, West SK, Oliva MS, Mmbaga BB. Prevalence of glaucoma in a rural East African population. *Invest Ophthalmol Vis Sci*. 2000;41:40-48.
- National Center for Health Statistics: 1990 National Health Interview Survey [on CD-ROM]. Washington, DC: National Center for Health Statistics; 1993. Series 10, 4 Sets, Version 1.21.
- Glynn RJ, Gurwitz JH, Bohn RL, Monane M, Chodnovskiy I, Avorn J. Old age and race as determinants of initiation of glaucoma therapy. *Am J Epidemiol*. 1993;138:395-406.
- Javitt JC, McBean M, Nicholson GA, Babish JD, Warren JL, Krakauer H. Undertreatment of glaucoma among black Americans. *N Engl J Med*. 1991;325:1418-1422.
- Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:714-720.
- Dielemans I, de Jong PTVM, Stolk R, Vingerling JR, Grobbee DE, Hofman A. Primary open-angle glaucoma, intraocular pressure, and diabetes mellitus in the general elderly population. *Ophthalmology*. 1996;103:1271-1275.
- Mitchell P, Smith W, Chey T, Healey PR. Open-angle glaucoma and diabetes: the Blue Mountains Eye Study, Australia. *Ophthalmology*. 1997;104:712-718.
- Klein BEK, Klein R, Jensen SC. Open-angle glaucoma and older-onset diabetes: the Beaver Dam Eye Study. *Ophthalmology*. 1994;101:1173-1177.
- AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS). *Am J Ophthalmol*. 2002;134:499-512.
- Tielsch JM, Katz J, Quigley HA, Javitt JC, Sommer A. Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore Eye Survey. *Ophthalmology*. 1995;102:48-53.
- Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure and primary open-angle glaucoma: a population-based assessment. *Arch Ophthalmol*. 1995;113:216-221.
- Wilson MR. The use of "race" for classification in medicine: is it valid? *J Glaucoma*. 2003;12:293-294.
- Sommer A. Epidemiology, ethnicity, race and risk. *Arch Ophthalmol*. 2003;121:1194.
- Schwartz RS. Racial profiling in medical research. *N Engl J Med*. 2001;344:1392-1393.
- Leske MC, Wu S-Y, Nemesure B, Hennis A, for the Barbados Study Group. Risk factors for incident nuclear opacities. *Ophthalmology*. 2002;109:1303-1308.
- Heijl A, Leske C, Bengtsson B, Hyman L, Bengtsson B, Hussein M. Reduction of intraocular pressure and glaucoma progression. *Arch Ophthalmol*. 2002;120:1268-1279.