Incident Open-angle Glaucoma and Intraocular Pressure

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Purpose: To evaluate the role of baseline intraocular pressure (b-IOP) as a risk factor for incident open-angle glaucoma (OAG) in participants of African origin from the Barbados Eye Studies.


Participants: Three thousand two hundred twenty-two persons examined during the study period who were free of glaucoma at baseline and at risk of developing OAG during the 9-year follow-up.

Methods: Study protocols were standardized and included ophthalmic and other measurements, automated perimetry, applanation tonometry, fundus photography, and comprehensive ophthalmologic examination for those referred. The product-limit approach was used to estimate incidence. Relationships between b-IOP and incidence were evaluated by adjusted relative risk ratios (RRs) with 95% confidence intervals (CIs), based on Cox regression models.

Main Outcome Measure: The 9-year incidence of OAG was based on both visual field and optic disc abnormalities, with ophthalmologic evaluations to exclude other possible causes.

Results: The overall 9-year incidence of OAG was 4.4% (95% CI, 3.7%–5.2%), and the mean (standard deviation) b-IOP among persons at risk was 18.0 mmHg (4.1). Among the 125 incident OAG cases, the mean b-IOP was 21.9 mmHg and 46% had b-IOP of $\geq 21$ mmHg. In contrast, the nonincident group had a mean b-IOP of 17.8 mmHg and only 12% had b-IOP of $>21$ mmHg. Overall, OAG risk increased by 12% with each 1-mmHg increase in IOP (RR, 1.12; 95% CI, 1.08–1.16). Incidence steadily increased from 1.8% (95% CI, 1.2%–2.7%) for persons with b-IOP of $\leq 17$ mmHg (referent group) to 22.3% (95% CI, 15.8%–31.1%) for those with b-IOP $>25$ mmHg, resulting in an adjusted RR of 13.1 (95% CI, 7.1–24.1) among the latter group. The attributable risk for IOP of $>25$ mmHg was 19%. Using 21 mmHg as a cutoff, the RR was 7.9 (95% CI, 3.8–16.2) and the attributable risk was 37%.

Conclusions: After 9 years’ follow-up, the risk of OAG was positively related to IOP levels at baseline. Although persons with b-IOP of $>25$ mmHg had a 13-fold RR of developing OAG, most cases arose with lower b-IOP. This study thus confirms the role of IOP as an influential risk factor, yet at the same time underscores its limitations in predicting OAG. Ophthalmology 2007;114:1810–1815 © 2007 by the American Academy of Ophthalmology.

Intraocular pressure (IOP) is a well-established risk factor for the development of open-angle glaucoma (OAG),1–3 a relationship confirmed most often by large prevalence studies. To date, however, only a limited number of reports on the incidence of OAG have originated from population-based studies4–10; of those, the Barbados Eye Studies provide the only longitudinal data, to the authors’ best knowledge, from a predominantly African origin population.7,8 The purpose of the present investigation was to assess the role of IOP as a risk factor for the 9-year incidence of OAG among the black participants of the Barbados Eye Studies.

Patients and Methods

The Barbados Eye Studies are a series of large, population-based investigations funded by the National Eye Institute and designed to evaluate the prevalence, incidence, and risk factors for the major ocular diseases in the predominantly African-origin population of Barbados, West Indies. The organizational structure of the studies included a coordinating center (Stony Brook University, Stony Brook, New York), a data collection center (Ministry of Health, Bridgetown, Barbados, West Indies), and a fundus photography reading center (The Johns Hopkins University, Baltimore, Maryland). The initial phase of these investigations, the Barbados Eye Study (BES; 1987–1992), provided baseline prevalence data on
4631 persons (84% of those eligible), 40 to 84 years of age, who were selected randomly from the country’s adult population. The distribution of self-reported race among the BES participants was 93% (n = 4314) African/black, 4% (n = 184) mixed (black and white), and 3% (n = 133) European/white or other, with the demographic characteristics of the cohort closely matching those of the census population in Barbados. Surviving members of the BES cohort were reexamined after 4 years (n = 3427) and 9 years (n = 2795), respectively, during the Barbados Incidence Study of Eye Diseases I (BISED I; 1992–1997) and BISED II (1997–2002), with 85% and 81% participation among those eligible, respectively. Population characteristics at baseline and follow-up indicated that those who participated after 9 years were younger, more likely to be female, and less likely to have hypertension and a reported history of diabetes. In addition, the mean (± standard deviation) baseline IOP among nonparticipants was higher than that among participants (19.4±5.7 mmHg vs. 18.1±4.6 mmHg). The BES, BISED I, and BISED II protocols were standardized and have been described previously in detail. In summary, the examination included ophthalmic and other measurements; refraction and best-corrected visual acuity; Humphrey automated perimetry (Zeiss-Humphrey Systems, Dublin, CA); applanation tonometry; lens gradings; color stereo fundus photography of the disc and macula; a comprehensive interview including demographic, ocular, and medical information; and venipuncture for glycosylated hemoglobin. All participants with positive examination findings (best-corrected visual acuity < 20/30; presence of visual field abnormalities; IOP > 21 mmHg; history of major ocular conditions; family history of glaucoma; a history of diabetes; inability to undergo perimetry, fundus photography, or lens gradings) and a 10% sample were referred for a comprehensive ophthalmologic examination.

Definitions
As described elsewhere, the study classification of open-angle glaucoma was determined at the Coordinating Center using a strict algorithm and all available data. The process also included an independent review by a glaucoma specialist (RH). Definite OAG required the presence of both visual field defects and optic disc damage, after exclusion of other possible causes by ophthalmologic examination. Visual field defects were evaluated using specific computer-based objective criteria based on full-threshold C24-2 or C30-2 algorithms with glaucoma hemifield tests, the suprathreshold C64 test, or both. Optical disc damage was determined from masked photographic gradings at the reading center and clinical gradings by the study ophthalmologists. Intraocular pressure was not considered in the definition of OAG. Participants who met some, but not all, of the criteria for OAG were classified as having suspect/probable OAG. Ocular hypertension (OH) was defined as an IOP of more than 21 mmHg (highest mean value of 3 measurements for each eye), use of IOP-lowering treatment, or both, in the absence of any glaucoma-related optic disc and visual field abnormalities.

Statistical Analyses
The 9-year cumulative incidence of OAG was estimated using the product-limit approach. Incidence was defined by the development of OAG in at least 1 eye during the 9-year period among persons without OAG in both eyes at baseline. Persons reporting ancestries other than African were excluded, because of their small numbers, as were persons with bilateral secondary or other types of glaucoma. After these exclusions, 4008 persons of African ancestry remained. Relative risk ratios (RRs) and 95% confidence intervals (CIs) were based on Cox regression models and were adjusted for age, gender, hypertension, and IOP-lowering treatment.

Results
Of the 4008 eligible participants at baseline, 3222 (80.4%) had at least 1 follow-up visit and belong to the population at risk for the incidence estimates. Table 1 presents the baseline characteristics of these individuals, indicating that the mean age was approximately 57 years and 41% were male. Approximately 39% had a history of diabetes and more than half were hypertensive. The mean baseline IOP (b-IOP) was 18 mmHg, 44% had a b-IOP of 17 mmHg or less, and 13% had a b-IOP of more than 21 mmHg. Only 1.6% of participants were receiving IOP-lowering treatment at the start of the study. Over the follow-up period, 125 persons developed definite OAG, for an overall 9-year incidence of 4.4% (95% CI, 3.7%–5.2%). Figure 1 presents the distribution of b-IOP among incident cases of OAG and persons without OAG at 9 years. Although there is a considerable overlap in the IOP distributions, the incident cases had higher b-IOP than those in whom OAG did not develop. The mean b-IOP among the incident cases was 21.9 mmHg, compared with 17.8 mmHg among those in whom OAG did not develop over the 9 years. In addition, 46% of incident cases had an IOP of more than 21 mmHg at baseline, whereas only 12% of nonincident cases had IOPs of more than 21 mmHg.

Table 2 provides the gender-specific 9-year incidence of OAG by categories of b-IOP, along with the adjusted RRs for each of these IOP levels. The incidence of OAG increased steadily with higher levels of b-IOP with no definite pattern noted by gender. Among individuals with a b-IOP of 17 mmHg or less, the 9-year incidence was 1.8%, reaching 22.3% with b-IOP of more than 25 mmHg. After adjusting for age, gender, hypertension, and IOP-lowering treatment, the 9-year risk of developing OAG rose with b-IOP levels. Thus, it was more than 5 times higher in persons with a b-IOP between 21 and 23 mmHg, compared with the reference group (IOP ≤ 17 mmHg); risk was 13 times higher among participants with b-IOP of more than 25 mmHg.

Table 1 presents the baseline characteristics of the study population at risk.

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>(n = 3222)</th>
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<tbody>
<tr>
<td>Mean age ± SD (median), yrs</td>
<td>56.9±11.3 (56.0)</td>
</tr>
<tr>
<td>% male</td>
<td>41.0%</td>
</tr>
<tr>
<td>Diabetes history</td>
<td>16.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52.4%</td>
</tr>
<tr>
<td>Mean IOP ± SD (median), mmHg*</td>
<td>18.0±4.1 (17.7)</td>
</tr>
<tr>
<td>IOP ≤ 17 mmHg*</td>
<td>43.8%</td>
</tr>
<tr>
<td>IOP &gt; 21 mmHg*</td>
<td>13.4%</td>
</tr>
<tr>
<td>IOP &gt; 25 mmHg*</td>
<td>4.4%</td>
</tr>
<tr>
<td>IOP-lowering treatment</td>
<td>1.6%</td>
</tr>
<tr>
<td>IOP = intraocular pressure; SD = standard deviation.</td>
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</table>

*Twelve persons had missing IOP measurements at baseline.
mmHg or more. Investigations were also performed for the commonly used higher cutoff values of 21 and 25 mmHg, which represent approximately the eightieth and ninety-fifth percentiles of the b-IOP distribution among the 3222 persons at risk. Incidence was more than 5 times higher among participants with b-IOP of more than 21 mmHg compared with persons with lower pressures (adjusted RR, 5.2; 95% CI, 3.5–7.6). A similar pattern was observed using an IOP cutoff of 25 mmHg (adjusted RR, 5.9; 95% CI, 3.6–9.4), with considerably higher rates in men than in women (29.5% vs. 17.0%), although based on small numbers. Based on these RRs, the attributable risks for IOP of more than 21 mmHg and IOP of more than 25 mmHg were 37% and 19%, respectively.

The previous results were based on IOP data from all persons at risk. Table 3 presents 9-year OAG incidence according to their classification as suspect/probable glaucoma or nonglaucoma at baseline. Among the 121 participants with suspect/probable glaucoma, the 9-year incidence was 37.5%, with higher rates among the subgroup with b-IOP of more than 21 mmHg or being treated versus the subgroup with b-IOP of 21 mmHg or less (41% vs. 33%). In contrast, individuals classified as nonglaucoma had a 9-year incidence of 3.2%, with ocular hypertensives having a considerably higher incidence than persons with b-IOP of 21 mmHg or less (10.9% vs. 0.7%).

Table 4 provides the age- and gender-specific 9-year incidence of OAG among persons with OH at baseline (n = 376). Overall, the 9-year incidence among those with OH was 10.9%, or an average of approximately 1%/year, and increased with age. There were no apparent gender-specific differences in incidence of OAG among persons with OH.

### Discussion

To the authors’ knowledge, this is the first large study to provide long-term longitudinal data on the incidence and risk factors for OAG and the relationship of incident OAG and IOP in a population of predominantly African origin. The 9-year incidence of OAG in this population was previously reported to be 4.4%. Findings from the present investigation indicate that the risk of experiencing OAG at follow-up increases with higher IOP, paralleling the results seen at baseline and the 4-year follow-up. After 9 years, the incidence of OAG was 1.8% among persons with b-IOP of 17 mmHg or less, compared with 22.3% among participants with b-IOP of more than 25 mmHg, for a 13-fold adjusted RR (Table 2).

### Intraocular Pressure Level and Incident Open-angle Glaucoma

In addition to the strong positive association between b-IOP levels and risk of OAG (approximate 12% increase in risk...
per 1-mmHg increase in IOP), data from the present study indicated that OAG developed at all levels of IOP. Because 46% of new cases arose with b-IOP of more than 21 mmHg (Fig 1), this means that more than half (54%) initially had b-IOP of 21 mmHg or less, a level not traditionally considered to be elevated. In fact, the present results showed that 18% of incident cases had b-IOP of 17 mmHg or less and 30% had b-IOP of 19 mmHg or less. However, 12% of nonincident participants had b-IOP of more than 21 mmHg (Fig 1), yet did not develop OAG. These findings emphasize the limitations of IOP as a long-term predictor of OAG risk. When a cutoff of more than 21 mmHg was used to define elevated IOP, the risk attributable to high IOP was 37%. Using a criterion of more than 25 mmHg, the attributable risk was 19%. This implies that a considerable extent of OAG risk can be attributed to other factors besides IOP. Nevertheless, the magnitude of the relative and attributable risks associated with elevated pressures in this investigation indicates that IOP plays a major role in the development of glaucoma. The influence of IOP is substantiated further by the finding that the 9-year incidence of OAG among persons without suspect/probable glaucoma and b-IOP of 21 mmHg or less was only 0.7% (Table 3).

Incident cases had considerable increases in IOP between baseline and follow-up. Whereas approximately half of the incident OAG cases had b-IOP of more than 21 mmHg or were receiving IOP-lowering treatment at baseline, more than 80% had reached those IOP levels, or were receiving treatment, when the disease was identified.

Because only 52 persons (1.6%) were treated at baseline, the influence of IOP-lowering treatment in this study could not be evaluated adequately. Persons receiving IOP-lowering medications had higher b-IOP levels than those without treatment (mean, 25.6 vs. 17.9 mmHg) and were likely to have had even higher IOPs before treatment. Not surprisingly, incidence rates were generally 2 times higher in treated versus untreated cases, a finding that probably reflects the adverse impact of elevated IOP on OAG development. It should be noted that the present multivariate results were adjusted for the potential effects of treatment. Because it still remains unclear why central corneal thickness has been shown to influence IOP in some populations but not others and because a previous investigation indicated that central corneal thickness had no impact on IOP in this population, the IOP data were not adjusted for corneal thickness in this study.

### 4-Year versus 9-Year Incidence Estimates

Although the highest degree of risk, as expected, was among participants in the group with the highest b-IOP (>25 mmHg), the 9-year RRs for the given IOP categories were generally lower than those seen in the 4-year incidence report. A comparison of the 4-year and 9-year results revealed an apparent large disparity in RR among persons with b-IOP of more than 25 mmHg (24.7 vs. 13.1, respectively), which at first glance would seem to reflect a real difference. Interpretation of these data should consider the overall increase in IOP from 4 to 9 years, which was particularly evident in the reference group, that is, persons with b-IOP of 17 mmHg or less. Among the 22 incident OAG cases with such IOP levels, the mean IOP increased from 14.7 mmHg at baseline to 22.7 mmHg at the 9-year follow-up. The magnitude of these increases was lower among incident OAG cases with b-IOP of more than 17 mmHg and 25 mmHg or less. In contrast, participants with b-IOP of more than 25 mmHg had decreases in mean IOP from 30.6 mmHg at baseline to 26.5 mmHg after 9 years. This reduction in pressure in the highest IOP group, combined with the IOP increases in the reference group during the same period, may explain the discrepancies in the 4- and 9-year RR among individuals in the highest IOP group. Additionally, the 9-year RR may have decreased because of selective mortality, which could have led to a lowering of the 9-year OAG incidence in the high IOP group. In fact, diabetes and hypertension were more common in participants with high IOP than in others and may have contributed to higher losses to follow-up in this group. Another plausible explanation for the lower risk at 9 versus 4 years among participants with b-IOP of more than 25 mmHg is that the influences of IOP on glaucoma development actually may decrease over time.

### Table 3. 9-Year Incidence of Open-angle Glaucoma by Baseline Classification and Intraocular Pressure

<table>
<thead>
<tr>
<th>Baseline Classification</th>
<th>No. at Risk</th>
<th>% Incidence (95% Confidence Interval)</th>
</tr>
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<tbody>
<tr>
<td>Suspect/probable glaucoma</td>
<td>121</td>
<td>37.5 (28.8–48.0)</td>
</tr>
<tr>
<td>IOP &gt; 21</td>
<td>74</td>
<td>41.0 (29.5–54.9)</td>
</tr>
<tr>
<td>mmHg/treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOP ≤ 21 mmHg</td>
<td>47</td>
<td>32.6 (20.5–49.3)</td>
</tr>
<tr>
<td>Nonglaucoma*</td>
<td>310</td>
<td>3.2 (2.6–3.9)</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>376</td>
<td>10.9 (7.9–15.1)</td>
</tr>
<tr>
<td>IOP ≤ 21 mmHg</td>
<td>2724</td>
<td>0.7 (0.4–1.1)</td>
</tr>
<tr>
<td>Overall</td>
<td>3222</td>
<td>4.4 (3.7–5.2)</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure.

*One person had missing data on IOP/treatment.

†Twelve persons had missing data on IOP.

### Table 4. Age- and Gender-Specific Incidence of Open-angle Glaucoma for Persons with Ocular Hypertension at Baseline

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Male No. at Risk</th>
<th>Male % (95% Confidence Interval)</th>
<th>Female No. at Risk</th>
<th>Female % (95% Confidence Interval)</th>
<th>Total No. at Risk</th>
<th>Total % (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–59</td>
<td>67</td>
<td>10.9 (5.3–21.6)</td>
<td>89</td>
<td>7.5 (3.5–16.0)</td>
<td>156</td>
<td>9.1 (5.4–15.2)</td>
</tr>
<tr>
<td>60+</td>
<td>82</td>
<td>11.2 (5.3–22.8)</td>
<td>138</td>
<td>13.5 (8.1–22.1)</td>
<td>199</td>
<td>12.7 (8.3–19.1)</td>
</tr>
<tr>
<td>Total</td>
<td>149</td>
<td>10.8 (6.4–17.7)</td>
<td>227</td>
<td>10.9 (7.2–16.6)</td>
<td>376</td>
<td>10.9 (7.9–15.1)</td>
</tr>
</tbody>
</table>
Incidence in Ocular Hypertensives

Only a subset of persons with OH eventually experience OAG,\textsuperscript{7,16,19–21} and some reports have documented the extent of this risk.\textsuperscript{7,19,22,23} The 4-year incidence of OAG among persons with OH in the BES was 4.9%,\textsuperscript{7} or an average of slightly more than 1% per year. Findings from the present investigation are consistent with the 4-year data, because 10.9% of participants with IOP of more than 25 mmHg or receiving IOP-lowering treatment at baseline developed OAG after 9 years, for a similar yearly average. One prospective study followed up 647 ocular hypertensives (27% of African origin) for a median duration of 6.2 years and found that 68 (10.5%) experienced visual field loss consistent with glaucoma during follow-up.\textsuperscript{23} A clinical trial, the Ocular Hypertension Treatment Study, included more than 1600 persons (25% African American), 40 to 80 years of age, with IOPs between 24 and 32 mmHg and not receiving IOP-lowering treatment at baseline. Participants were randomized to treatment versus non-treatment and, after a median follow-up of 78 months, the incidence of OAG among African-Americans in the untreated group was 16%.\textsuperscript{24} A further evaluation among untreated participants in the BES indicated that the incidence of OAG for persons with IOP of more than 25 mmHg was 15%, a result comparable with that found in the Ocular Hypertension Treatment Study. It should be noted however, that the definition of OAG in the Ocular Hypertension Treatment Study required the presence of visual field or optic disc abnormalities, whereas the present study required both to be present. In addition to the different criteria used to define OAG, the studies differed in their design, eligibility criteria, and selection methods, among other study-related features.

Strengths and Weaknesses

The BES has many strengths, including the large, population-based sample of predominantly African origin, high participation rates during the 9-year study period, standardized protocols, and high data completion. As with most longitudinal studies, losses to follow-up are a limiting factor, because these losses can lead to biases in the estimation of long-term incidence and risk. In BISED II, good representation of the original cohort was achieved. Despite being older and having a lower percentage of females in the group, the demographics of nonparticipants were comparable with those of participants,\textsuperscript{11} with no significant differences in the prevalence of OAG at baseline noted between the 2 groups. It is possible, however, that losses to follow-up may bias the findings. For example, the higher baseline IOPs in nonparticipants could lead to a possible underestimation of incidence. One other potential limitation of this study relates to the possible misclassification of IOP, especially at baseline, as a result of the variability of the measurement. However, it is unlikely that such error would change the findings of the present investigation significantly.

In summary, the evaluation of the 9-year incidence of OAG at various IOP levels provides important information on the RR of OAG developing with increasing IOP. This study confirmed the strong relationship between high IOP and incident OAG, yet highlighted the limitations of IOP as a predictor of risk.

References


