The Ocular Hypertension Treatment Study (OHTS)

Supported by the National Eye Institute, National Center on Minority Health and Health Disparities, Research to Prevent Blindness, and Merck Research Laboratories
Ocular Hypertension

- Elevated IOP in the absence of clinically detectable optic nerve or visual field changes
- A common finding
- What to do?
  - Treat all?
  - Treat no one?
  - Treat some? Then who?
Why did we do this study?

Don’t we know that treatment prevents open angle glaucoma?
Does Treatment of Ocular Hypertension prevent POAG?

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Protective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham</td>
<td>no</td>
</tr>
<tr>
<td>Norskov</td>
<td>no</td>
</tr>
<tr>
<td>Levene</td>
<td>no</td>
</tr>
<tr>
<td>David et al.</td>
<td>no</td>
</tr>
<tr>
<td>Chisholm</td>
<td>no</td>
</tr>
<tr>
<td>Schulzer et al.</td>
<td>no</td>
</tr>
<tr>
<td>Heijl et al.</td>
<td>no</td>
</tr>
<tr>
<td>Kamal et al.</td>
<td>no</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Protective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becker &amp; Morton</td>
<td>yes</td>
</tr>
<tr>
<td>Shin et al.</td>
<td>yes</td>
</tr>
<tr>
<td>Kitazawa</td>
<td>yes</td>
</tr>
<tr>
<td>Epstein et al.</td>
<td>yes</td>
</tr>
<tr>
<td>Kass et al.</td>
<td>yes</td>
</tr>
</tbody>
</table>

Limitations of previous studies:
- Varying endpoints
- Limited treatment regimens
- Small sample size

June, 2002
Ocular Hypertension Treatment Study (OHTS)

*Primary Goals*

- Evaluate the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the development of POAG in individuals with elevated IOP

- Identify baseline demographic and clinical factors that predict which participants will develop POAG
The OHTS Entry Criteria

- Age 40 - 80
- Normal visual fields
  - Humphrey 30-2
- Normal optic discs
- Untreated IOP:
  - 24 to 32 mmHg in qualifying eye
  - 21 to 32 mmHg in fellow eye
Patient found eligible for OHTS
- Eligible untreated IOPs on 2 visits
- 2 sets of normal & reliable HVFs per VFRC
- Optic discs judged normal by ODRC

Randomization

Medication
Topical treatment to lower IOP 20% and IOP ≤ 24 mm Hg
Adjust therapy if target not met

Observation
No topical treatment to lower IOP

Monitoring
Humphrey 30-2 q6 months
Stereoscopic disc photos annually

Reproducible Abnormality
3 consecutive visual fields and/or 2 consecutive sets of optic disc photographs as determined by masked readers at ODRC or VFRC

POAG
Visual field and/or optic disc changes attributed to POAG by masked Endpoint Committee

June, 2002
### Baseline Characteristics by Randomization Group

#### Gender & Age

<table>
<thead>
<tr>
<th>Ages</th>
<th>Medication n=817</th>
<th>Observation n=819</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>43.9%</td>
<td>42.2%</td>
</tr>
<tr>
<td>Female</td>
<td>56.1%</td>
<td>57.8%</td>
</tr>
<tr>
<td>40 to 50</td>
<td>35.6%</td>
<td>35.0%</td>
</tr>
<tr>
<td>&gt; 50 to 60</td>
<td>33.0%</td>
<td>31.6%</td>
</tr>
<tr>
<td>&gt; 60 to 70</td>
<td>24.7%</td>
<td>25.6%</td>
</tr>
<tr>
<td>&gt; 70 to 80</td>
<td>6.6%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

June, 2002
## Baseline Characteristics by Randomization Group

### Self-designated Race

<table>
<thead>
<tr>
<th>Race</th>
<th>Medication n=817</th>
<th>Observation n=819</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native American</td>
<td>0.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Asian</td>
<td>0.5%</td>
<td>1.2%</td>
</tr>
<tr>
<td>African American</td>
<td>25.0%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.9%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>70.6%</td>
<td>68.4%</td>
</tr>
<tr>
<td>Other</td>
<td>1.0%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

June, 2002
## Baseline Characteristics by Randomization Group

**Ophthalmic Measurements**

<table>
<thead>
<tr>
<th></th>
<th><strong>Medication</strong> (n=817)</th>
<th><strong>Observation</strong> (n=819)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IOP (mm Hg)</strong></td>
<td>24.9 ± 2.6</td>
<td>24.9 ± 2.7</td>
</tr>
<tr>
<td><strong>Cup:Disc Ratio (Horizontal)</strong></td>
<td>0.36 ± 0.19</td>
<td>0.36 ± 0.18</td>
</tr>
<tr>
<td><strong>Cup:Disc Ratio (Vertical)</strong></td>
<td>0.39 ± 0.20</td>
<td>0.39 ± 0.19</td>
</tr>
<tr>
<td><strong>Central Corneal Thickness (microns)</strong>*</td>
<td>570.5 ± 38.9</td>
<td>574.5 ± 37.7</td>
</tr>
<tr>
<td><strong>Refraction (spherical equivalent in Diopters)</strong></td>
<td>-0.67 ± 2.31</td>
<td>-0.60 ± 2.35</td>
</tr>
</tbody>
</table>

* Overall n=1398 for central corneal thickness, n=699 (86%) per randomization group. Measurements were conducted after 1999, about 2 years after the last participant was randomized.
Baseline Characteristics by Randomization Group

Visual Field Indices

<table>
<thead>
<tr>
<th></th>
<th>Medication</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=817</td>
<td>n=819</td>
</tr>
<tr>
<td></td>
<td>(mean ± S.D.)</td>
<td>(mean ± S.D.)</td>
</tr>
<tr>
<td>Mean Deviation (dB)</td>
<td>+0.27 ± 1.07</td>
<td>+0.21 ± 1.03</td>
</tr>
<tr>
<td>Pattern Standard Deviation (dB)</td>
<td>1.92 ± 0.21</td>
<td>1.90 ± 0.21</td>
</tr>
<tr>
<td>Corrected Pattern Standard Deviation (dB)</td>
<td>1.12 ± 0.34</td>
<td>1.12 ± 0.36</td>
</tr>
</tbody>
</table>
### Baseline Characteristics by Randomization Group

#### Possible Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>Medication n=817</th>
<th>Observation n=819</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior use of Ocular Hypotensive Medication</td>
<td>35.0%</td>
<td>39.3%</td>
</tr>
<tr>
<td>First Degree Family History of Glaucoma</td>
<td>34.0%</td>
<td>35.6%</td>
</tr>
<tr>
<td>Myopia &gt; 1 diopter Spherical Equivalent</td>
<td>34.4%</td>
<td>33.7%</td>
</tr>
<tr>
<td>Oral Beta Adrenergic Antagonist</td>
<td>5.4%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Oral Calcium Channel Blocker</td>
<td>12.8%</td>
<td>14.0%</td>
</tr>
</tbody>
</table>
## Baseline Characteristics by Randomization Group

### Medical History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medication n=817</th>
<th>Observation n=819</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>10.4%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11.5%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37.5%</td>
<td>38.1%</td>
</tr>
<tr>
<td>Low Blood Pressure</td>
<td>4.8%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>5.8%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.9%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>
Box Plot of IOP by Randomization Group

Median IOP is joined by a line. Box: 25% and 75%  Whiskers: 10% and 90%
## IOP By Race

<table>
<thead>
<tr>
<th></th>
<th>Medication</th>
<th></th>
<th>Observation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>African American</td>
<td>Other</td>
<td>African American</td>
<td>Other</td>
</tr>
<tr>
<td>IOP at baseline</td>
<td>25.1 ± 2.9</td>
<td>24.9 ± 2.6</td>
<td>25.1 ± 2.8</td>
<td>24.9 ± 2.7</td>
</tr>
<tr>
<td>IOP averaged over scheduled follow-up visits</td>
<td>19.3 ± 2.3</td>
<td>19.3 ± 2.1</td>
<td>23.9 ± 3.2</td>
<td>23.9 ± 2.8</td>
</tr>
<tr>
<td>Percent reduction from baseline</td>
<td>-22.9 ± 10%</td>
<td>-22.4 ± 10%</td>
<td>-4.7 ± 13%</td>
<td>-3.8 ± 11%</td>
</tr>
</tbody>
</table>
Percent of Medication Patients on Different Medications

Patients may be on more than one medication

Patients may be on more than one medication.
## Progress and Outcome of Study Participants

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Medication</th>
<th>Observation</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Randomized</td>
<td>817</td>
<td>100</td>
<td>819</td>
</tr>
<tr>
<td>Died</td>
<td>26</td>
<td>3.2</td>
<td>29</td>
</tr>
<tr>
<td>Inactive</td>
<td>89</td>
<td>10.9</td>
<td>84</td>
</tr>
<tr>
<td>Non-adherence to randomization</td>
<td>40</td>
<td>4.9</td>
<td>42</td>
</tr>
<tr>
<td>Reproducible VF or Optic Disc abnormality due to any cause</td>
<td>81</td>
<td>9.9</td>
<td>137</td>
</tr>
<tr>
<td>Endpoints attributed to POAG</td>
<td>36</td>
<td>4.4</td>
<td>89</td>
</tr>
</tbody>
</table>

Log rank p<0.001
Primary POAG Endpoints*

Log Rank P-value <0.001, Hazard Ratio 0.40, 95% CI (0.27, 0.59)

Proportion POAG

Months

June, 2002

*through 8 Nov 2001
**1st Visual Field POAG Endpoint**

Log Rank P-value = 0.002, Hazard Ratio = 0.45, 95% CI (0.26, 0.76)

*through 8 Nov 2001*
1st Optic Disc POAG Endpoint*

Log Rank P-value < 0.001, Hazard Ratio 0.36, 95% CI (0.23, 0.56)

Medication

Observation

Proportion POAG

6 12 18 24 30 36 42 48 54 60 66 72 78 84

Months

*through 8 Nov 2001
# First POAG Endpoint per Participant

<table>
<thead>
<tr>
<th></th>
<th>Medication</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>%</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>Visual Field</td>
<td>15</td>
<td>41.7</td>
</tr>
<tr>
<td>Optic Disc</td>
<td>18</td>
<td>50.0</td>
</tr>
<tr>
<td>Concurrent Visual Field and Optic Disc</td>
<td>3</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>36</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

June, 2002
All cause reproducible abnormalities in visual fields and/or optic discs were significantly reduced in medication group.

Hazard ratio 0.58, 95% CI (0.44-0.76)

P=0.00008
Treatment perhaps less protective in African Americans

African Americans
- 12.7% POAG endpoints in observation group
- 6.9% POAG endpoints in medication group
- Hazard Ratio 0.54
- P value for interaction 0.26

Others
- 10.2% POAG endpoints in observation group
- 3.6% POAG endpoints in medication group
- Hazard Ratio 0.34

June, 2002
No Significant Safety Difference Between Randomization Groups

- Mortality
- Hospitalizations
- New Medical Conditions
- Worsening of Pre-existing Conditions
- SF – 36/any subscale
- Patient Reported Ocular and Systemic Symptoms
Percent Reporting Changes in Iris, Lids or Lashes

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent Reporting</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin analog &gt; 6 months</td>
<td>17%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Observation group</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>n = 380</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 631</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
No difference between randomization groups in serious AEs for 9 of 11 organ systems.
Borderline Safety Differences Between Randomization Groups

- Cataract surgery
- Serious psychiatric adverse events
- Serious genitourinary adverse events
Summary

- Treatment produced about a 20% reduction in IOP.

- Treatment reduced incidence of POAG in OHT participants by more than 50% at 5 years from 9.5% in the Observation Group to 4.4% in the Medication Group.

- Little evidence of safety concerns.
### Significant Baseline Predictive Factors from Univariate Proportional Hazards Models

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Decade</td>
<td>1.43 (1.19, 1.71)</td>
</tr>
<tr>
<td>African American origin</td>
<td>1.59 (1.09, 2.32)</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.87 (1.31, 2.67)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.40 (0.18, 0.92)</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>2.11 (1.23, 3.62)</td>
</tr>
<tr>
<td>IOP per mm Hg</td>
<td>1.11 (1.04, 1.18)</td>
</tr>
<tr>
<td>CCT per 40 microns decrease</td>
<td>1.88 (1.55, 2.29)</td>
</tr>
<tr>
<td>PSD per 0.2 dB increase</td>
<td>1.36 (1.16, 1.60)</td>
</tr>
<tr>
<td>Horizontal C/D Ratio</td>
<td>1.25 (1.14, 1.38)</td>
</tr>
<tr>
<td>Vertical C/D Ratio</td>
<td>1.32 (1.19, 1.46)</td>
</tr>
</tbody>
</table>
Non Significant Baseline Predictive Factors from Univariate Proportional Hazards Models

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History Glaucoma</td>
<td>1.10 (0.7, 1.59)</td>
</tr>
<tr>
<td>Oral Beta Adrenergic Antagonists</td>
<td>0.70 (0.26, 1.89)</td>
</tr>
<tr>
<td>Oral Calcium Channel Blocker</td>
<td>1.35 (0.83, 2.19)</td>
</tr>
<tr>
<td>Migraine</td>
<td>1.01 (0.58, 1.76)</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>1.31 (0.92, 1.87)</td>
</tr>
<tr>
<td>Low Blood Pressure</td>
<td>1.49 (0.73, 3.05)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.42 (0.35, 5.75)</td>
</tr>
<tr>
<td>CPSD per 0.3 dB</td>
<td>1.16 (0.99, 1.35)</td>
</tr>
<tr>
<td>Mean Deviation</td>
<td>0.86 (0.73, 1.02)</td>
</tr>
<tr>
<td>Myopia</td>
<td>(0.91 (0.62, 1.32)</td>
</tr>
</tbody>
</table>

June, 2002
Significant Baseline Predictive Factors from Multivariate Proportional Hazard Models

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (decade)</td>
<td>1.22 (1.01, 1.49)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.37 (0.15, 0.90)</td>
</tr>
<tr>
<td>IOP (per mmHg)</td>
<td>1.10 (1.04, 1.17)</td>
</tr>
<tr>
<td>CCT (per 40 µM decrease)</td>
<td>1.71 (1.40, 2.09)</td>
</tr>
<tr>
<td>PSD (per 0.2 dB increase)</td>
<td>1.27 (1.06, 1.52)</td>
</tr>
<tr>
<td>Horizontal C/D Ratio (per 0.1 increase)</td>
<td>1.27 (1.14, 1.40)</td>
</tr>
<tr>
<td>Vertical C/D Ratio (per 0.1 increase)</td>
<td>1.32 (1.19, 1.47)</td>
</tr>
</tbody>
</table>
- African Americans have a higher prevalence and incidence of POAG.

- OHTS data suggests that this racial effect may be due to thinner central corneas and larger cup/disc ratios.
POAG Endpoints by Central Corneal Thickness and Baseline IOP (mmHg) in Observation Group*

Baseline IOP (mmHg)

- >25.75
  - 36%
  - 12%
  - 17%

- >23.75 to ≤ 25.75
  - 13%
  - 10%
  - 9%

- ≤ 23.75
  - 6%
  - 7%
  - 2%

Central Corneal Thickness (microns)

- ≤ 555
  - 17%
  - 9%
  - 2%

- >555 to ≤ 588
  - 36%
  - 10%

- >588
  - 13%
  - 7%

* through 8 Nov 2001
POAG Endpoints by Central Corneal Thickness and Baseline Vertical C/D Ratio in Observation Group*

<table>
<thead>
<tr>
<th>Vertical C/D Ratio</th>
<th>≤ 555</th>
<th>&gt;555 to ≤ 588</th>
<th>&gt;588</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.30</td>
<td>15%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>&gt;0.30 to &lt;0.50</td>
<td>26%</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>≥0.50</td>
<td>22%</td>
<td>16%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Central Corneal Thickness (microns)

* through 8 Nov 2001
60-year-old WF

- IOP: 24 / 24
- C/D ratio: 0.1 vertical
- Corneal thickness: 600 µ
- Risk of POAG: ~1% / 5 years
60-year-old WF

- IOP 24 / 24
- C/D ratio 0.3
- Corneal thickness 540 μ
- Risk of POAG ~ 7% / 5 years

June, 2002
60-year-old WF

- IOP: 28 / 28
- C/D ratio: 0.1
- Corneal thickness: 600 µ
- Risk of POAG: ~ 2% / 5 years
# 60-year-old WF

- **IOP**: 24 / 24
- **C/D ratio**: 0.5
- **Corneal thickness**: 490 μ
- **Risk of POAG**: ~ 20% / 5 years
72-year-old BM

- IOP: 25 / 25
- C/D ratio: 0.6
- Corneal thickness: 510 μ
- Risk of POAG: ~ 35% / 5 years
Strengths

1. Large sample size
2. Careful follow-up
3. Masked assessment of endpoints
4. Attribution of endpoints to cause by masked committee
5. Inclusion of all commercially available drugs
6. Careful quality control and feedback to technicians and photographers
7. True-incidence cases
Weaknesses

1. Convenience sample rather than population based
2. Relatively small number of POAG endpoints
3. Healthy volunteers
4. Limited IOP range
5. Limited to patients with reliable visual fields
6. “Squeaky clean” participants at baseline
7. High thresholds for endpoints
8. Some risk factors under-represented

June, 2002
Summary

- Not every patient with OHT should be treated.
- Offer treatment to OHT patient at moderate to high risk taking into consideration:
  - Age
  - Medical status
  - Life expectancy
  - Likely treatment benefit
- Consider measuring corneal thickness in all patients with OHT or glaucoma.
Possible Misinterpretations of OHTS

1. Treat all patients with elevated IOP.
2. Risk of POAG is low in this population.
3. Glaucoma medications are harmless.
4. Risk factors for developing POAG are clearly delineated; influence of race, gender, hypertension, heart disease, family history, blood pressure, and diabetes are all clear.
5. 20% lowering of IOP is the correct target for OHT.
6. Drug X is proven to prevent glaucoma in OHT.
OHTS Resource Centers

Study Chairman’s Office
&
Coordinating Center
Washington University
St. Louis, MO

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

Visual Field Reading Center
University of California, Davis
Sacramento, CA

June, 2002
OHTS Clinical Centers

- Bascom Palmer Eye Institute
- Eye Consultants of Atlanta
- Eye Physicians and Surgeons
- Cullen Eye Institute
- Devers Eye Institute
- Emory Eye Institute
- Henry Ford Hospitals
- Johns Hopkins University
- Krieger Eye Institute
- Howard University
- University of Maryland
- University of California, Los Angeles
- Charles Drew University
- Kellogg Eye Center
- Kresge Eye Institute
- Great Lakes Eye Institute
- University of Louisville
- Mayo Clinic
- New York Eye & Ear Infirmary
- Ohio State University
- Ophthalmic Surgeons & Consultants
- Pennsylvania College of Optometry
- MCP/Hahnemann University
- Scheie Eye Institute
- University of California, Davis
- University of California, San Diego
- University of California, San Francisco
- University Suburban Health Center
- University of Ophthalmic Consultants
- Washington Eye Physicians & Surgeons
- Eye Associates of Washington, DC
- Washington University, St. Louis

June, 2002