The Ocular Hypertension Treatment Study

Design and Baseline Description of the Participants

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Background: The Ocular Hypertension Treatment Study (OHTS) seeks to evaluate the safety and efficacy of topical ocular hypotensive medication in preventing or delaying the onset of visual field loss and/or optic nerve damage in subjects with ocular hypertension at moderate risk for developing primary open angle glaucoma.

Objective: To describe the study protocol, the questions to be answered, and the baseline characteristics of the subjects.

Design: Multicenter randomized clinical trial with 2 groups: topical ocular hypotensive medication and close observation.

Setting: Subjects were enrolled and evaluated at 22 participating clinical centers. Visual fields and stereoscopic optic disc photographs were read in masked fashion.

Methods: We determined eligibility from a comprehensive eye examination, medical and ocular history, visual field testing, and stereoscopic optic disc photography.

Results: We describe the baseline characteristics of 1637 subjects randomized between February 28, 1994, and October 31, 1996. The mean age was 55 years; 56.9% of the subjects were women; and 25% were African American. The baseline intraocular pressure was 24.9 ± 2.7 mm Hg (mean ± SD). Systemic diseases and conditions reported by subjects included previous use of medication for ocular hypertension, 37%; systemic hypertension, 38%; cardiovascular disease, 6%; diabetes mellitus, 12%; and family history of glaucoma, 44%. The mean horizontal cup-disc ratio by contour estimated from stereophotography was 0.36 ± 0.18. Qualifying Humphrey 30-2 visual fields had to be normal and reliable for entry into the study. Health-related quality of life (36-item short form health survey) scores in the OHTS sample were better than the age- and sex-matched population norms. African American subjects had larger baseline cup-disc ratios and higher reported rates of elevated blood pressure and diabetes than the rest of the subjects.

Conclusions: The intraocular pressure among enrolled subjects was sufficiently high to provide an adequate test of the potential benefit of ocular hypotensive medication in preventing or delaying glaucomatous damage. The large number of African American subjects enrolled should provide a good estimate of the African American response to topical medication.

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In all surveys, glaucoma is among the leading causes of blindness in the United States and other industrialized countries.[1-3] By the year 2000, it is estimated that 2.47 million people in the United States will have glaucoma and that more than 130 540 persons will be legally blind from the disease.[4] Many more individuals will be visually handicapped by this disease.[5,6] Epidemiological studies have found that fewer than 50% of cases of visual field loss due to glaucoma have been diagnosed.[7-9] It is now clear that glaucoma is the leading cause of blindness in African Americans.[2,10,11] 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 whites, ranging from 1.2% in African Americans aged 40 through 49 years to 11.3% in those 80 years or older.[12] The Barbados Eye Study in a Carribean population of African origin confirmed the high prevalence of glaucoma in such populations.[7] The 4-year incidence rate of POAG in this population was 2.2% overall and 5.8% among persons with ocular hypertension,[13] which is more than 5 times higher than the estimated incidence in a predominantly white population.[14]

It is estimated that 3 to 6 million people in the United States, including 4% to 7% of the population older than age 40 years, have elevated intraocular pressure (IOP) without detectable glaucoma-

tous damage using current clinical tests.[15] Thus, these individuals are at an increased risk for developing POAG.[13,16,17] Up to now there has been no consensus on how to manage this large group of people, who are referred to as ocular hypertensives or glaucoma suspects. Quigley et al[18,19] reported that 12% to 63% of optic nerve fibers can be lost before glaucomatous visual field defects are detected by routine kinetic perimetry. The findings of Quigley et al, the high prevalence of glaucoma, and the potentially serious consequences of this disease suggest the need for widespread glaucoma screening and early treatment. This aggressive approach is buttressed by evidence from randomized clinical studies[20-24] as well as by the almost universal clinical impression that treatment initiated early in the course of glaucoma is far more effective in preventing progressive visual loss than is treatment initiated late in the course of the disease. However, the approach of widespread glaucoma screening and early treatment has been challenged by investigators who point out that there is insufficient scientific information to support a major health initiative.[23] One of the prerequisites for any screening program is that there must be an effective treatment for the disease. Surprisingly, there is no consensus on the efficacy of medical treatment in preventing or delaying the onset of damage due to POAG.[25-27]

Therefore, we designed the Ocular Hypertension Treatment Study (OHTS) to evaluate the safety and efficacy of topical ocular hypotensive medication in preventing or delaying the onset of visual field loss and/or optic nerve damage in subjects with ocular hypertension at moderate risk for developing POAG. The secondary aim of OHTS is to identify risk factors that predict which subjects with ocular hypertension are most likely to develop visual field loss and/or optic nerve damage due to POAG. Potential risk factors include age, cup-disc ratio, IOP, myopia, systemic vascular disease, family history of glaucoma, and race.

This article describes the study protocol and baseline characteristics of study participants and serves as a reference for future publications of the OHTS.

DESIGN AND METHODS

STUDY SYNOPSIS

The Ocular Hypertension Treatment Study is a multicenter randomized controlled clinical trial. See the box on page 581 for a description of the study organization and a list of participating clinics. A data and safety monitoring committee monitors the ethical conduct of the study and the accumulating data for evidence of adverse and beneficial treatment effects.

The study protocol is described in detail in the study manual[28] and is summarized in **Table 1**. Eligibility was determined by a comprehensive eye examination, medical and ocular history, masked evaluation of Humphrey 30-2 visual fields by the Visual Field Reading Center, and masked evaluation of stereoscopic optic disc photographs by the Optic Disc Reading Center. Following a discussion of the study, subjects were requested to sign an informed consent form. Eligibility and exclusion criteria are summarized in **Table 2**. Eligible subjects were randomized at their baseline/randomization visit over the telephone by the Coordinating Center to either the close observation group or medication group. Subjects randomized to the medication group began a stepped medical regimen to reduce IOP by at least 20% from the average of the IOPs measured at the qualifying and baseline visits, to 24 mm Hg or less. Follow-up visits are at 6-month intervals for a minimum of 5 years or until a closure date determined by the Data and Safety Monitoring Committee (**Table 3**). Visual field testing is performed every 6 months and optic disc photography is performed every 12 months.

The primary study end point is the development of either a reproducible visual field abnormality or reproducible progressive optic disc cupping due to POAG. The presence of a visual field abnormality is determined by masked readers at the Visual Field Reading Center, and the presence of optic disc progression is determined by masked, certified readers at the Optic Disc Reading Center. When an abnormality is detected by the reading center, the subject is recalled for retesting to confirm the abnormality. When an abnormality is confirmed on the second test, the Endpoint Committee reviews the subject's ocular and medical history in a masked fashion to determine if the abnormality is attributable to POAG. Independent, masked determination of a reproducible visual field abnormality and/or reproducible progressive optic disc cupping and attribution of the abnormality to POAG is required, as neither the subject nor the clinician is masked as to randomization assignment. Subjects with a reproducible abnormality due to POAG continue the same follow-up visit schedule and receive the same tests and measures. The treatment course for this group of subjects is at the discretion of the treating clinician.

ELIGIBILITY ASSESSMENT

Intraocular Pressure

To reduce potential bias, IOP is measured by 2 certified study personnel (an operator and a recorder) using a calibrated Goldmann applanation tonometer. The operator initially sets the dial at 10 mm Hg, then looks through the slitlamp and adjusts the dial while the recorder reads and records the results. The procedure is repeated on the same eye. If the 2 readings differ by 2 mm Hg or less, the average of the 2 readings serves as the IOP measurement. If the 2 readings differ by more than 2 mm Hg, then a third reading is performed and the median reading serves as the IOP measurement. This IOP measurement protocol was adapted from the Advanced Glaucoma Intervention Study[29] and the Glaucoma Laser Trial.[30]

The OHTS eligibility criteria were intended to select ocular hypertensive subjects at moderate risk for developing glaucoma because this group presents the greatest clinical uncertainty to the clinician. The qualifying IOP must be at least 24 mm Hg but less than 32 mm Hg in at least 1 eye calculated from 2 separate consecutive measurements taken at least 2 hours but not more than 12 weeks apart. The fellow eye must have an IOP of at least 21 mm Hg but less than 32 mm Hg on 2 separate IOP measurements. All IOP readings for eligibility as-

Table 1. Design Synopsis

Type of trial	Treatment assignment
Therapeutic	Random
Centers	Patient is randomization and treatment unit
22 Clinical centers	Stratified by clinic and race
Chairman's office	Bias control
Coordinating center	Masked evaluation of visual fields
Optic disc photography reading center	Masked evaluation of optic disc stereophotographs
Visual field reading center	Masked ascertainment of cause of abnormality by Endpoint Committee
Treatments	Patient recruitment
Close observation	1500 subjects (calculated)
Topical ocular hypotensive medication according to a stepped medical regimen	1637 subjects (achieved)
Outcome measures	Follow-up
Reproducible visual field abnormality due to primary open angle glaucoma	Minimum 5 years (planned)
Reproducible optic disc cupping due to primary open angle glaucoma	

sessment were performed after appropriate washout of the following prestudy topical ocular medications: parasympathomimetic agents (1 week), β-adrenergic blockers (4 weeks), dipivefrin and epinephrine products (4 weeks), α_2-agonists (4 weeks), and carbonic anhydrase inhibitors (2 weeks).

For purposes of analyses, the baseline IOP of each eye is the IOP measurement at the baseline/randomization visit.

Humphrey 30-2 Visual Fields

Qualifying Humphrey 30-2 visual fields must be normal and reliable in both eyes as determined by the Visual Field Reading Center prior to randomization. A reliable visual field is defined as less than 33% false positives, false negatives, and fixation losses. A normal field is determined by clinical review at the Visual Field Reading Center and by STATPAC 2 criteria for global indices within the 95% age-specific population norms and the glaucoma hemifield test within the 97% age-specific population norm. Two of a maximum of 3 visual fields for each eye must meet all entry criteria. The visual field testing sessions during qualifying assessment must be separated by a minimum of 1 hour and a maximum of 12 weeks.

Stereoscopic Optic Disc Photographs

Stereoscopic optic disc photographs must be judged normal by 2 independent, masked, certified readers at the Optic Disc Reading Center prior to randomization. Subjects were excluded from the study if the photographs document an optic disc hemorrhage, a localized notch or thinning of the rim, a diffuse or localized area of pallor, or a difference in the cup-disc ratios between the 2 eyes greater than 0.2 disc diameters. Subjects were also excluded if they had optic disc drusen, pits, colobomas, atrophy, or other severe anomalies.

TREATMENT ASSIGNMENT

Half of the subjects were randomized to the close observation group and half were randomized to the medication group. Randomization was stratified by clinic and race so that in any given clinic there was an approximately equal number of African Americans allocated to the close observation and medication groups irrespective of the actual number enrolled. The randomization unit is the subject. Randomization was completed by the Coordinating Center over the telephone during the subject's randomization visit. The date of randomization serves as the official date of entry into the study.

Table 2. Major Inclusion and Exclusion Criteria*

Inclusion Criteria
IOP in at least 1 eye of each patient ≥24 mm Hg and ≤32 mm Hg
IOP in fellow eye ≥21 mm Hg and ≤32 mm Hg
Age 40 to 80 years, inclusive
Normal and reliable Humphrey 30-2 visual fields for both eyes as determined by the Visual Field Reading Center
Normal optic discs in both eyes on clinical examination and on stereoscopic photographs as determined by the Optic Disc Reading Center
Informed consent
Exclusion Criteria
Best-corrected visual acuity worse than 20/40 in either eye
Previous intraocular surgery, except for uncomplicated extracapsular cataract extraction with posterior chamber–intraocular lens implant and no escape of vitreous to the anterior chamber, strabismus, cosmetic eyelid surgery, and radial keratotomy
A life-threatening or debilitating disease
Secondary causes of elevated IOP, including ocular and systemic corticosteroid use
Angle closure glaucoma or anatomically narrow angles—75% of the circumference of the angle must be grade 2 or more by Shaffer criteria
Other diseases that cause visual field loss or optic disc abnormalities
Difference in cup-disc ratios (horizontal by contour) of the 2 eyes >0.2
Background diabetic retinopathy, defined as at least 1 microaneurysm seen on direct ophthalmoscopy with dilated pupil. Retinal hemorrhage is **not an exclusion** unless associated with background or proliferative diabetic retinopathy
Inability to visualize or photograph the optic discs
Pregnant or nursing women as determined by patient self-report and testing

**IOP indicates intraocular pressure.*

TESTS AND MEASURES

Randomized subjects complete regularly scheduled follow-up visits at 6-month intervals. Semiannual visits (months 6,18, 30, 42, 54, etc) include a patient-completed symptom checklist, ocular and medical his-

Table 3. Measurement and Examination Procedures for Scheduled Visits*

Visit	Quality of Life	Symptom Checklist	Medical History	Refraction	Visual Acuity	Visual Field	Eye Examination	IOP	Ophthalmoscopy	Gonioscopy	Dilated Fundus	Stereoscopic Optic Disc Photography
Qualifying assessment			X	X	X	X	X	X	X	X	X	X
Baseline/randomization	X	X						X				
IOP confirmation		X					X	X	X			
Follow-up												
Semiannual (6 months, 18 months, etc)		X	X	X	X	X	X	X	X			
Annual (12 months, 24 months, etc)	X	X	X		X	X	X	X	X		X	X

*IOP indicates intraocular pressure.

tory, refraction, best-corrected visual acuity, Humphrey 30-2 visual fields, slitlamp examination, direct ophthalmoscopy, and IOP measurement. Annual visits (months 12, 24, 36, 48, 60, etc) include most of the measures at semiannual visits plus completion of the 36-item short form health survey (SF-36),[31] dilated fundus examination, and stereoscopic optic disc photographs. A listing of regularly scheduled tests and measures is given in Table 3. Pachymetry is performed once during follow-up and repeated only if the patient has refractive or intraocular surgery.

TREATMENT REGIMEN

Subjects randomized to the medication group began the stepped medical regimen with a therapeutic trial in the eye with the higher IOP. Subjects returned in 4 ± 2 weeks for evaluation of therapeutic response. If drug therapy was ineffective or minimally effective (IOP reduction <10% from the average of the qualifying and baseline IOP), it was stopped and another drug was substituted. If drug therapy was moderately effective (IOP reduction 10% to 20% from the average of the qualifying and baseline IOP), the clinician had the choice of substituting another drug or adding a drug. The drug regimen includes all commercially available topical ocular hypotensive medications and reflects standard clinical practice in the United States. As new drugs become commercially available in the United States, they are added to the treatment options. All study drugs are provided free of charge to the subjects and are distributed to participating clinics from the study's central pharmacy.

TREATMENT GOAL

The treatment goals for subjects randomized to the medication group are an IOP of 24 mm Hg or less and a 20% reduction in IOP from the average of the qualifying and baseline IOP. The 20% reduction is not necessary if the IOP is 18 mm Hg or less. Topical medical therapy is changed and/or added until both of these goals are met or until the subject is receiving maximum tolerated topical medical therapy. Subjects in the medication group who do not meet these goals despite maximum tolerated topical medical therapy continue to be evaluated in the trial and continue following the same schedule of tests and measurements. We believe these treatment goals constitute an adequate test of the primary hypothesis and reflect current clinical practice.

CONFIRMATION OF VISUAL FIELD ABNORMALITY

A technically acceptable visual field is considered abnormal if $P<.05$ for the corrected pattern SD or if the results of the glaucoma hemifield test are outside normal limits ($P<.01$). The study originally defined 2 consecutive abnormal visual fields as confirmation of visual field abnormality; however, a high percentage of abnormal visual fields on the first test were found to be normal on retesting. Accordingly, a more stringent criterion for the confirmation of visual field abnormality was adopted effective January 1, 1998, at the recommendation of the Data and Safety Monitoring Committee, Steering Committee, and Full Investigative Group. The protocol was changed so that confirmation of a visual field abnormality requires 3 consecutive visual field tests. Thus, a patient with an abnormal visual field is tested at the next regularly scheduled follow-up visit in 6 months. If the Visual Field Reading Center considers the second visual field abnormal, a third visual field test is scheduled for 1 day to 8 weeks after the second visual field test.

When such a sequence of abnormal follow-up visual fields is received, the visual fields are evaluated by 2 independent senior readers who are masked as to clinic and randomization status. They decide whether the visual field abnormality is of the same character and in the same location on all 3 visual fields. If the visual field abnormality is confirmed, the Visual Field Reading Center prepares a brief narrative description of the abnormality and sends all visual fields for the affected eye to the Coordinating Center for review by the Endpoint Committee.

CONFIRMATION OF OPTIC DISC PROGRESSION

We defined optic disc progression as generalized or localized thinning of the optic disc rim compared with baseline as judged by 1 or more of the following characteristics: change in the position of the vessels greater than expected from a shift in the position of the eye, development of a notch, development of an acquired pita, thinning of the rim, or development of localized or diffuse

pallor. Disc hemorrhage, nerve fiber layer dropout, and change in the depth of the cup are not considered optic disc end points.

The follow-up optic disc photographs and baseline photographs are compared by 2 independent, certified readers at the Optic Disc Reading Center who are masked as to the order of the photographs, randomization assignment of the patient, clinic, and previous optic disc assessments. If one or both of the initial readers detect a difference between the 2 sets of photographs and identify their correct order, the photographs are reviewed in a similar masked fashion by a senior reader at the Optic Disc Reading Center. If the senior reader's assessment agrees with that of the initial reader or readers, the Optic Disc Reading Center requests the clinic to recall the patient for a second set of photographs for the affected eye within 4 ± 2 weeks. The second set of photographs is compared with baseline photographs in the same manner as the initial review. If a difference is confirmed and correctly sequenced, the senior reader reviews the photographs in a masked fashion and makes the final decision as to the occurrence of progressive damage. If the second set of photographs is judged to confirm the occurrence of progressive optic disc cupping, the Optic Disc Reading Center prepares a brief narrative description of the findings and sends all optic disc photographs of the affected eye to the Coordinating Center for review by the Endpoint Committee.

DETERMINATION OF POAG END POINT

When visual fields and/or optic disc photographs confirm the presence of an abnormality, the appropriate reading center completes a report describing the abnormality. The Endpoint Committee, which is masked as to the randomization assignment of the patient and the end point status of the fellow eye, reviews the reading center report, the patient's medical and ocular history from the study forms, and the visual fields and stereoscopic optic disc photographs of the affected eye to determine if the abnormality is attributable to POAG.

On determination of a POAG end point by the Endpoint Committee, either visual field or optic disc progression, a patient randomized to close observation begins the stepped medical regimen and continues scheduled follow-up tests and measures until study closeout. Similarly, a patient randomized to the medication group continues scheduled follow-up tests and measures until study closeout. In such subjects, additional medications are added as necessary, including systemic carbonic anhydrase inhibitors. In some cases, clinicians may advise laser trabeculoplasty or filtering surgery.

ADVERSE EVENTS AND PATIENT SAFETY

At 6-month intervals, a medical and ocular history is taken and subjects complete a "symptom checklist" for possible ocular and systemic side effects of medication. At 12-month intervals, subjects complete a health-related quality of life survey (SF-36). Hospital discharge summaries for inpatient hospitalizations are retrieved.

STATISTICAL ANALYSIS

The necessary sample size was estimated to be 1500 total subjects (750 subjects per group) on the basis of the following assumptions: a 40% reduction in the 5-year incidence of POAG, from 15% in the close observation group to 9% in the medication group; 2-sided α error of .05 and power of .90; a comparison of 2 proportions using an arcsine transformation; 15% of subjects unavailable for follow-up; and 10% crossover between randomization groups. Because the sample size calculations assume a comparison at a fixed time, the statistical power could be slightly higher in analyses that take failure time into consideration. The sample size estimates were based on studies that did not use strategies to enhance adherence to the medication regimen. Thus, estimates of the efficacy of treatment do not assume optimization of adherence to the medication regimen. Recruitment was extended 6 months to ensure adequate representation of African American participants. The primary analysis is an intent-to-treat analysis in which study outcomes are analyzed by randomization assignment.

ANCILLARY STUDIES

The OHTS provides a unique opportunity to conduct ancillary studies on the early diagnosis of glaucoma damage and the effect of medical treatment on the eye. These ancillary studies are described briefly below. Their data are monitored by the OHTS Data and Safety Monitoring Committee. Clinical center investigators are masked to the results of ancillary study measures and have agreed not to use ancillary study data to make treatment decisions for OHTS subjects.

CONFOCAL SCANNING LASER OPHTHALMOSCOPY OF THE OPTIC DISC

The purpose of the confocal scanning laser ophthalmoscopy ancillary study is to determine the effectiveness of the laser in detecting the presence and progression of glaucomatous optic disc damage and to determine whether optic disc measurement with this instrument is an accurate predictor of visual field loss. Confocal scanning laser ophthalmoscopy using the Heidelberg Retina Tomograph (Heidelberg Engineering, Heidelberg, Germany), is performed at the annual OHTS examinations to coincide with the dilated examination and stereoscopic optic disc photography. The organization of the confocal scanning laser ophthalmoscopy ancillary study consists of a reading center and 7 participating OHTS clinical centers. As of June 30, 1998, 453 subjects were enrolled in this ancillary study.

SHORT WAVELENGTH AUTOMATED PERIMETRY

The purpose of the short wavelength automated perimetry ancillary study is to determine if this visual field test, which measures the sensitivity of short wavelength (blue) sensitive visual mechanisms, is more responsive to early functional losses in glaucoma than conventional white-on-white automated perimetry. Short wavelength perimetry is performed at the OHTS 6-month follow-up visits on

Table 4. Distribution of Race

Race	Subjects, No. (%)
American Indian or Alaskan Native	4 (0.2)
Asian or Pacific Islander	14 (0.9)
African American	409 (25.0)
Hispanic	59 (3.6)
White	1138 (69.5)
Other or unknown	13 (0.8)
Total	**1637 (100.0)**

1 eye at each visit after the completion of conventional perimetry. The fellow eye is then tested at the next visit. The organization of the shortwave length automated perimetry ancillary study consists of a reading center and 7 participating OHTS clinical centers. As of September 9, 1998, 334 subjects were enrolled in this ancillary study.

CORNEAL ENDOTHELIAL CELL MORPHOLOGY

The purpose of the corneal endothelial cell morphology ancillary study is to determine whether topical ocular hypotensive medications (or the preservatives in the solutions) affect corneal endothelial morphologic characteristics. Central endothelial photographs of both eyes are taken with a wide-field specular microscope at the OHTS baseline examination and at annual follow-up examinations to coincide with stereoscopic optic disc photography. At the same visit, central corneal thickness is measured ultrasonically. The organization of the corneal endothelial cell morphology ancillary study consists of a reading center and 1 participating OHTS clinical center. Fifty-four subjects were enrolled in this ancillary study.

RESULTS

Between February 28, 1994, and October 31, 1996, 3328 subjects were considered for study participation. Of these, 108 subjects withdrew prior to eligibility assessment, 1371 subjects did not meet the eligibility criteria, 210 subjects signed a "Decline to Participate" form or withdrew prior to randomization, and 2 eligible subjects died prior to randomization. Of the 1637 randomized subjects, 818 were assigned to receive topical ocular hypotensive medication and 819 to close observation. The interval from completion of qualifying assessment to randomization was 54 ± 32 days (mean ± SD).

By self-attribution, 69% of the subjects were "white, not of Hispanic origin," 25% were "black, not of Hispanic origin," 3.6% were "Hispanic," and the balance were "American Indian or Alaskan Native," "Asian or Pacific Islander," or "other" (**Table 4**). **Table 5** through **Table 8** present demographic and clinical data for the overall sample and by race, grouped by African American and other. Equivalence of demographic and clinical baseline characteristics for the African American and other groups was tested by multivariate models using SAS software (SAS Inc, Cary, NC).[32] Racial equivalence of categorical variables was analyzed by logistic regression models, and continuous variables were analyzed by a generalized least squares model. Multivariate models were adjusted for potential confounders, such as age, sex, marital status, education, history of diabetes, and history of high blood pressure, as specified in footnotes to the tables.

Table 5. Demographic Characteristics of Randomized Subjects

	African American, No. (%)	Other, No. (%)	Overall, No. (%)
Sex*			
Male	140 (34)	565 (46)	705 (43)
Female	269 (66)	663 (54)	932 (57)
Age, y*			
Mean ± SD	54.5 ± 9.0	55.7 ± 9.7	55.4 ± 9.6
40 to <50	137 (34)	385 (31)	522 (32)
50 to <60	143 (35)	400 (33)	543 (33)
60 to <70	107 (26)	318 (26)	425 (26)
70 to 80	22 (5)	125 (10)	145 (9)
Marital status*			
Single	65 (16)	146 (12)	211 (13)
Married	198 (48)	857 (70)	1055 (64)
Divorced/separated	102 (25)	158 (13)	260 (16)
Widowed	44 (11)	67 (6)	111 (7)
Education*			
Grade 6 or less	4 (1)	12 (1)	16 (1)
Grade 7-11	53 (13)	44 (4)	97 (6)
Grade 12/GED†	141 (35)	287 (23)	428 (26)
1+ years of college	171 (42)	584 (48)	755 (46)
1+ years of graduate school	40 (10)	300 (24)	340 (21)

**Significant difference between African American and other (P<.05).*
†GED indicates graduate equivalency degree.

The age of the overall sample at entry was 55.4 ± 9.6 years (mean ± SD). African American subjects were slightly younger than other subjects (54.5 ± 9.0 vs 55.7 ± 9.7 years) (Table 5). A higher percentage of African American subjects were female and divorced, separated, or widowed. Educational attainment was high in the overall sample. Fifty-two percent of African American and 72% of other subjects reported completing 1 or more years of college.

Table 6 reports baseline clinical characteristics for African Americans, others, and the overall sample. Baseline measurements that were used to establish eligibility are noted because their range is truncated in the sample. Eye-specific measures are reported separately for right and left eyes as well as averaged for both eyes for the entire sample. The official baseline IOP for analytic purposes is the mean baseline IOP measurement, which was taken at the baseline/randomization examination after eligibility had been established in the qualifying assessment period. The baseline IOP measurement, which represents 2 or 3 IOP readings taken during the baseline/randomization examination, was 24.9 ± 2.7 mm Hg (average of right and left eyes) for the entire sample, 25.1 ± 2.8 mm Hg for African Americans, and 24.9 ± 2.6 mm Hg for others (**Figure 1**). Sixty percent of all subjects had baseline IOP measurements greater than 24 mm Hg in both eyes. The mean cup-disc ratio (horizontal by contour; average of values for the right and left eyes) as determined by the Optic Disc Reading Center was substantially greater for African Americans (0.42 ± 0.17) than for others (0.34 ± 0.19, $P<.001$) (**Figure 2**). The Humphrey Visual Field thresholds of the 2 qualifying visual fields were averaged. While neither the pattern SD nor the corrected pattern SD of the qualifying visual fields dif-

Table 6. Baseline Clinical Characteristics

	African American		Other		
	Right Eye	Left Eye	Right Eye	Left Eye	Overall*
Intraocular pressure, mm Hg†‡	25.2 ± 3.0	25.0 ± 3.1	25.0 ± 3.0	24.7 ± 2.9	24.9 ± 2.7
Refractive error, D†	−0.35 ± 2.01	−0.32 ± 1.99	−0.72 ± 2.46	−0.74 ± 2.49	−0.63 ± 2.33
Cup-disc ratio†‡	0.42 ± 0.18	0.42 ± 0.17	0.34 ± 0.19	0.35 ± 0.19	0.36 ± 0.18
Visual field mean deviation, dB†‡§	0.06 ± 1.11	0.06 ± 1.14	0.29 ± 1.07	0.31 ± 1.13	0.24 ± 1.05
Visual field pattern SD, dB†‡	1.93 ± 0.25	1.91 ± 0.24	1.92 ± 0.24	1.90 ± 0.26	1.91 ± 0.21
Visual field corrected pattern SD, dB†‡	1.06 ± 0.46	1.10 ± 0.45	1.14 ± 0.45	1.12 ± 0.46	1.12 ± 0.35

	African American	Other	Overall
Previous topical ocular hypotensive medication, %	38	37	37
Family history of glaucoma, %	43	44	44
High blood pressure, %§‖	56	32	38
Heart disease, %	9	5	6
Diabetes, %§¶	19	10	12

**For eye-specific variables the overall value represents the average of the mean for the right and left eyes.*
†Values are expressed as mean ± SD.
‡Eligibility criterion.
§Significant difference between African American and other (P<.05).
‖History of high blood pressure was tested controlling for age, sex, marital status, education, and history of diabetes.
¶History of diabetes was tested controlling for age, sex, marital status, education, and history of high blood pressure.

Table 7. Subjects Reporting Ocular Symptoms Within 4 Weeks Prior to Baseline Visit

Ocular Symptom	African American, %	Other, %	Overall, %
Blurry/dim vision*	33	21	24
Burning, smarting, stinging	24	19	21
Dryness	19	23	22
Halos around lights*	9	12	11
Hard to see in dark	21	19	19
Hard to see in daylight	8	6	6
Itching*	41	30	33
Something in eye*	33	19	22
Soreness, tiredness*	24	26	25
Tearing	40	26	29

**Significant difference between African American and other (P<.05), tested controlling for age, sex, marital status, education, history of diabetes, and history of high blood pressure.*

Table 8. Subjects Reporting Systemic Symptoms Within 4 Weeks Prior to Baseline Visit

Systemic Symptom	African American, %	Other, %	Overall, %
Difficulty sleeping*	49	54	53
Upset stomach	30	30	30
Diarrhea	18	20	20
Headache	52	53	53
Headache above eyes	43	38	39
Breathing difficult	20	18	19
Shortness of breath	28	24	25
Irregular heart beat	19	18	18
Trouble concentrating	33	28	29
Feeling depressed	39	36	36
Less interest in sex*	36	28	30
Food tastes metallic*	9	4	6
Numbness in limbs	37	29	31
Weakness	23	20	20

**Significant difference between African American and other (P<.05), tested controlling for age, sex, marital status, education, history of diabetes, and history of high blood pressure.*

fered by race, the mean deviation (average of values for the right and left eyes) for African American subjects (0.06 ± 1.05) was significantly different from that for other subjects (0.30 ± 1.04, $P<.005$).

Overall, 44% of the subjects reported a family history of glaucoma and 37% reported previous use of topical ocular hypotensive medication prior to study enrollment. Neither of these factors differed by race. Substantially more African American subjects than other subjects reported diabetes and high blood pressure (Table 6). African Americans differed from others in this sample with regard to age, sex, marital status, education, history of diabetes, and high blood pressure; therefore, statistical analyses to estimate possible racial differences were adjusted for these factors (Table 6).

A high percentage of all subjects reported 1 or more ocular symptoms (Table 7) or systemic symptoms (Table 8) during the 4-week period prior to randomization. Because subjects with a history of ocular hypotensive medications may report residual ocular symptoms even after appropriate washout, we compared ocular symptoms reported by subjects with vs without a history of ocular hypotensive medication. Seventy percent of the subjects with a history of medication usage reported ocular symptoms in at least 1 eye, compared with 65% of subjects with no history. African American subjects reported a higher frequency of some ocular symptoms (blurry vision, itching, foreign body sensation, and tearing). There were few differences between African Americans and others in the systemic symptoms reported.

Table 9 gives the SF-36 profile for African American and other subjects.[28] The SF-36 profile for the entire OHTS sample was better than age- and sex-matched population-based norms ($P<.001$ for all subscales). The SF-36 profile for African American and other subjects did

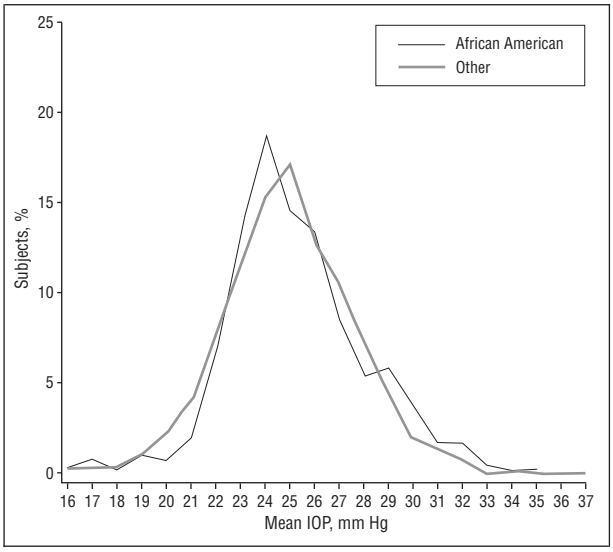

Figure 1. *Distribution of baseline IOP by race. The IOPs of the right and left eyes of subjects are averaged.*

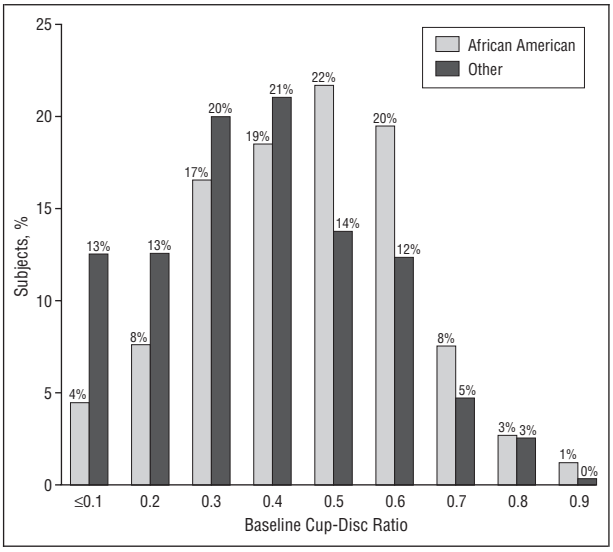

Figure 2. *Distribution of baseline cup-disc ratio (horizontal by contour) by race. The cup-disc ratios of the right and left eyes are averaged.*

Table 9. Mean Baseline SF-36 Scale Scores*

	African American		Other		
	Mean ± SD	Adjusted Mean†	Mean ± SD	Adjusted Mean†	Overall, Mean ± SD
Physical function‡	81 ± 24	84	87 ± 18	86	86 ± 20
Role—physical	84 ± 32	86	89 ± 27	88	88 ± 28
Bodily pain	77 ± 23	80	79 ± 21	78	79 ± 22
General health	74 ± 20	77	78 ± 18	77	77 ± 18
Vitality	68 ± 18	70	70 ± 17	69	69 ± 18
Social functioning	88 ± 19	90	92 ± 17	91	91 ± 17
Role—emotional	86 ± 29	88	91 ± 23	90	90 ± 25
Mental health	80 ± 16	82	81 ± 15	80	81 ± 15

**SF-36 indicates 36-item short form health survey, with scores ranging from 0 (worst) to 100 (best).*

†Least squares means, calculated using the observed marginals option of the general linear models procedure of SAS software (SAS Inc, Cary, NC). Means were adjusted for age, sex, marital status, education, history of diabetes, and history of high blood pressure.

‡Significant difference between African American and other (P<.05), tested controlling for age, sex, marital status, education, history of diabetes, and history of high blood pressure.

not differ after adjustment for demographic factors and systemic comorbid conditions, except for the physical function scale score, which was lower for African Americans than for others ($P<.03$).

To evaluate the equivalency of the medication and close observation groups achieved by randomization, we compared baseline values for the following prognostic factors: age, sex, race, IOP, visual field indices, cup-disc ratio, myopia (spherical equivalent), history of hypertension and diabetes, and family history of glaucoma. The 2 groups were compared using *t* tests, Wilcoxon rank sum tests, and χ^2 tests. No statistically significant differences ($P<.05$) were found between the medication and close observation groups for these prognostic factors.

COMMENT

The efficacy of topical ocular hypotensive medication in preventing or delaying the onset of glaucomatous damage has never been proven conclusively. In fact, the published studies are divided almost evenly between those that find prophylactic treatment to be of benefit and those that find no benefit.[24,26] Clearly, this issue must be resolved before embarking on a campaign to screen and detect large numbers of glaucoma suspects. The OHTS was designed to settle this important issue and has met and exceeded its recruitment goals within the proposed recruitment period; however, the subjects in the study are ocular hypertensives at moderate risk for developing POAG. Therefore, the OHTS sample should provide adequate statistical power to answer the question of the efficacy of prophylactic medical treatment.

Primary open angle glaucoma is the leading cause of blindness in African Americans.[2] Because of the high prevalence of POAG in the African American population and the seriousness of the disease, OHTS set a goal of 25% African American recruitment. Since we were able to reach this recruitment goal, the study may be able to answer important questions about glaucoma treatment in African Americans, including the protective effect of topical ocular hypotensive medication, the incidence of POAG in individuals with ocular hypertension, and the IOP response to topical ocular hypotensive medication.

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It is well known that volunteers for some studies may not resemble the general population. It is of note that the volunteers for the OHTS seem to be more educated, have higher socioeconomic status, and report higher health-related quality of life on the SF-36 than the general population. The African American and non–African American groups are similar in most demographic characteristics and almost all health-related quality of life scales; however, there are a few clinically significant differences between the African Americans and non–African Americans recruited for this study, including a larger baseline cup-disc ratio (horizontal by contour) and higher reported rates of high blood pressure and diabetes among African Americans.

An important function of the OHTS will be to refine models of risk for POAG in a national sample. A number of investigators have attempted to quantify risk factors in ocular hypertensive populations; however, none of the previous attempts have looked at large national samples. Possible risk factors include age, cup-disc ratio, IOP, myopia, systemic vascular disease, family history of glaucoma, and race.

A high proportion of the OHTS subjects reported ocular symptoms at baseline. More than 66% of the subjects reported 1 or more ocular symptoms, including tearing, soreness/tiredness, blurry/dim vision, itching, foreign body sensation, and burning/smarting/stinging. This indicates the need for appropriate control groups when evaluating the impact of medications on patient symptoms.

Another important function of the OHTS may be to redefine early damage in POAG. A subset of subjects in the OHTS are participating in ancillary studies to evaluate the prognostic value of scanning laser ophthalmoscopy of the optic disc and short wavelength automated perimetry. These tests may help us to define early structural and functional damage for POAG. The availability of a large number of visual field tests and stereoscopic optic disc photographs in this carefully studied sample should allow us to assess these tests of early glaucomatous damage.

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