Managing Patients With Ocular Hypertension

Results From The Ocular Hypertension Treatment Study (OHTS)

The American Glaucoma Society
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The Ocular Hypertension Treatment Study Group (OHTS)
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OHTS

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Ocular Hypertension

A common condition

- What to do with these patients?
- How often should they be examined?
- Is preventative treatment effective?
- Who should be treated?

Ocular Hypertension

1. IOP ≥ 21 mmHg
2. No detectable visual field loss
3. No detectable optic disc or nerve fiber layer damage
4. Open angles
5. No ocular or systemic cause of increased IOP

Ocular Hypertension

- 119 million people in US over age 40 (Census 2000)
- 4%-8% of people in the United States over age 40 (4.8 – 9.5 million people) have OHT
- The number of affected people will increase with the aging of the population
- Managing this large group of people is associated with substantial costs for examinations, tests and treatment

Ocular Hypertension

- Elevated IOP is a leading risk factor for development of POAG
- Only modifiable risk factor for POAG
- Patients can lose a substantial proportion of their nerve fiber layer before POAG is detected by standard clinical tests

Quigley HA, et al. Arch Ophthal 1981;99:635

Does Treatment of Ocular Hypertension Prevent POAG?

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

Investigator	Protective
Becker & Morton	yes
Shin *et al.*	yes
Kitizawa	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

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Kass, et al. 2002

The OHTS Entry Criteria

- Age 40 - 80
- Normal visual fields
  - Humphrey 30-2
- Normal optic discs
- Untreated IOP:
  - 24 to 32 mm Hg in one eye
  - 21 to 32 mm Hg in fellow eye

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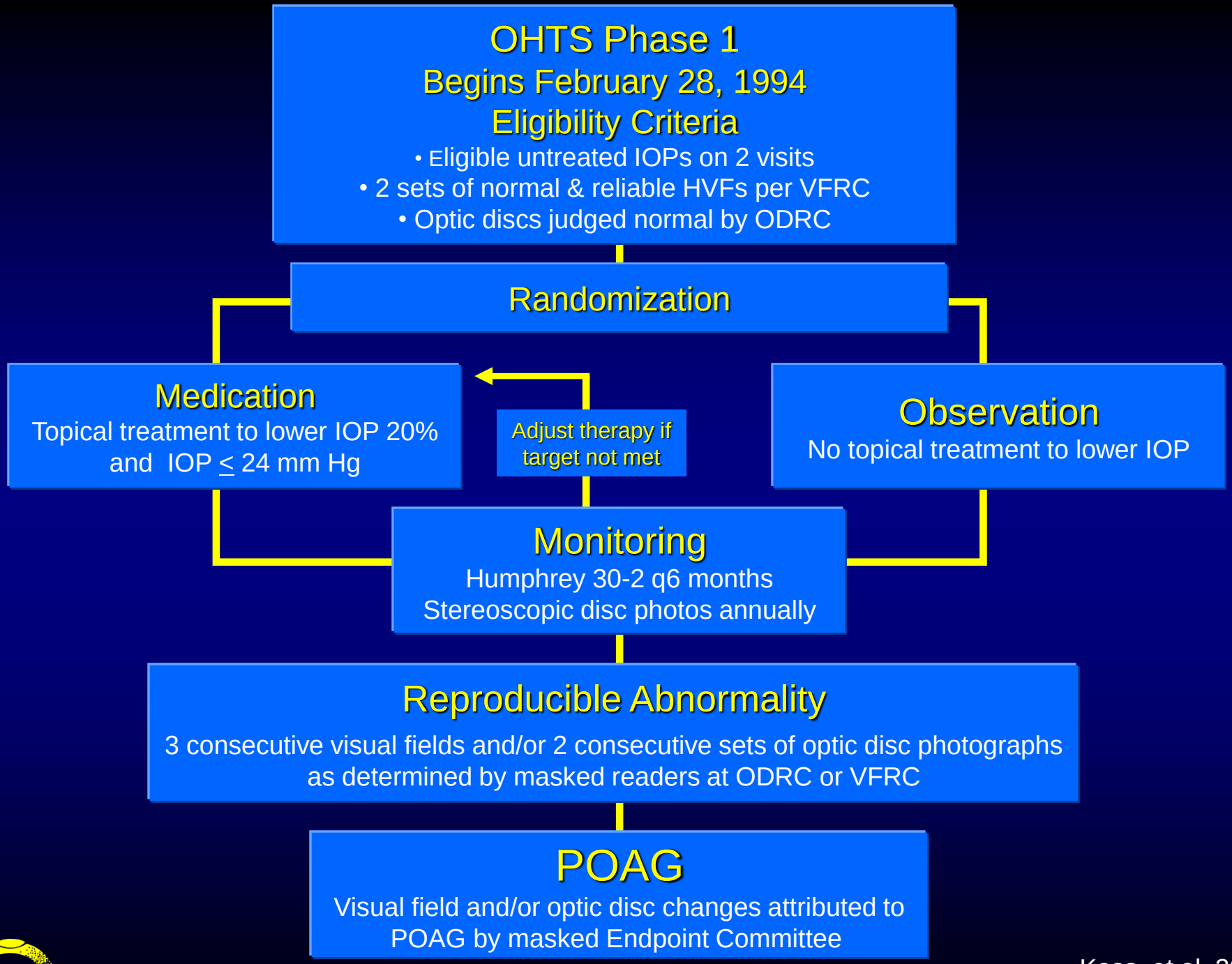

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Baseline Characteristics

	Baseline Characteristics N=1,636
Age (mean ±SD)	55.4 ±9.6 SD
White	70%
African American	25%
Hispanic	4%
Other	1%
Sex	
Male	43%
Female	57%
IOP, mm Hg	24.9 ±2.7 SD
Vertical CD	0.39 ±0.2 SD
CCT	572 ±38.4 SD

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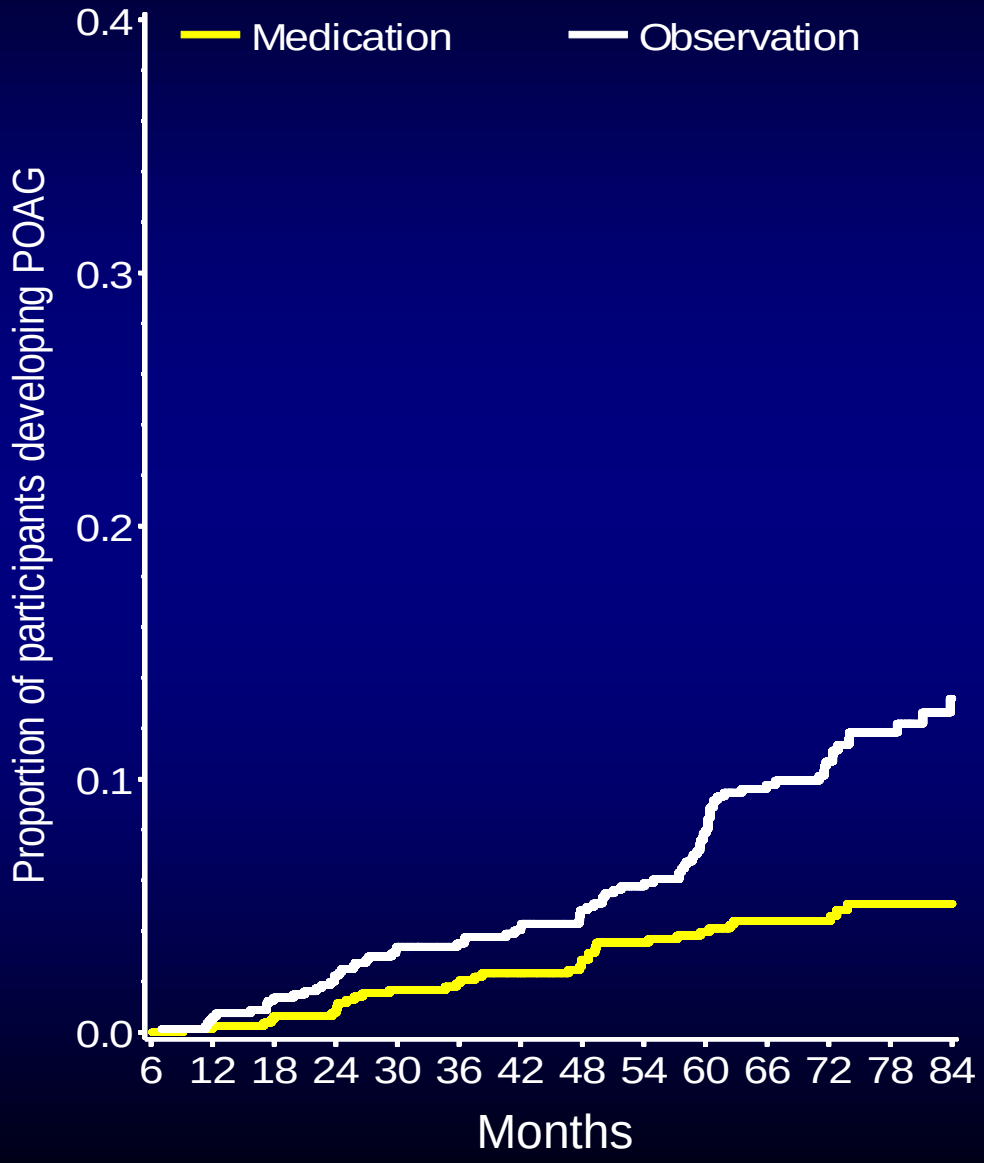
OHTS Phase 1: Primary POAG Endpoints

Log rank P-value<0.001, hazard ratio 0.40, 95% confidence interval (0.27, 0.59)
Cumulative proportion POAG at 60 months, 9.5% in OBS and 4.4% in MEDS



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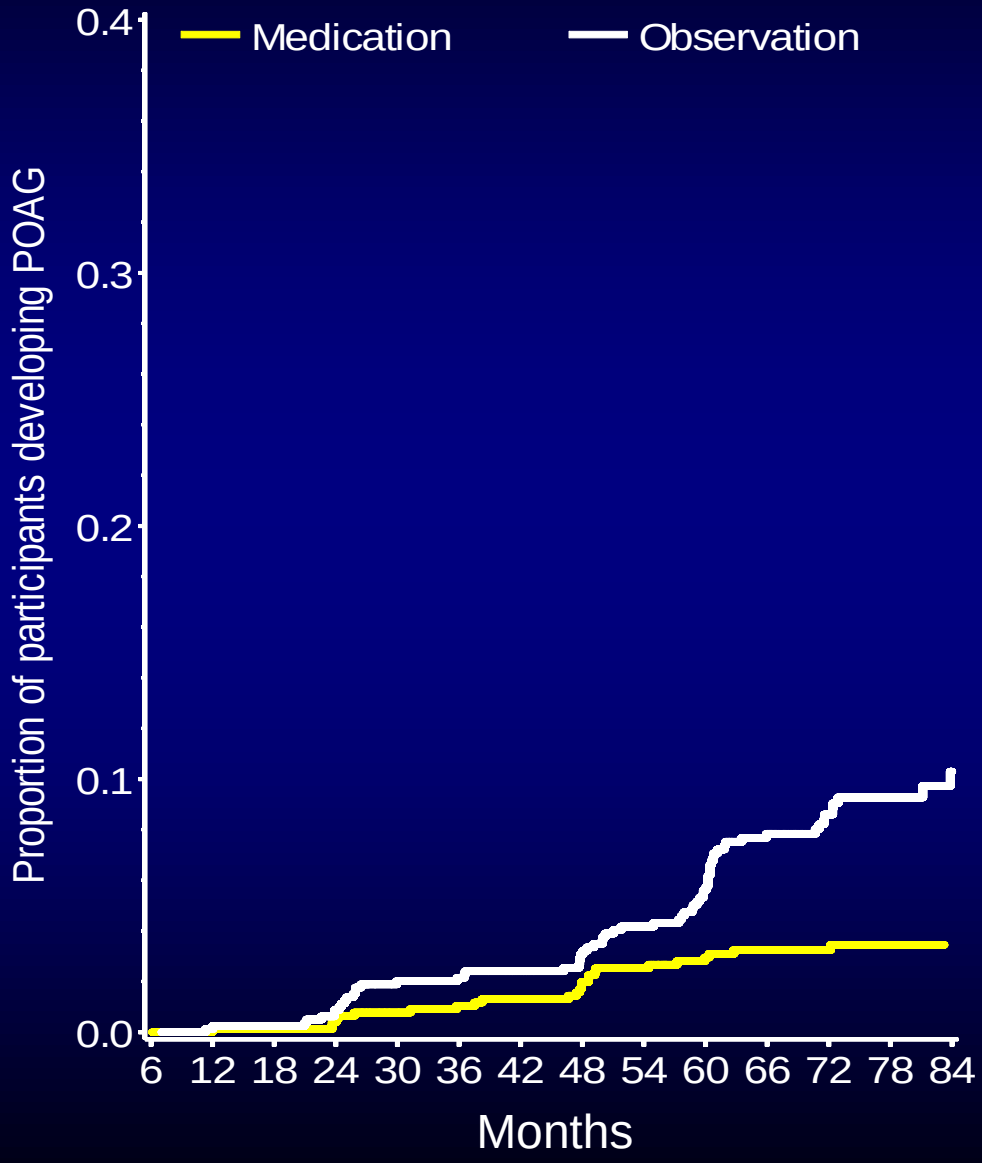
OHTS Phase 1: First Optic Disc POAG Endpoint

Log rank P-value<.0001, hazard ratio 0.36, 95% confidence interval (0.23, 0.56)
Cumulative proportion POAG at 60 months, 7.7% in OBS and 3.2% in MEDS



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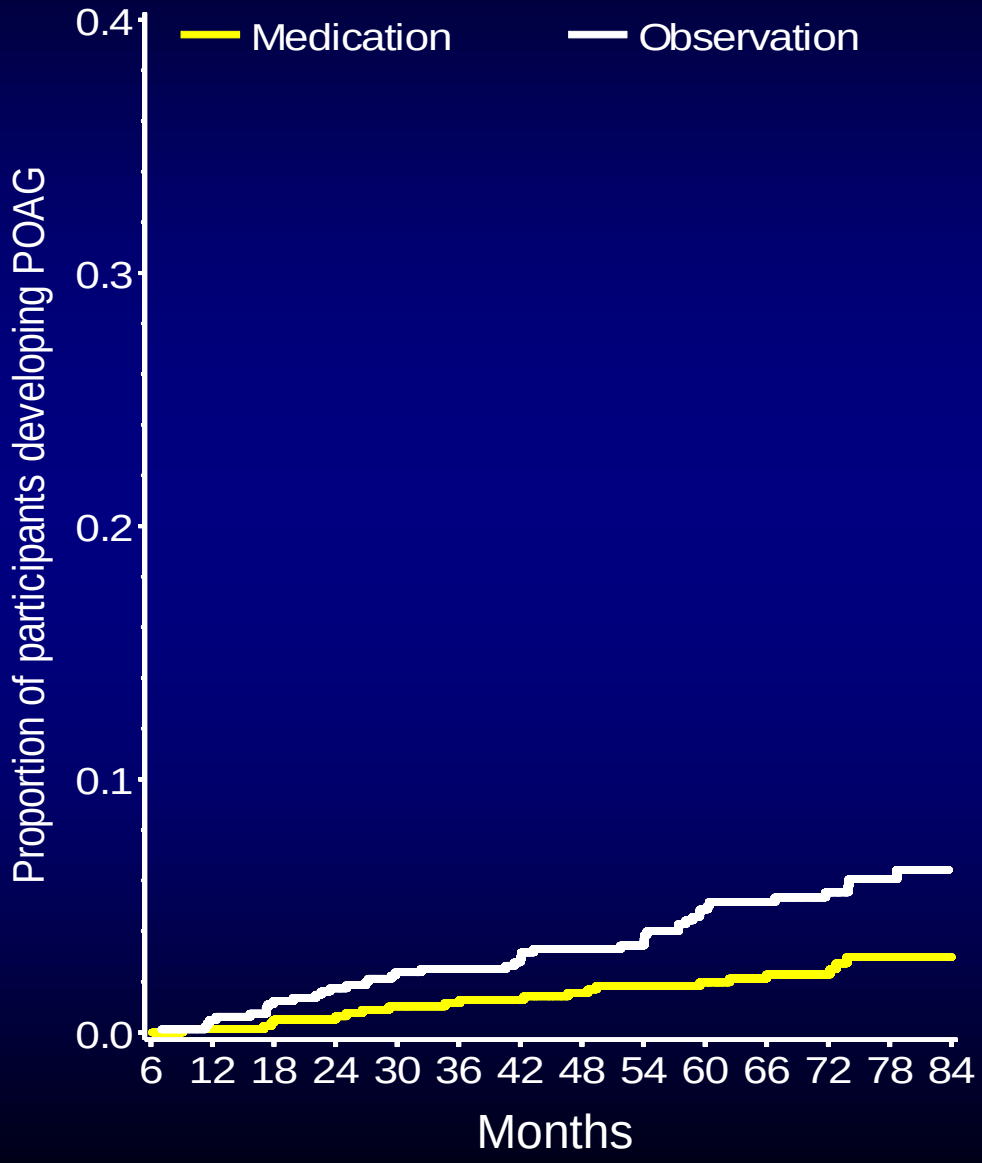
OHTS Phase 1: First Visual Field POAG Endpoint

Log rank P-value=0.002, hazard ratio 0.45, 95% confidence interval (0.26, 0.76)
Cumulative proportion POAG at 60 months, 5.2% in OBS and 2.1% in MEDS



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OHTS Phase 1: First POAG Endpoint per Participant

	Observation N=89	Medication N=36
	Percent	Percent
Optic Disc	57.3%	50.0 %
Visual Field	32.6%	41.7%
Concurrent Visual Field and Optic Disc	10.1%	8.3%
Total	100%	100%

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OHTS Phase 1: Summary

- Medication produced about a 20% reduction in IOP.
- Medication 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.

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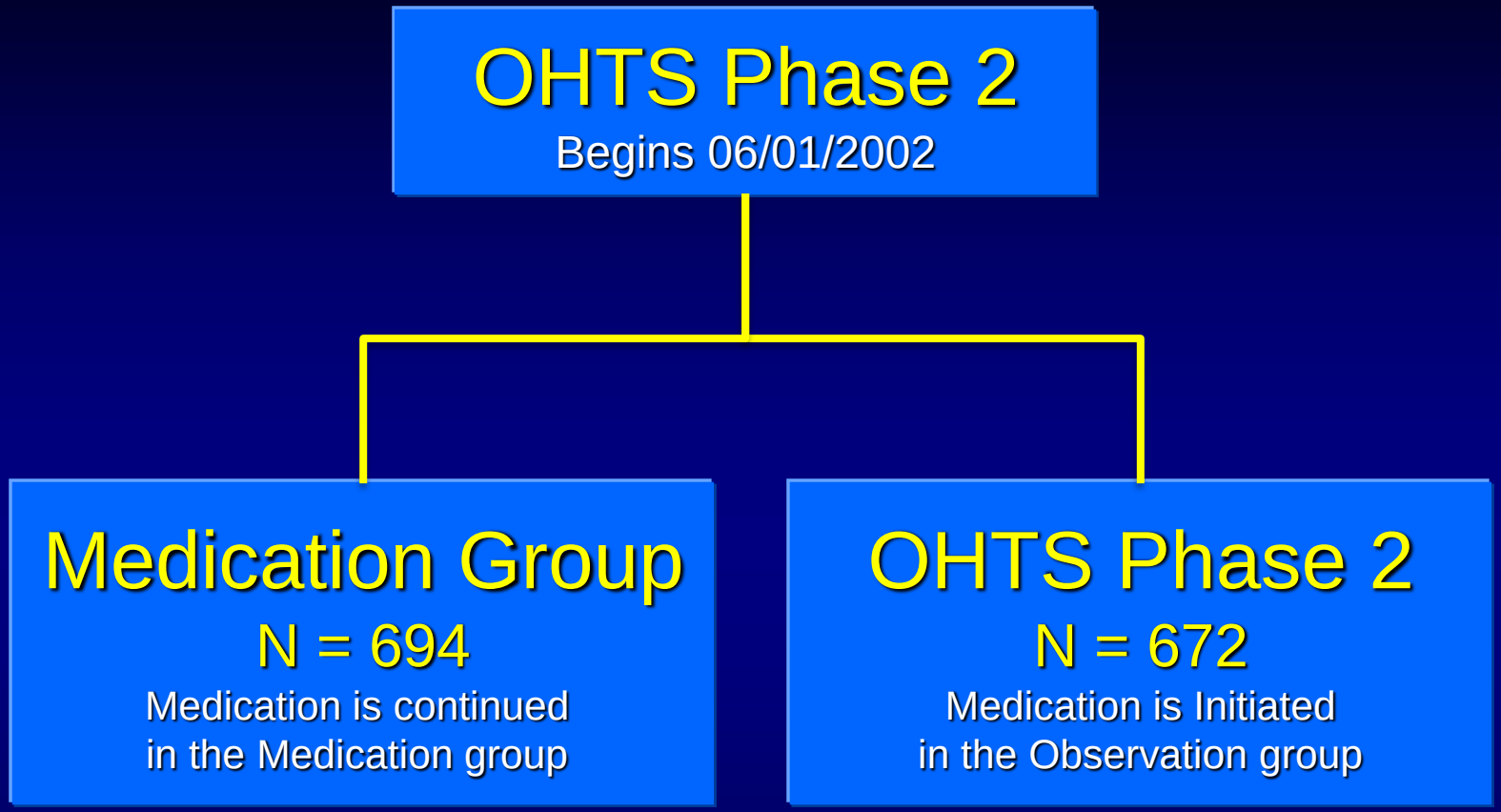
OHTS Phase 2: Rationale

- OHTS Phase 1 provides proof of concept: medication reduces the incidence of POAG.
- OHTS Phase 1 does not indicate when medication should begin.
- OHTS Phase 1 does not indicate if all OHT patients should receive early medication.
- Is there a penalty for delaying medication in OHT?


OHTS Phase 2
Begins 06/01/2002
Medication Group
N = 694
Medication is continued
in the Medication group
OHTS Phase 2
N = 672
Medication is Initiated
in the Observation group

OHTS Phase 2: Methods

- After 7.5 years of observation, participants originally randomized to observation group start medication.

- This creates:

  Delayed treatment group

  Observation group followed for 7.5 years then treated for 5.5 years

  Early treatment group

  Medication group treated for median of 13 years from the beginning

- Compare incidence of POAG at 13.0 years

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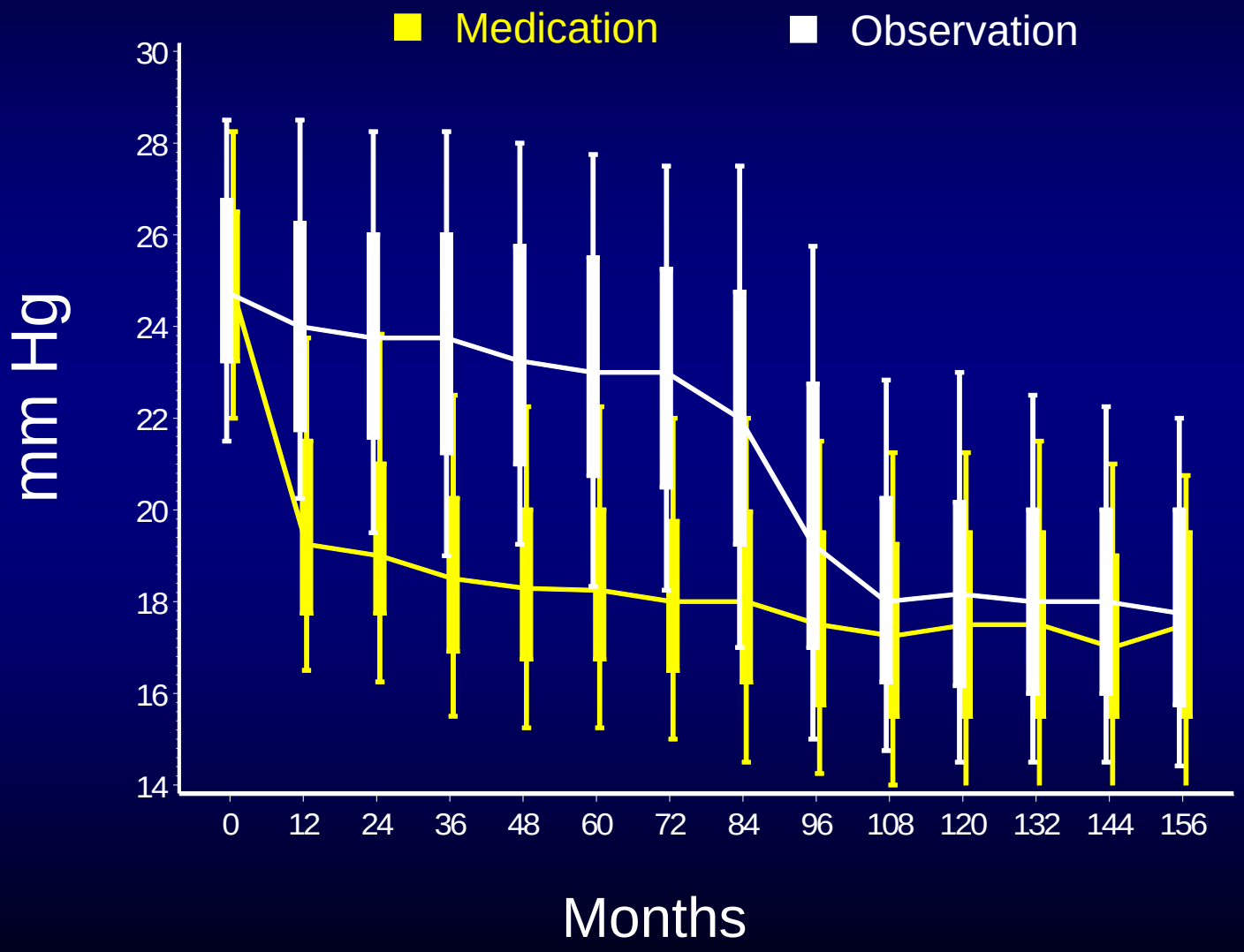
Median IOP thru 13 Yrs by Randomization Group



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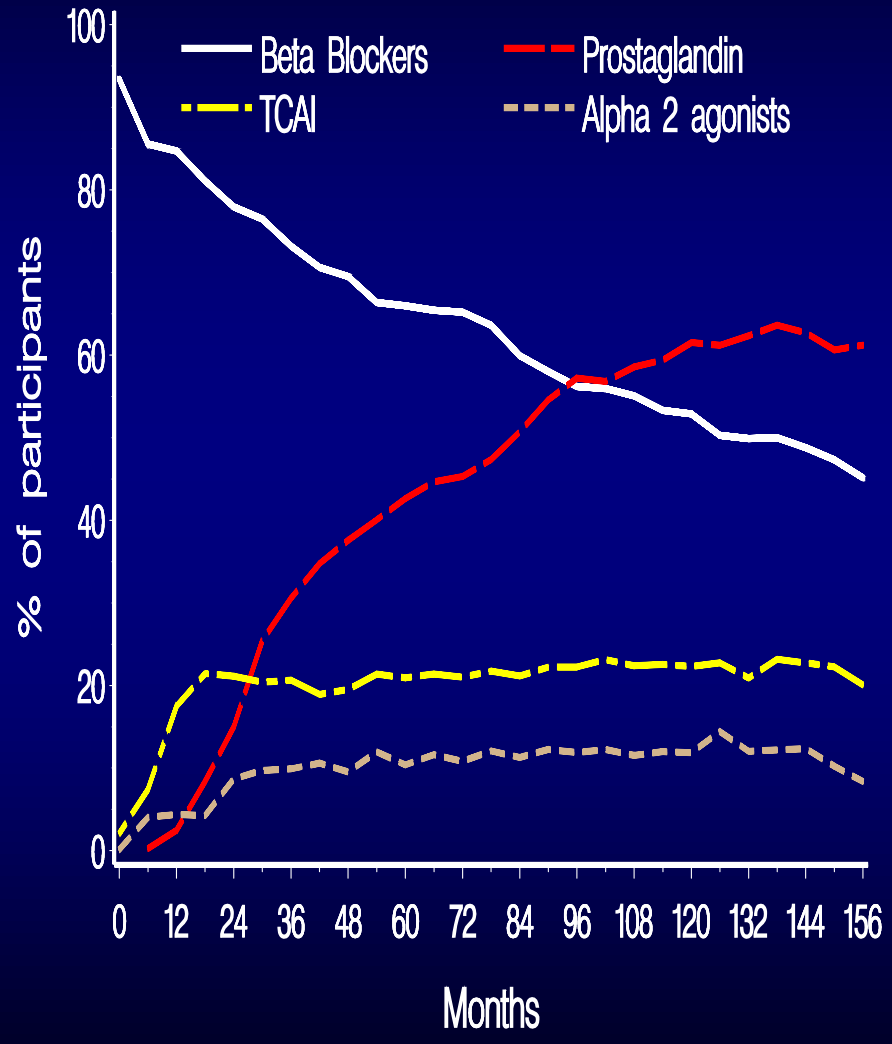
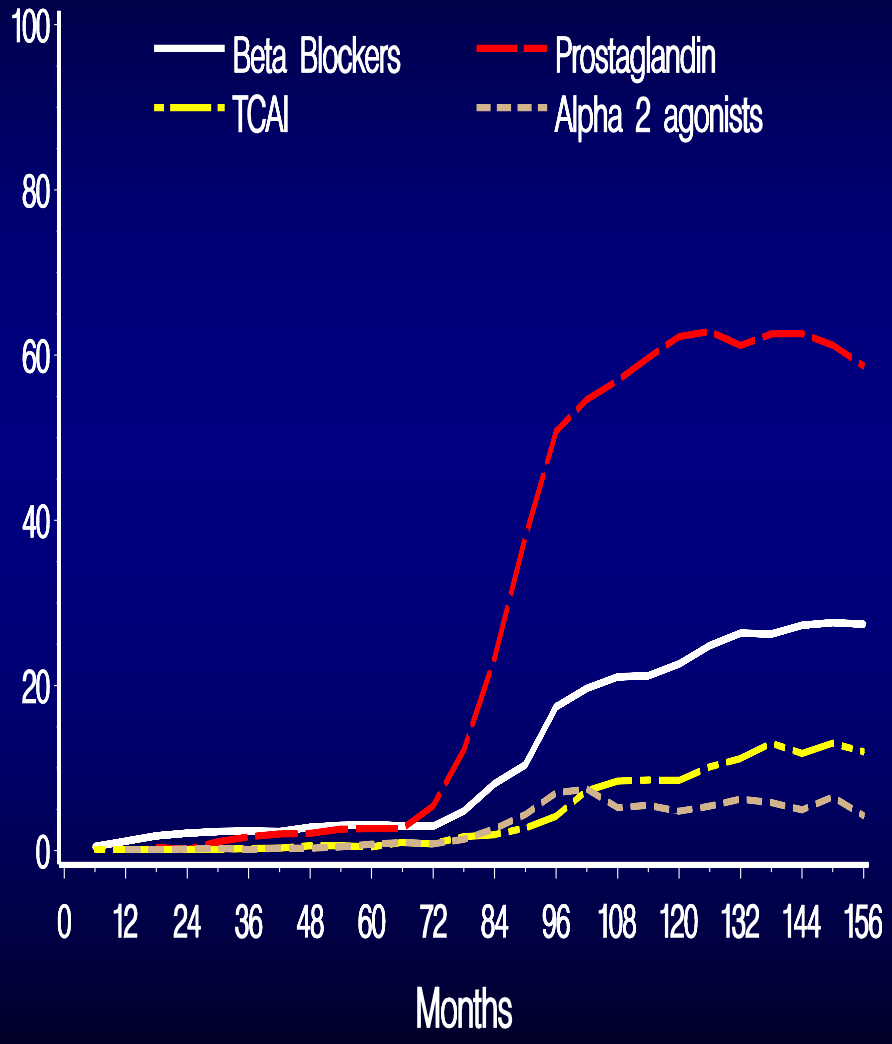
OHTS: Medication Participants



OHTS: Observation Participants



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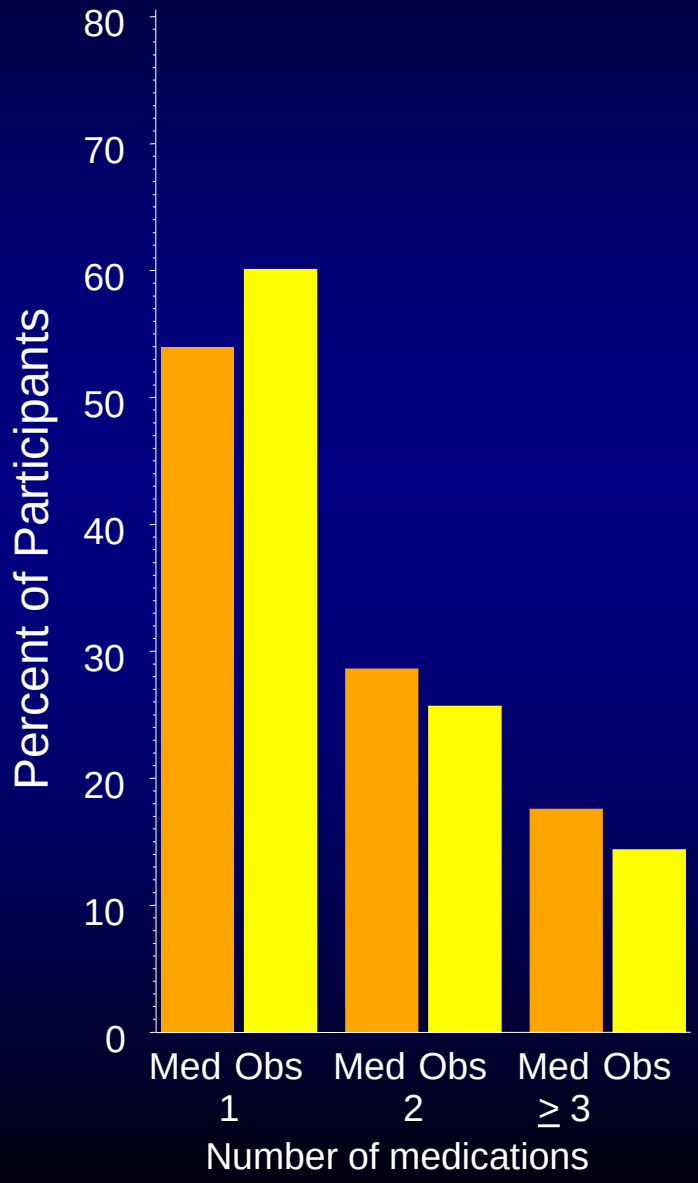
Number of Medications Prescribed at Last Visit

Only includes participants who were on medications.



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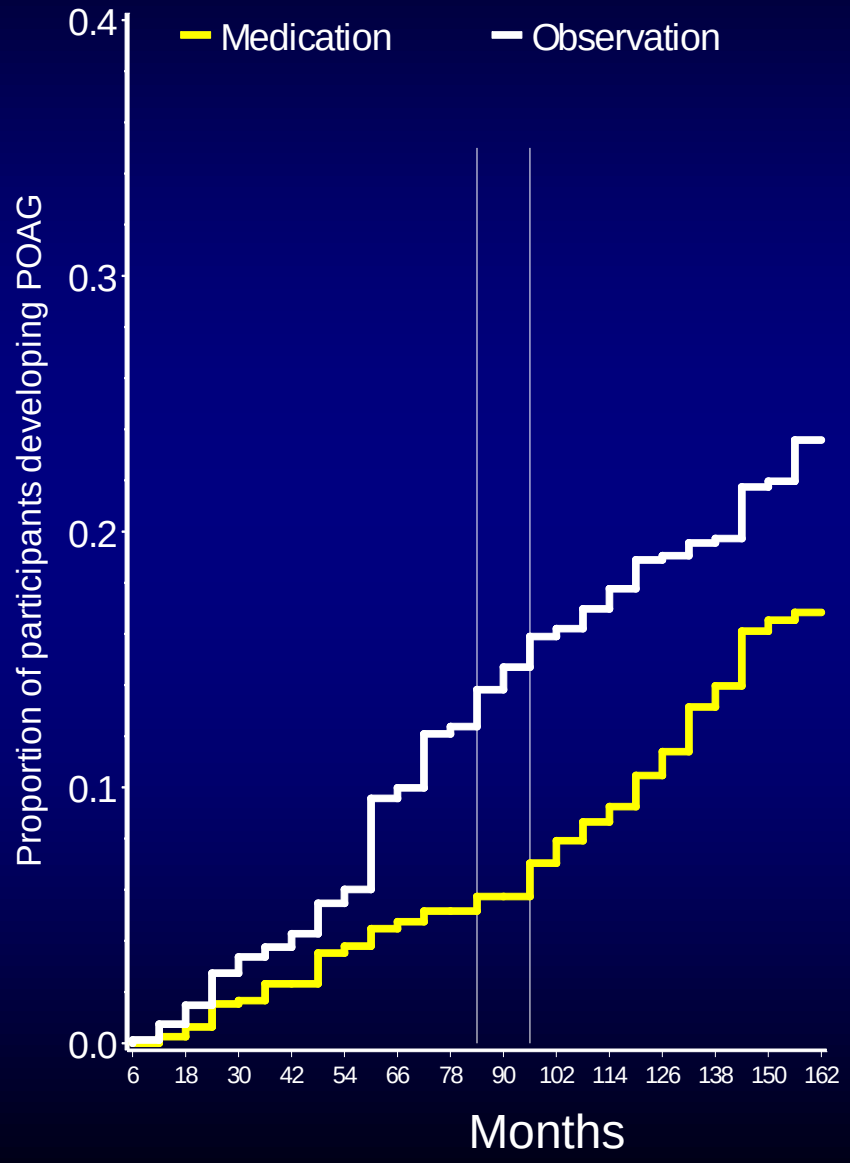
OHTS: Cumulative Incidence of POAG by Randomization Group

Complementary log log at 13 years, p=0.009

Cumulative proportion POAG at 13 years, 22% in OBS and 16% in MEDS



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Median Time to Develop POAG

Observation Group	6.0 years
Medication Group	8.7 years

$P \leq .001$

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OHTS Phase 1

Incidence of POAG is nearly 60% lower in the Medication Group

Hazard ratio for medication group at 60 months
0.40 (0.27-0.59); $P \leq .001$

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OHTS Phase 2

Incidence of POAG is not different between observation and medication groups

Hazard Ratio for medication group
1.06 (0.74-1.50); $P = .77$

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Burden of Disease to Study End

Participants who Developed POAG in 0,1,2 Eyes

Eyes Developing POAG	OBS		MEDS	
	n	%	n	%
0 Eyes	655	80%	702	86%
1 Eye	113	14%	83	10%
2 Eyes	51	6%	32	4%
Total	819	100%	817	100%

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Burden of Disease to Study End

Participants who Developed POAG Visual Field Loss and/or Disc Deterioration

Eyes Developing POAG		OBS N=819	MEDS N=817
VF POAG	0	88%	91%
	1	10%	8%
	2	2%	1%
Optic Disc POAG	0	84%	89%
	1	11%	8%
	2	5%	3%
VF and Optic Disc POAG	0	92%	95%
	1	7%	4%
	2	1%	1%

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Cumulative Proportion Developing POAG at 13 Yrs. by Race

African Americans	0.28	(0.23-0.33)
Others	0.16	(0.14-0.19)

P = .001

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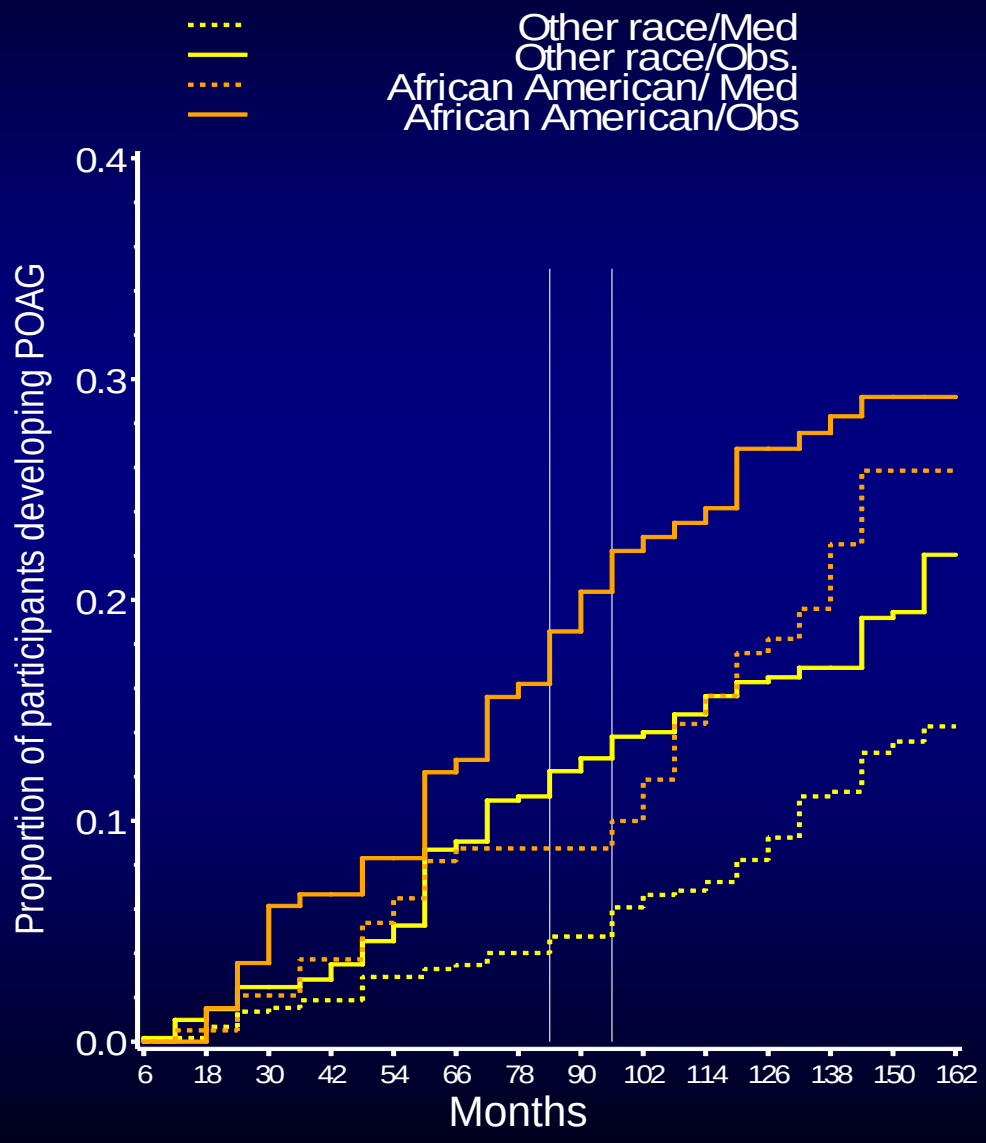
OHTS: Cumulative Proportion POAG at 13 yrs by Race

Other Races: 19.5% OBS and 13% MEDS

African Americans: 29% OBS and 26% MEDS



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- Self-identified race not significant predictor of POAG in a multivariate model.

- Race not significant when central corneal thickness and baseline cup-disc ratio included.

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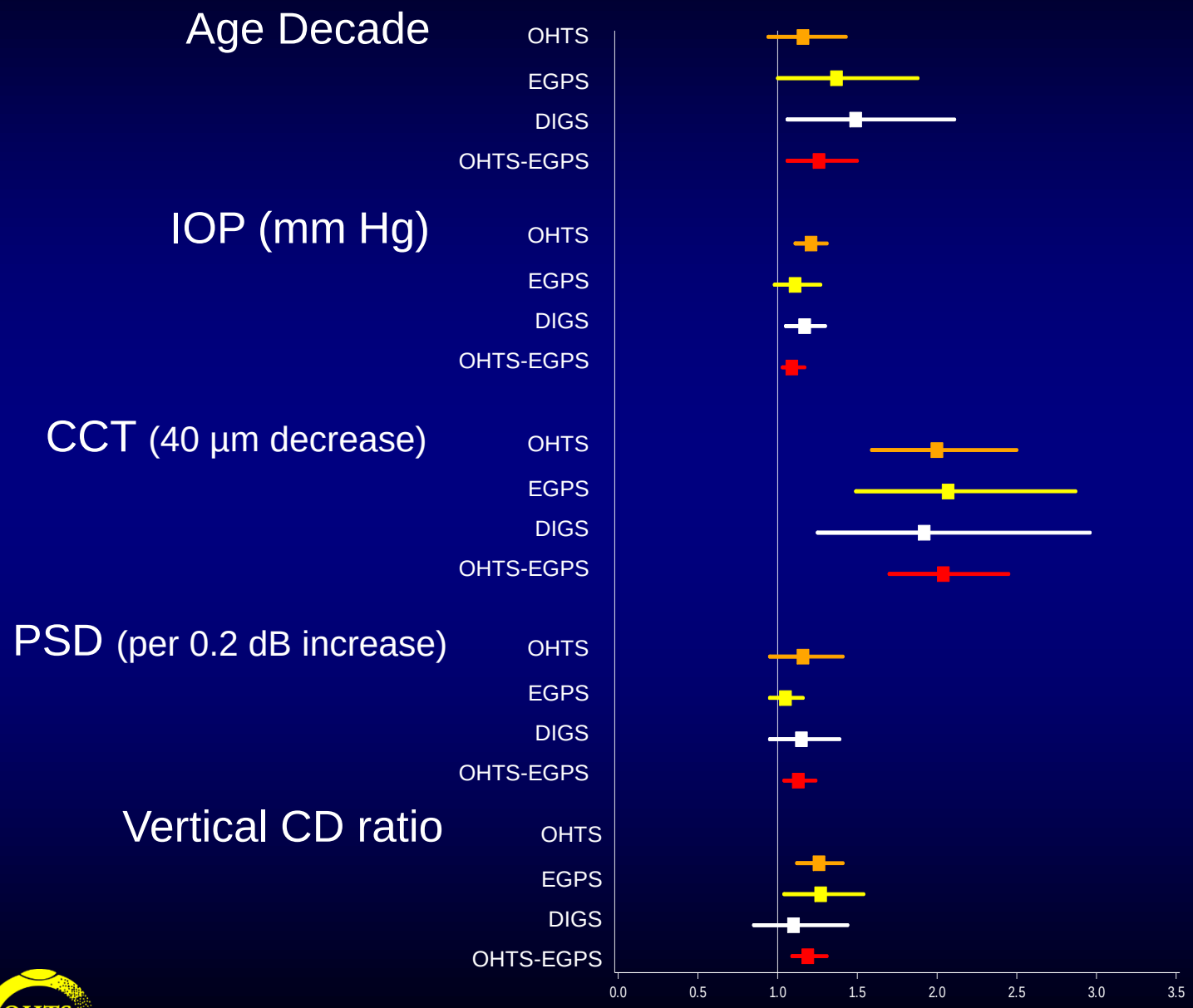
Baseline Predictive Factors for the Development of POAG

- Age
- IOP
- CCT
- Vertical C/D Ratio
- PSD

Multivariate Hazard Ratios for Predictors of POAG

OHTS Observation group, EGPS Placebo group, DIGS and OHTS/EGPS



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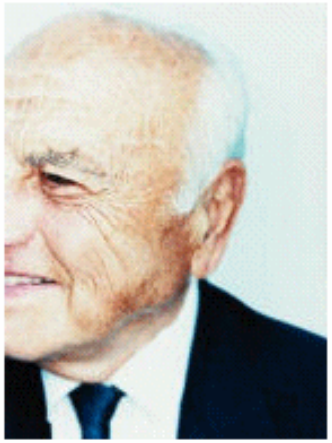
OHTS/EGPS 2007

Using the OHTS/EGPS Prediction Model for the Development of POAG

- Available on web free of charge
- http://ohts.wustl.edu/risk

The following example estimates the 5-year risk of developing POAG using the continuous method:

- 55 year-old
- Whose IOPs are right eye: 22, 23, 21 and left eye: 28, 24, 26
- Whose CCTs are right eye: 530, 536, 530 and left eye: 550, 545, 549
- Whose VCDs are right eye: 0.40 and left eye: 0.40
- Whose PSDs (Humphrey) are right eye: 1.8, 2.6 and left eye: 2.2, 2.2



FACTORS

Age 55	RIGHT EYE MEASUREMENTS			LEFT EYE MEASUREMENTS		
	1st	2nd	3rd	1st	2nd	3rd
Untreated Intraocular Pressure *(mm Hg)*	22	23	21	28	24	26
Central Corneal Thickness *(microns)*	530	536	530	550	545	549
Vertical Cup to Disc Ratio by Contour	0.40			0.40		
Pattern Standard Deviation ◉ Humphrey *(dB)* ○ Octopus loss variance *(dB)*	1.8	2.6		2.2	2.2	

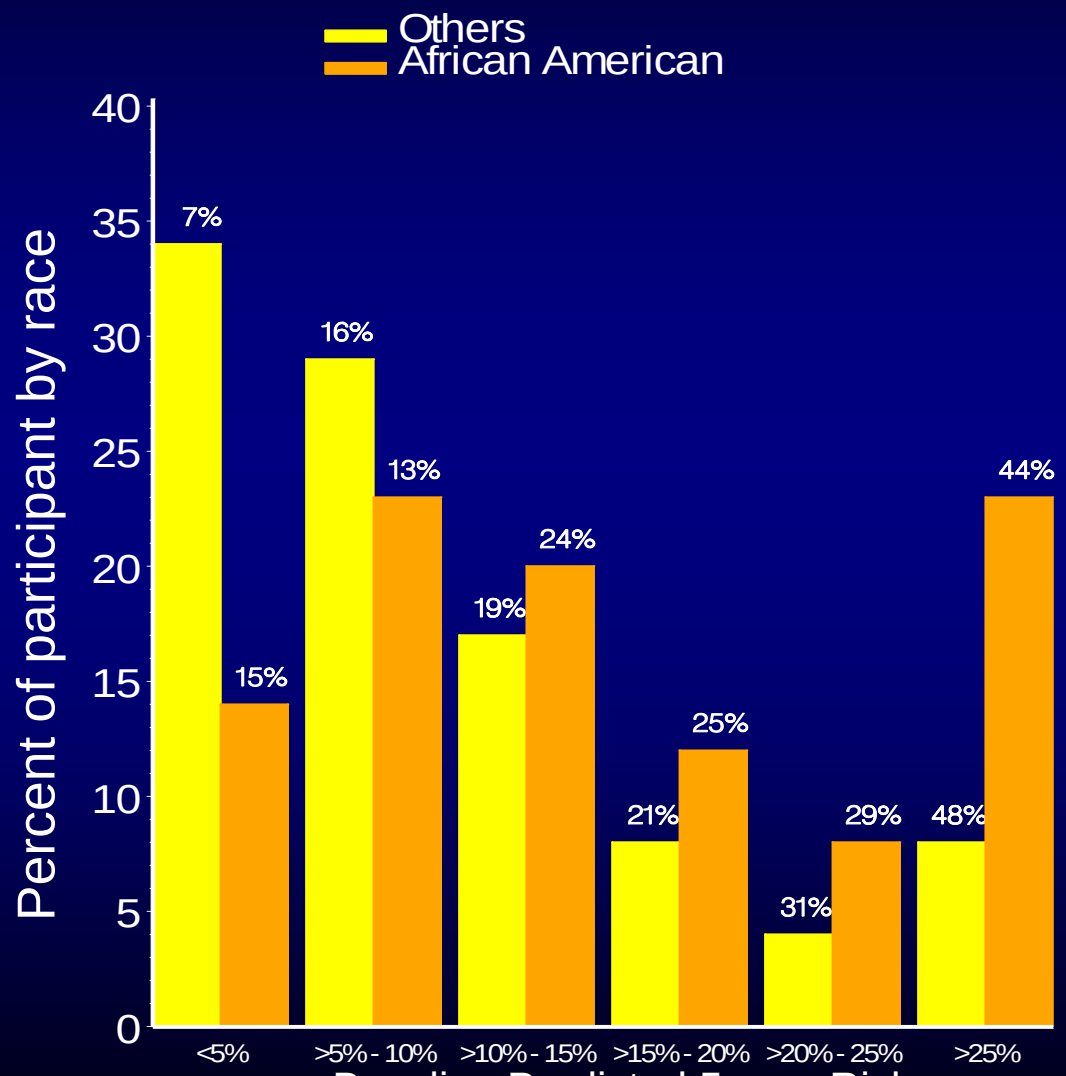
Close Window

16.9%

The patient's estimated 5-year risk (%) of developing early glaucoma in at least one eye.

Baseline Risk of Developing POAG by Race

At each level of risk. the percent of African Americans and “Other” participants developing POAG is similar.
Percent of Participants Developing POAG to study end on top of bars



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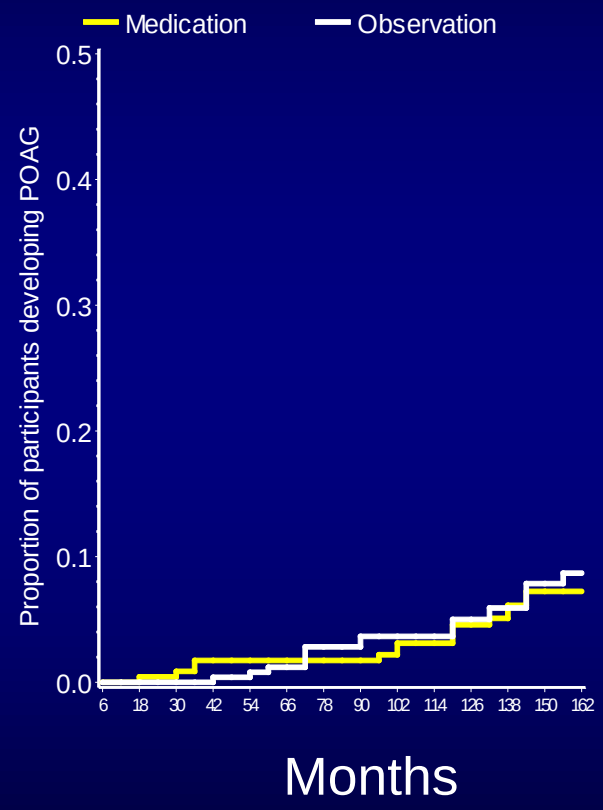
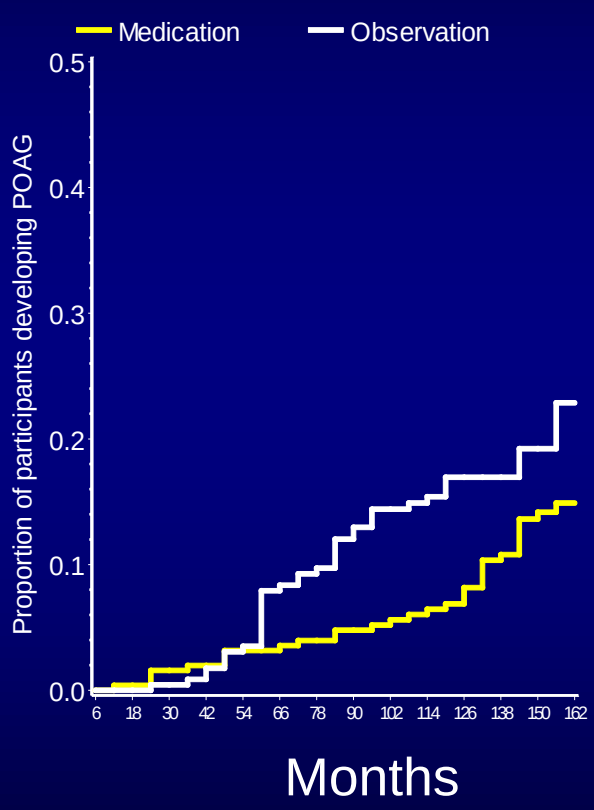
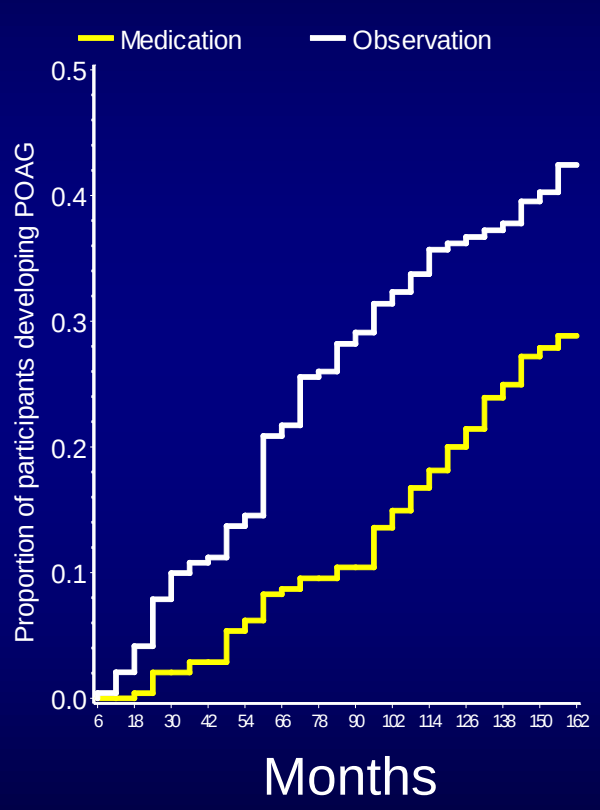
Cumulative Incidence of POAG in the “Lowest”, “Middle” and “Highest” Baseline Risk Groups for Developing POAG*







* Risk estimated by OHTS/EGPS risk calculator, 2007

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OHTS

Cumulative 13 year Incidence of POAG for "Lowest", "Middle" and "Highest" Baseline Risk Group*

	Lowest Risk < 6%	Middle Risk 6% to 13%	Highest Risk > 13%
Medication group	7% 4%-11%	14% 9%-18%	28% 22%-34%
Observation group	8% 4%-11%	19% 14%-25%	40% 33%-46%
P-Value	0.81	0.11	0.009

* OHTS/EGPS Risk Calculator, 2007

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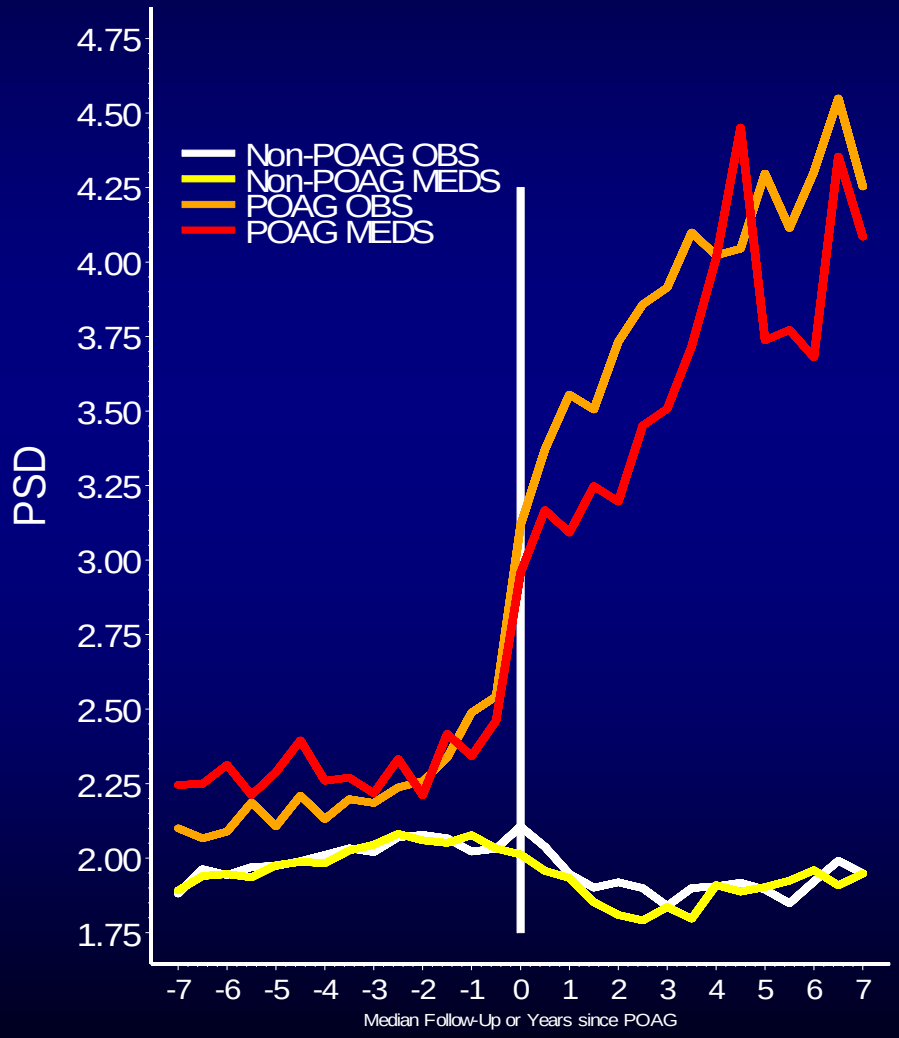
Mean PSD (Unadjusted) Before and After POAG (Vertical Line at "0")

- Patients who developed POAG had worse PSD at entry and worsened over time
- Patients who did not develop POAG did not change



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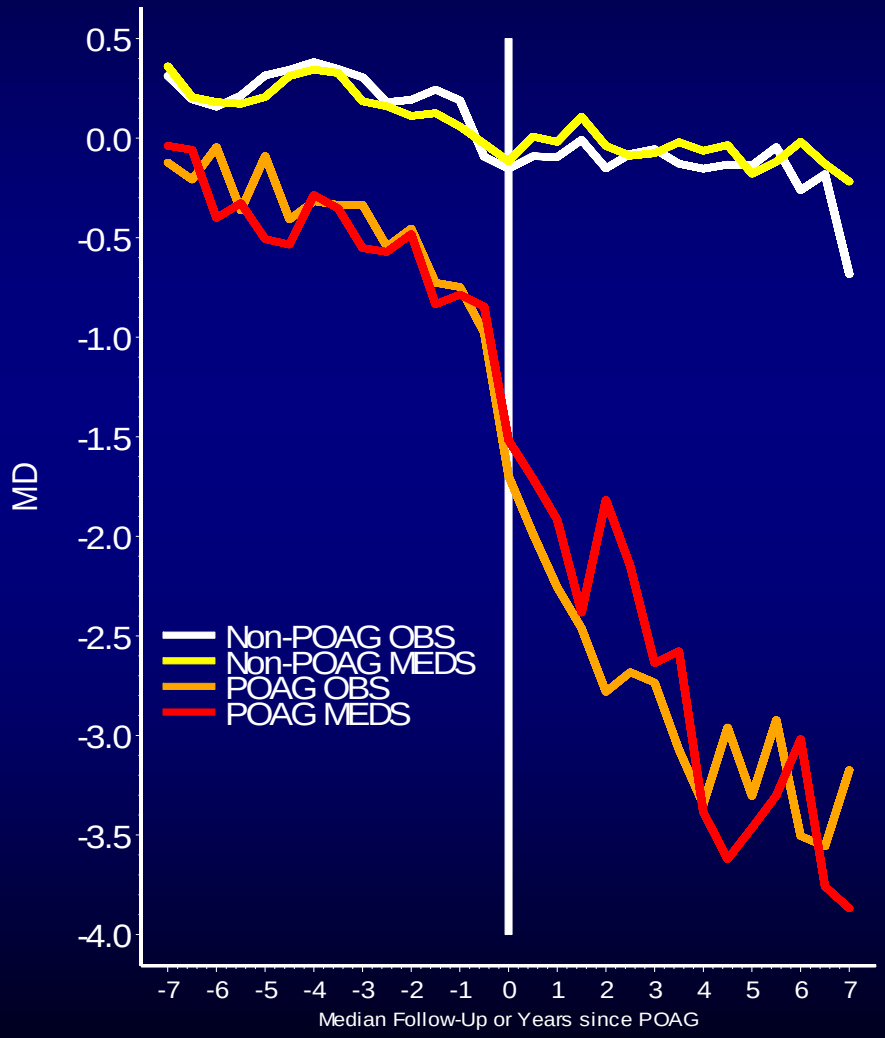
Mean MD (Unadjusted) Before and After POAG (Vertical Line at "0")

- Patients who developed POAG had worse MD at study entry and worsened over time
- Patients who did not develop POAG did not change



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Safety

No safety differences between randomization groups

- Mortality
- Adverse events
- Glaucoma Symptom Scale
- NEI VFQ
- MOS-SF 36

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Delaying Treatment of OHT

1. Increased cumulative incidence of POAG at 13 years (22% vs.16%)

2. More eyes with structural and functional damage (8% vs. 5%)

3. More participants with bilateral disease (6% vs. 4%)

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Delaying Treatment of OHT …

4. Shorter time to develop POAG (6.0 vs. 8.7 years)

5. Waiting does not have a large effect on MD and PSD (0.5db for PSD) within 5 years of developing POAG.

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How to Incorporate Information From OHTS Into Clinical Practice?

- Most OHT patients are at low risk. Most low risk OHT patients can be followed without medication.
- Delaying treatment for 7.5 years resulted in only a small absolute increase in POAG in low risk participants.
- Starting treatment of POAG at diagnosis has no major negative effect on prognosis over 5 years.

- High risk OHT patients may benefit from more frequent examinations and early treatment taking into consideration:
  - Patient age
  - Health status
  - Life expectancy
  - Personal preference

- Some clinicians may elect to follow all OHT patients without treatment.

  Requires timely visits, appropriate tests and interpretation. Risk status changes over time.

Limitations of OHTS

1. Study IOP goal was 20% reduction. May not be sufficient.
2. No measure of medication adherence.
3. Convenience sample, not population-based epidemiologic study.
4. Participants healthy and “squeaky clean” at baseline.
5. High threshold for diagnosing POAG.

OHTS Summary

1. Early medical treatment reduces the cumulative incidence of POAG.
2. The absolute effect is greatest in high risk individuals.
3. There is little absolute benefit of early treatment in low risk individuals.

OHTS Summary

4. There are safe and effective treatment options for most ocular hypertensive patients.

5. The risk of developing POAG continues over at least a 15 year follow-up.

OHTS Summary

6. African Americans develop POAG at a higher rate despite similar treatment and similar levels of IOP. Higher incidence is related to baseline risk factors.

7. Individualized assessment of risk is useful to patients and clinicians.

OHTS Clinical Centers

- Bascom Palmer Eye Institute
- Baylor Eye Clinic
- Charles R. Drew University
- Devers Eye Institute
- Emory University Eye Center
- Eye Associates of Washington, DC
- Eye Consultants of Atlanta
- Eye Doctors of Washington
- Eye Physicians and Surgeons of Atlanta
- Glaucoma Care Center
- Great Lakes Ophthalmology
- Henry Ford Hospitals
- Johns Hopkins University
- Jules Stein Eye Institute, UCLA
- Kellogg Eye Center
- Kresge Eye Institute
- Krieger Eye Institute
- Maryland Center for Eye Care
- Mayo Clinic/Foundation
- New York Eye & Ear Infirmary
- Ohio State University
- Salus University
- Scheie Eye Institute
- University of California, Davis
- University of California, San Diego
- University of California, San Francisco
- University of Louisville
- University Suburban Health Center
- Washington Eye Physicians & Surgeons
- Washington University, St. Louis

March 2010

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