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?

Investigator	Protective
Graham	no
Norskov	no
Levene	no
David *et al.*	no
Chisholm	no
Schulzer *et al.*	no
Heijl *et al.*	no
Kamal *et al.*	no

Investigator	Protective
Becker & Morton	yes
Shin *et al.*	yes
Kitazawa	yes
Epstein *et al.*	yes
Kass *et al.*	yes

Limitations of previous studies:

- Varying endpoints
- Limited treatment regimens
- Small sample size

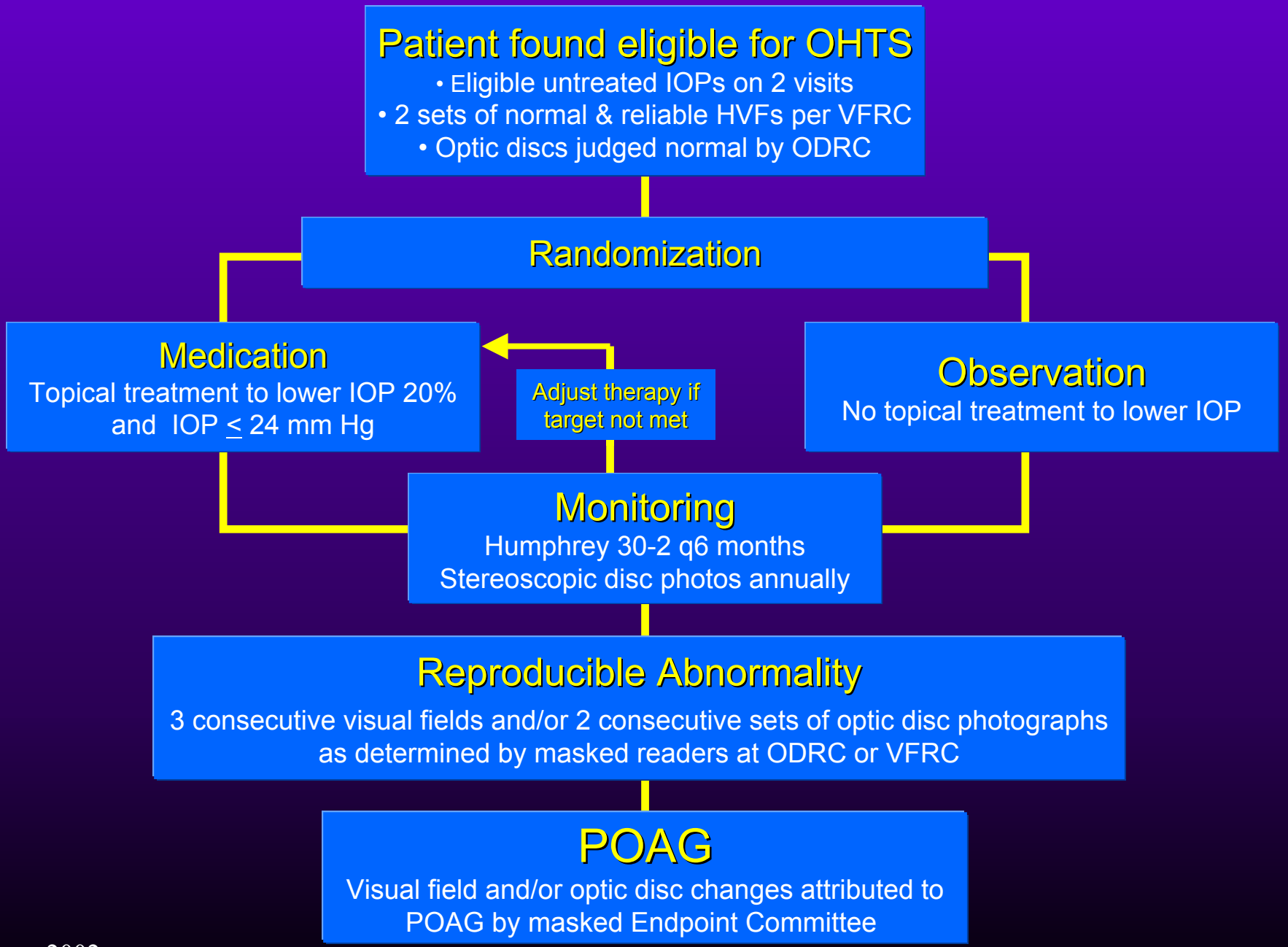
Ocular Hypertension Treatment Study (OHTS)
Primary Goals

- 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

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Baseline Characteristics by Randomization Group
Gender & Age

	Medication n=817	Observation n=819
Male	43.9%	42.2%
Female	56.1%	57.8%

Ages	40 to 50	35.6%	35.0%
	> 50 to 60	33.0%	31.6%
	> 60 to 70	24.7%	25.6%
	> 70 to 80	6.6%	7.7%

Baseline Characteristics by Randomization Group
Self-designated Race

	Medication n=817	**Observation** n=819
Native American	0.1%	0.4%
Asian	0.5%	1.2%
African American	25.0%	25.0%
Hispanic	2.9%	4.3%
Caucasian	70.6%	68.4%
Other	1.0%	0.7%

Baseline Characteristics by Randomization Group
Ophthalmic Measurements

	Medication n=817 (mean ± S.D.)	**Observation** n=819 (mean ± S.D.)
IOP (mm Hg)	24.9 ± 2.6	24.9 ± 2.7
Cup:Disc Ratio (Horizontal)	0.36 ± 0.19	0.36 ± 0.18
Cup:Disc Ratio (Vertical)	0.39 ± 0.20	0.39 ± 0.19
Central Corneal Thickness (microns)*	570.5 ± 38.9	574.5 ± 37.7
Refraction (spherical equivalent in Diopters)	-0.67 ± 2.31	-0.60 ± 2.35

* 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

	Medication n=817 (mean ± S.D.)	**Observation** n=819 (mean ± S.D.)
Mean Deviation (dB)	+0.27 ± 1.07	+0.21 ± 1.03
Pattern Standard Deviation (dB)	1.92 ± 0.21	1.90 ± 0.21
Corrected Pattern Standard Deviation (dB)	1.12 ± 0.34	1.12 ± 0.36

Baseline Characteristics by Randomization Group
Possible Risk Factors

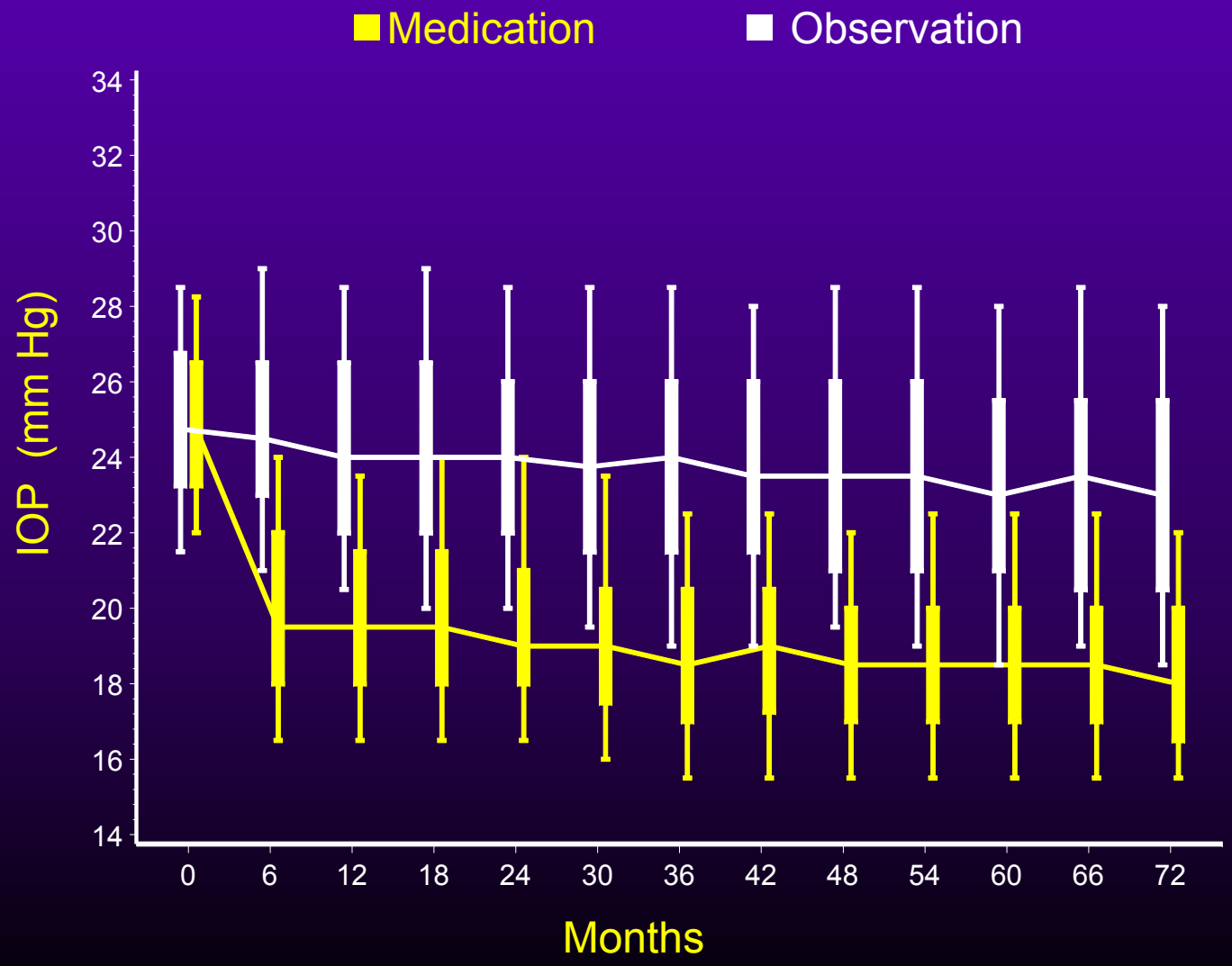
	Medication n=817	**Observation** n=819
Prior use of Ocular Hypotensive Medication	35.0%	39.3%
First Degree Family History of Glaucoma	34.0%	35.6%
Myopia ≥ 1 diopter Spherical Equivalent	34.4%	33.7%
Oral Beta Adrenergic Antagonist	5.4%	4.6%
Oral Calcium Channel Blocker	12.8%	14.0%

Baseline Characteristics by Randomization Group
Medical History

	Medication n=817	**Observation** n=819
Migraine	10.4%	11.7%
Diabetes	11.5%	12.1%
Hypertension	37.5%	38.1%
Low Blood Pressure	4.8%	4.0%
Cardiovascular Disease	5.8%	6.5%
Stroke	0.9%	1.6%

Box Plot of IOP by Randomization Group

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



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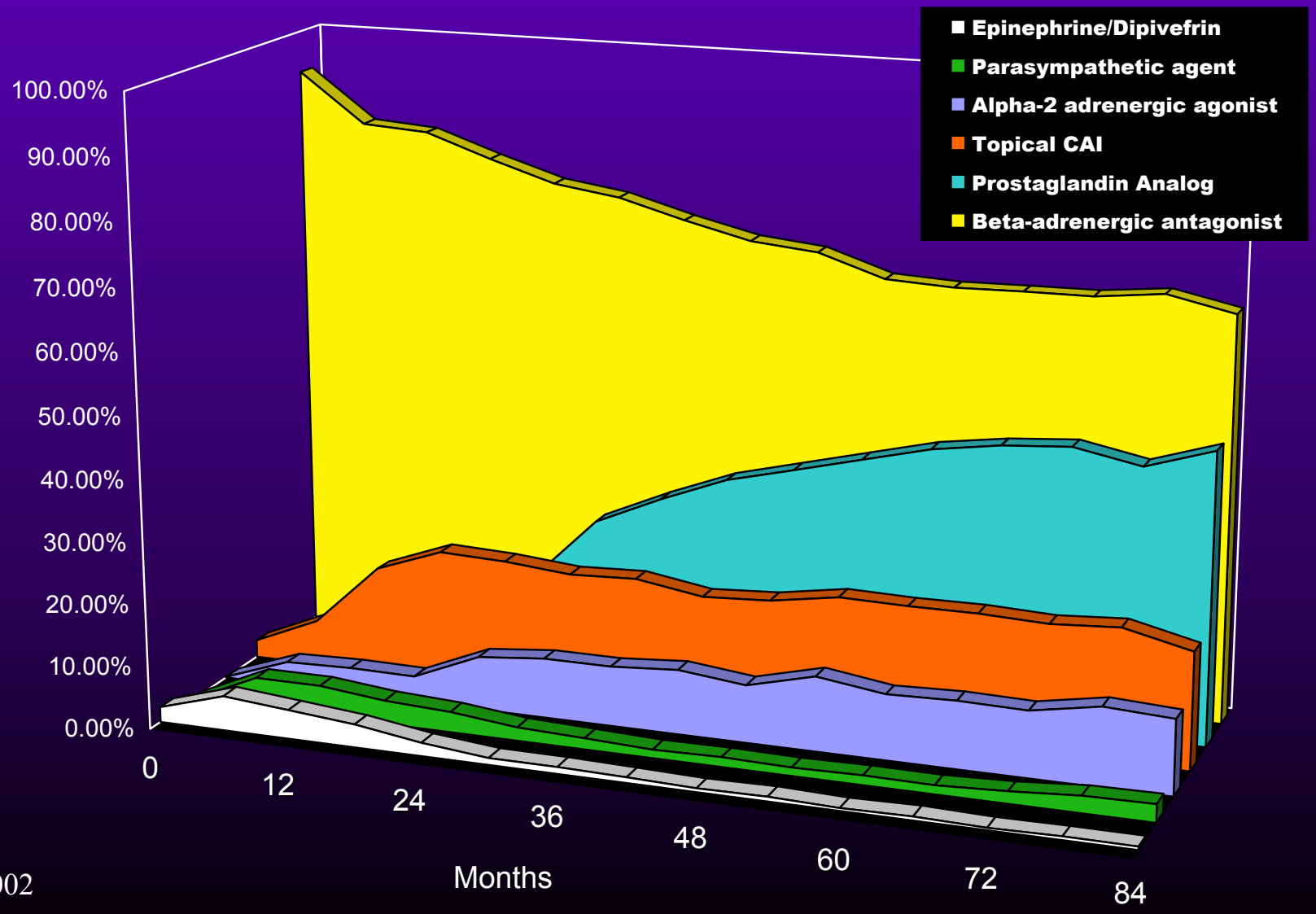
IOP By Race

	Medication		Observation	
	African American n=203	Other n=614	African American n=205	Other n=614
IOP at baseline	25.1 ± 2.9	24.9 ± 2.6	25.1 ± 2.8	24.9 ± 2.7
IOP averaged over scheduled follow-up visits	19.3 ± 2.3	19.3 ± 2.1	23.9 ± 3.2	23.9 ± 2.8
Percent reduction from baseline	-22.9 ± 10%	-22.4 ± 10%	-4.7 ± 13%	-3.8 ± 11%

Percent of Medication Patients on Different Medications

Patients may be on more than one medication



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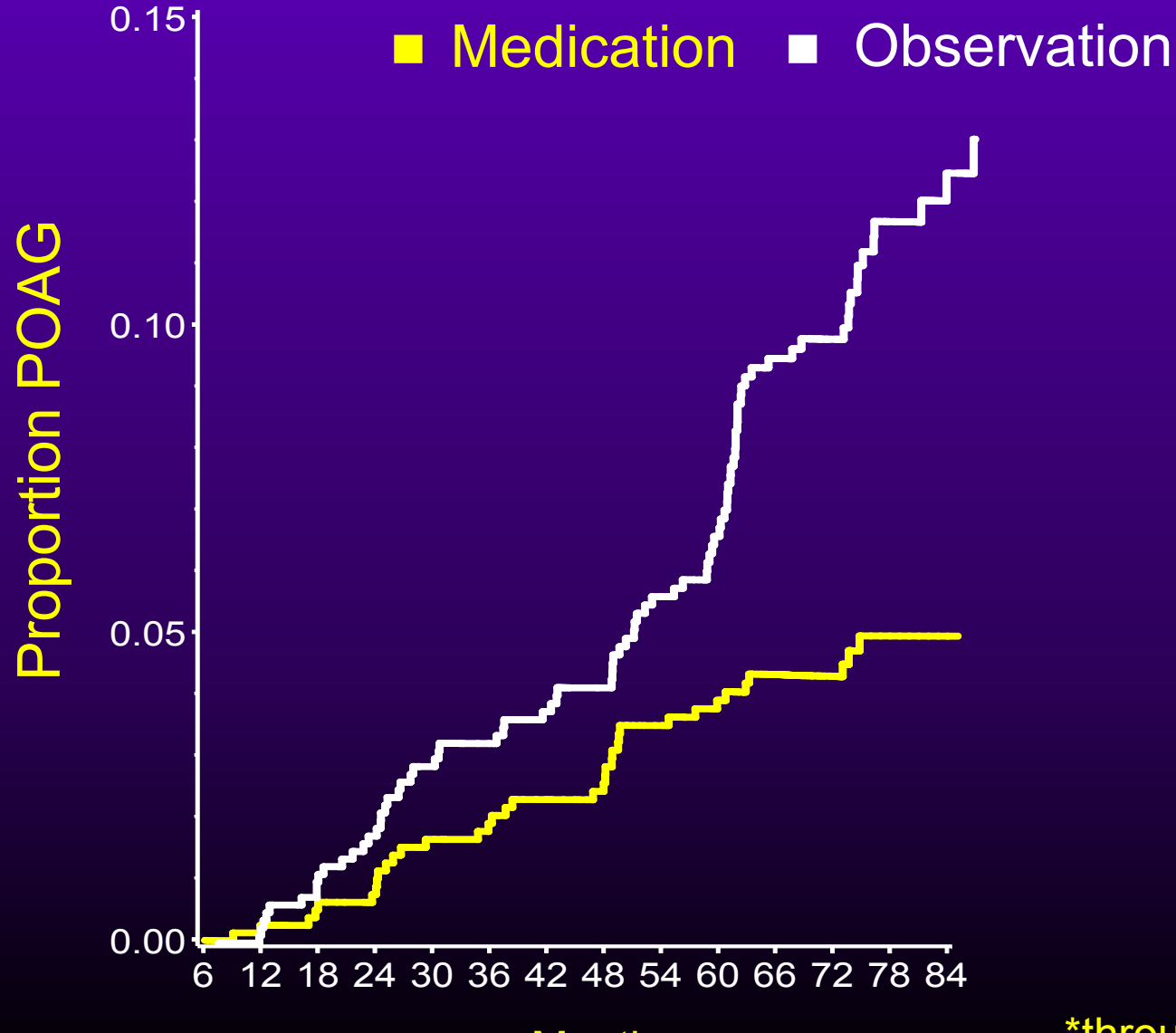
Progress and Outcome of Study Participants

	Medication		Observation		All	
	n	%	n	%	n	%
Randomized	817	100	819	100	1636	100
Died	26	3.2	29	3.5	55	3.4
Inactive	89	10.9	84	10.2	173	10.6
Non-adherence to randomization	40	4.9	42	5.1	82	5.0
Reproducible VF or Optic Disc abnormality due to any cause	81	9.9	137	16.7	218	13.3
Endpoints attributed to POAG	36	4.4	89	10.9	125	7.6

Log rank p<0.001

Primary POAG Endpoints*

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



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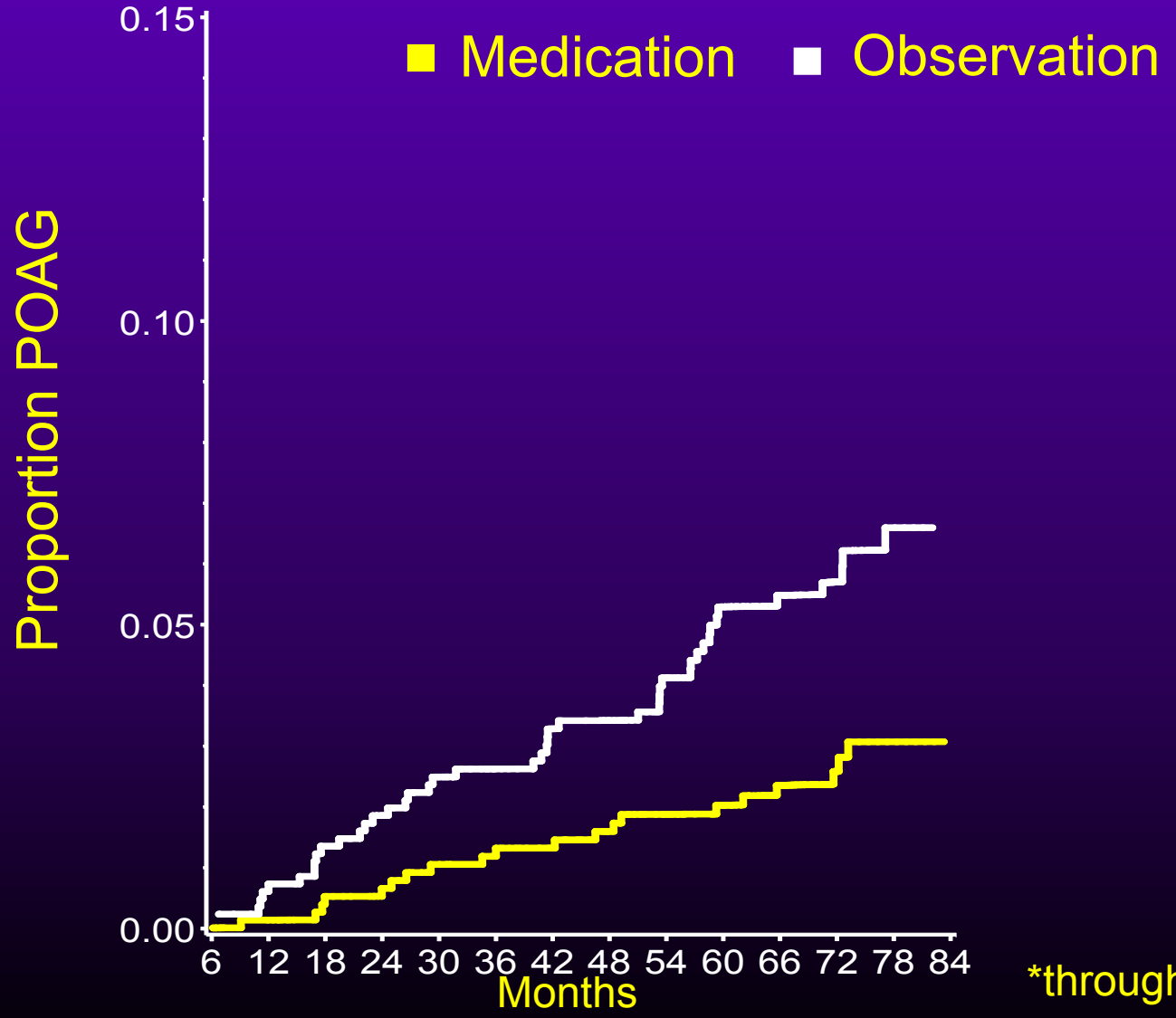
*through 8 Nov 200

1st Visual Field POAG Endpoint*

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



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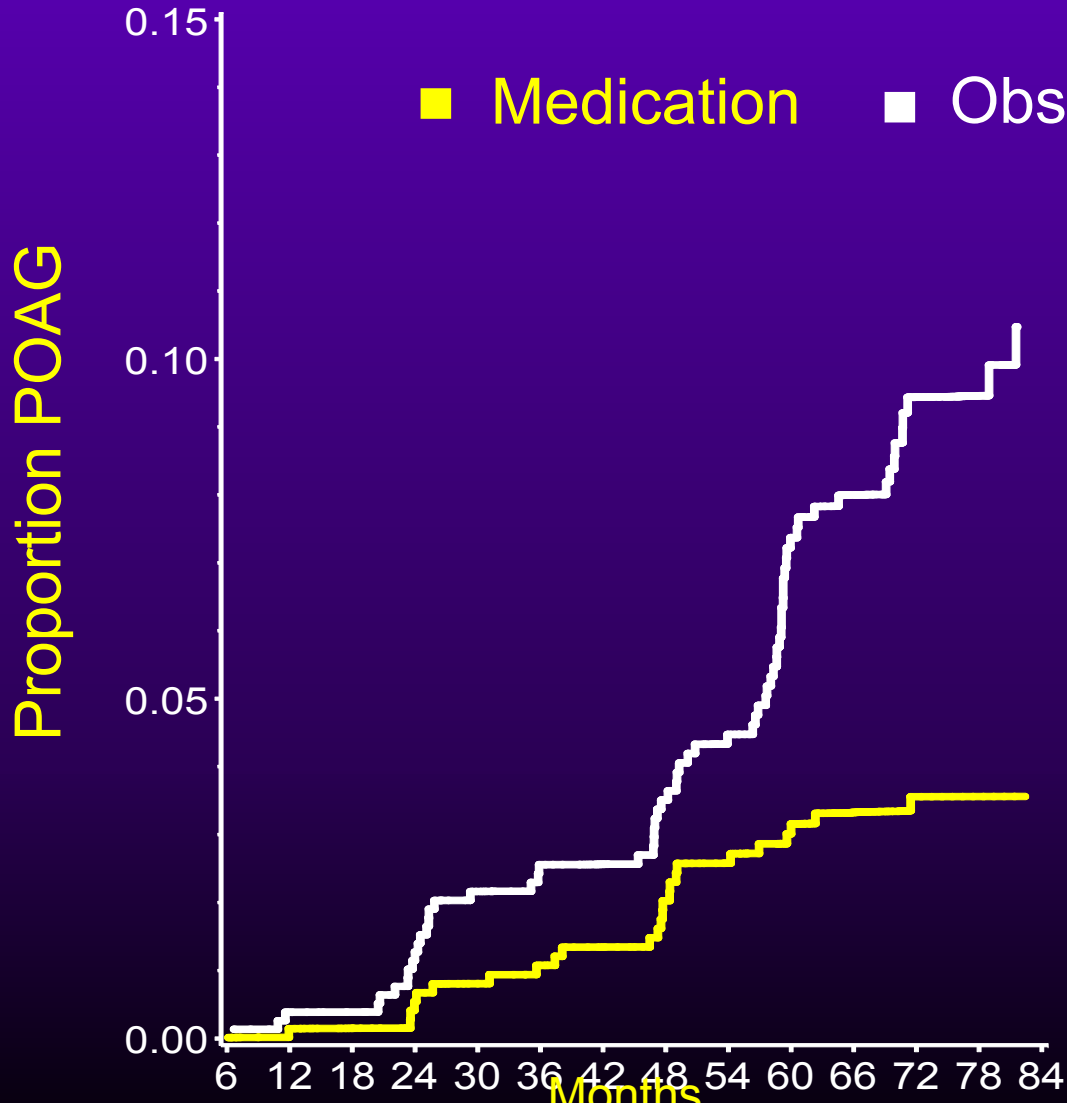
*through 8 Nov 2001

1st Optic Disc POAG Endpoint*

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



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*through 8 Nov 2001

First POAG Endpoint per Participant

	Medication		Observation	
	N	%	N	%
Visual Field	15	41.7	29	32.6
Optic Disc	18	50.0	51	57.3
Concurrent Visual Field and Optic Disc	3	8.3	9	10.1
Total	36	100	89	100

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

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

Prostaglandin analog > 6 months n = 380	17%
Observation group n = 631	8%

P <0.001

No difference between randomization groups in serious AEs for 9 of 11 organ systems.

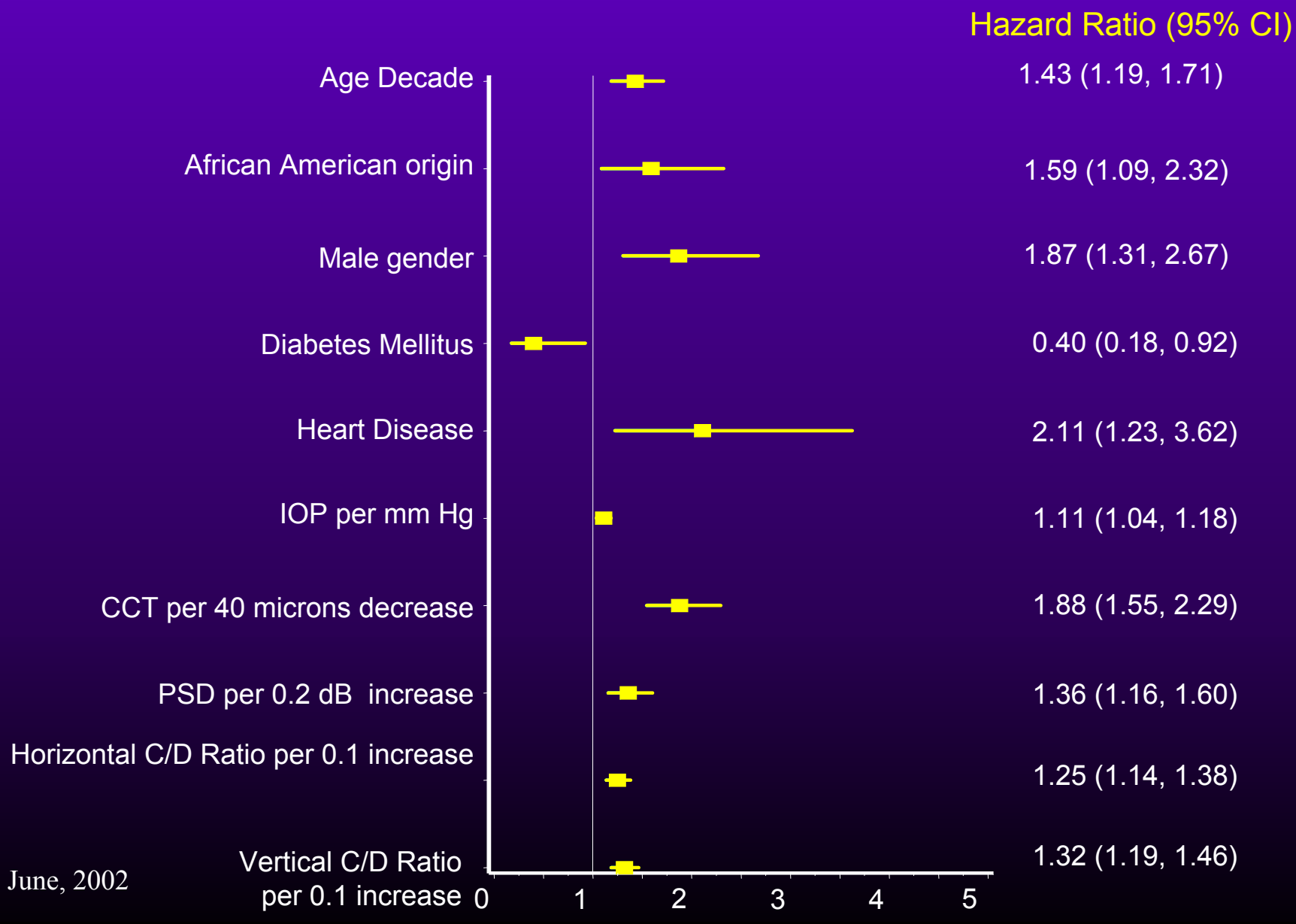
Borderline Safety Differences Between Randomization Groups

- 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



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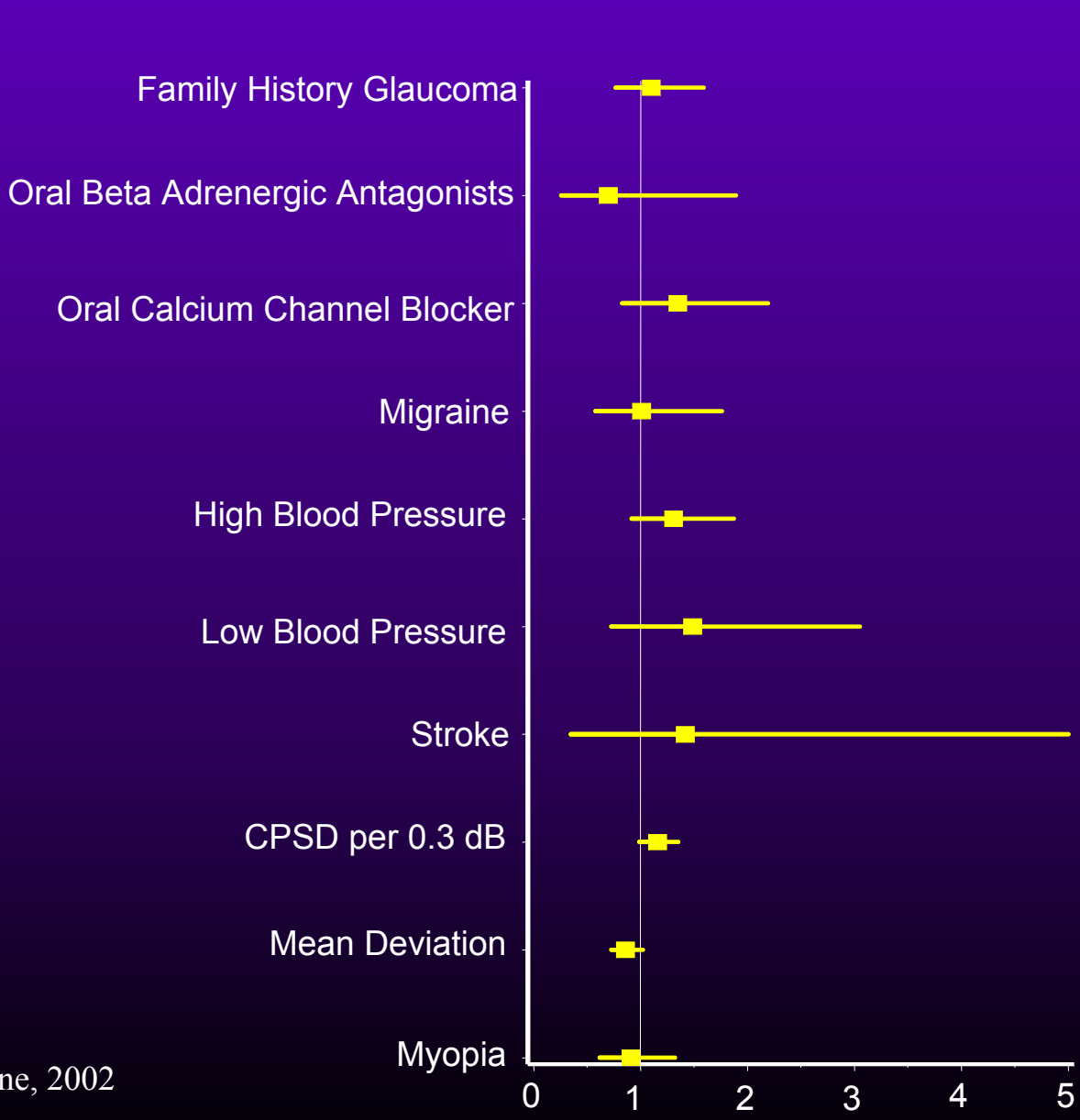

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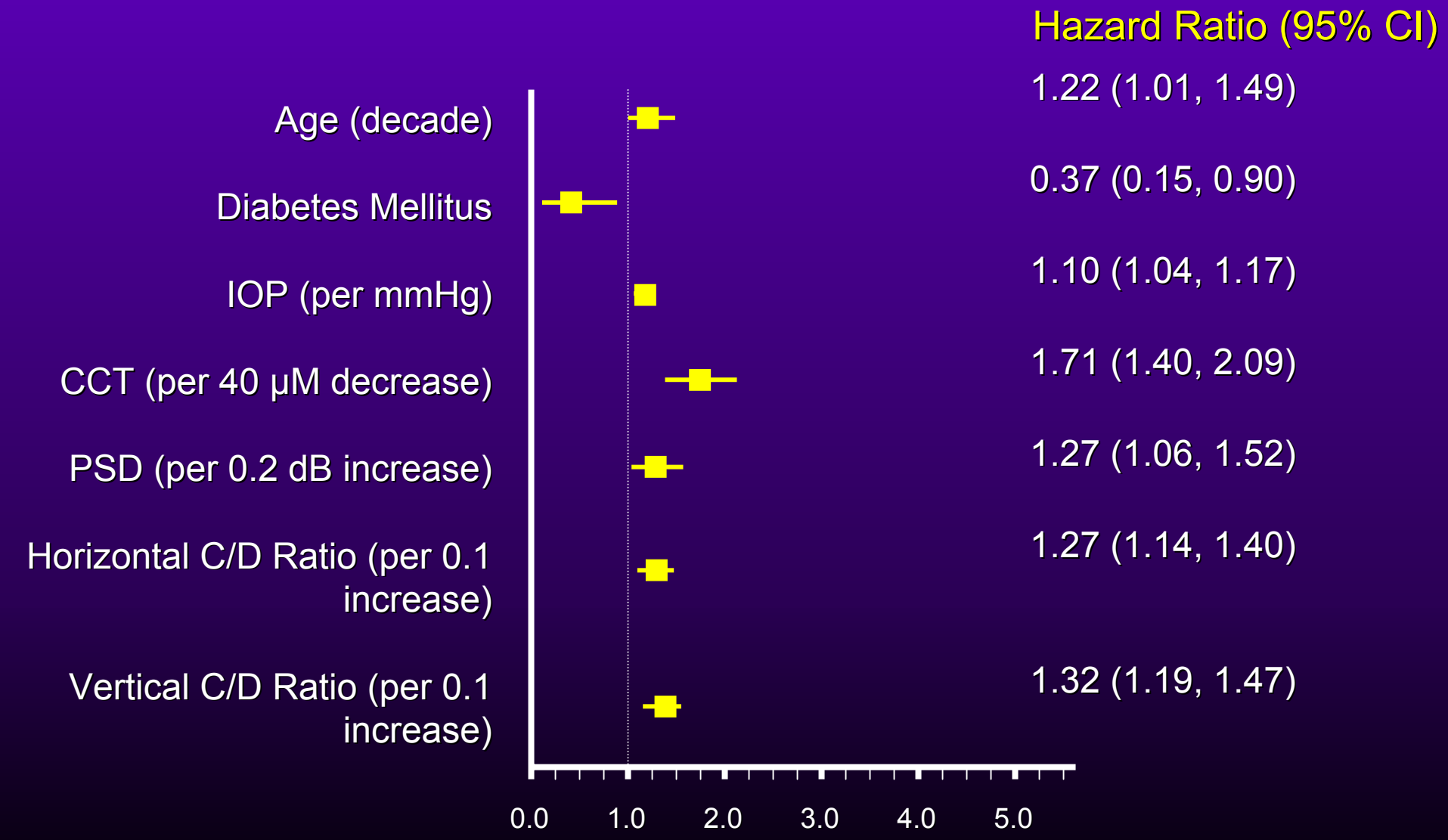
Significant Baseline Predictive Factors
from Multivariate Proportional Hazard Models



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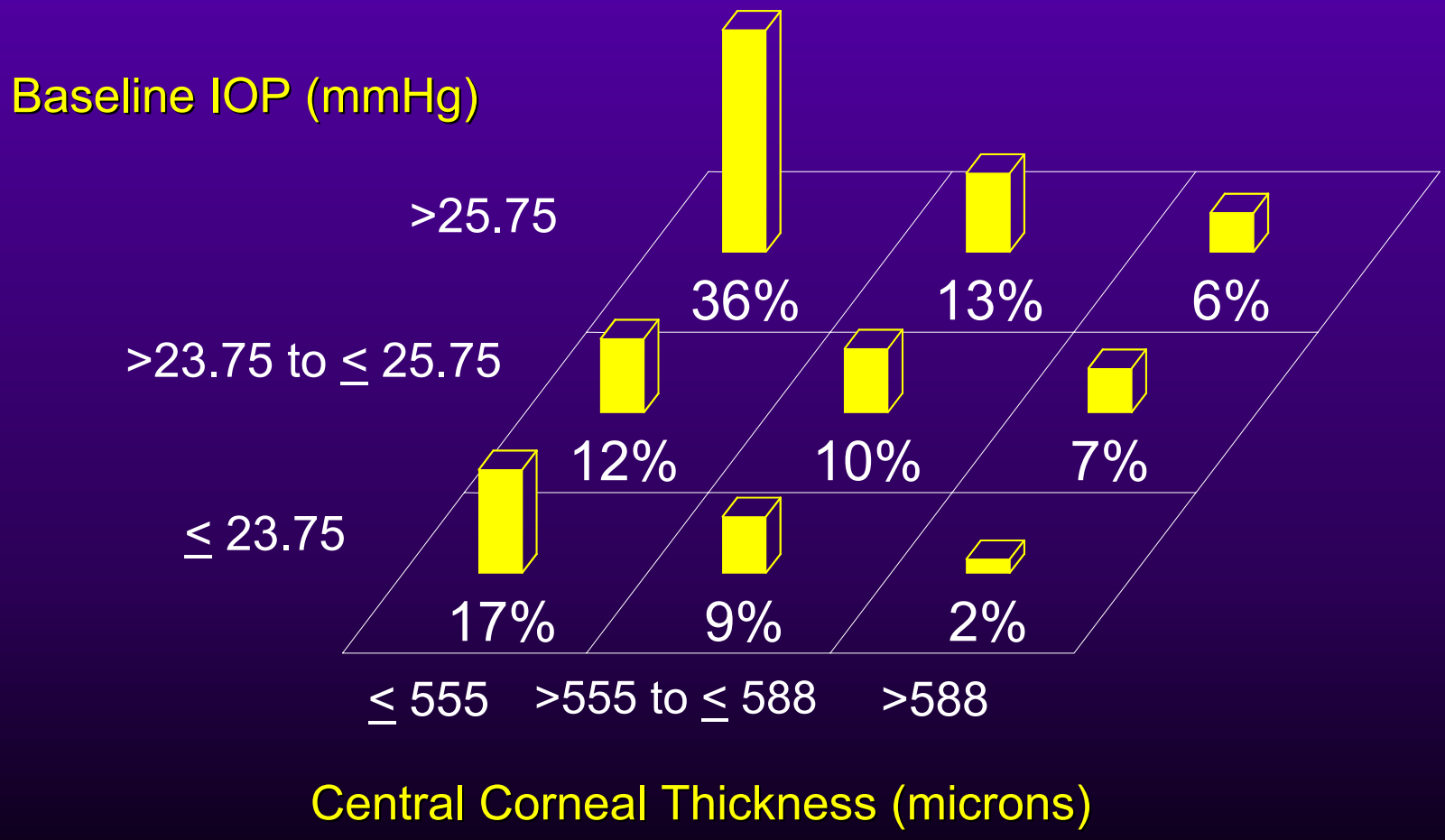
- African Americans have a higher prevalence and incidence of POAG.
- OHTS data suggests that this racial effect may be due to thinner central corneas and larger cup/disc ratios.

POAG Endpoints by Central Corneal Thickness and Baseline IOP (mmHg) in Observation Group*



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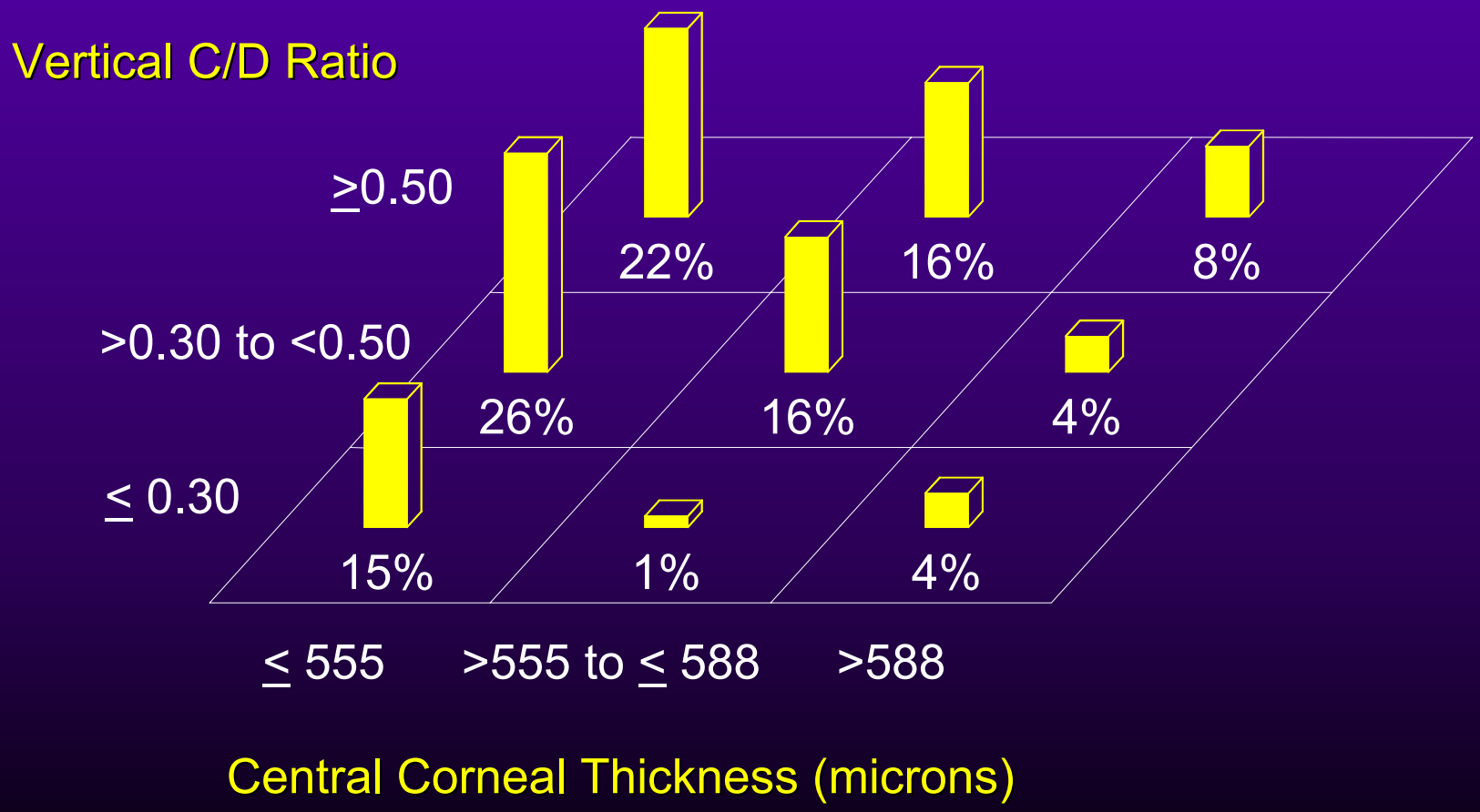
* through 8 Nov 2001

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



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* 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

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

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

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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

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