PGA’s: The Paradigm in Glaucoma Therapy

Dr. James Thimons

Chairman, National Glaucoma Society

Medical Director/ Founding Partner Ophthalmic Consultants of CT

Welcome to Connecticut

Risk Factors for Glaucoma

- Elevated intraocular pressure (IOP)
- Diurnal fluctuation in IOP
- Patient characteristics
  - Cup/disc
  - Corneal thickness
  - Advanced age
  - Race (Blacks 6-8 X Non-Blacks)
  - Family history (parents, siblings, children)
  - Concomitant conditions (e.g., diabetes, myopia, hypertension)
- Compromised ocular hemodynamics

WHAT IS THE ROLE OF IOP IN GLAUCOMA?

- Elevated pressure
- Normal pressure
- Low pressure
- Associated systemic disease
- Environmental
- Clinician induced

The Role of IOP in Glaucoma

- Elevated IOP Does Not Define Glaucoma
- 2% between the ages of 40-50 have elevated IOP
- 8% over 70 have elevated IOP
- Most Patients With Mildly Elevated IOP Do Not Develop Glaucoma Damage
  - Only 1% of Ocular Hypertensives develop a VF defect per year
  - Over treating 75-90% of Ocular Hypertensives
  - Side Effects, Inconvenience, and Cost of Meds
- Elevated IOP Is a Risk Factor for Glaucoma
- The Higher the IOP the Greater the Risk
- Treat Based on Optic Nerve Status and Not Just Elevated IOP

Normal IOP Does Not Exclude Glaucoma

- The Baltimore Eye Survey:
- Up to 50% of the Patients Diagnosed With Glaucoma (Based on Optic Nerve and VF) Had an Initial IOP Reading Below 21Mm Hg
- Tonometry Is Not a Glaucoma Test
- Glaucoma Testing Is a Complete Eye Exam
- If You Are Not Diagnosing Glaucoma in Patients With Normal IOP, Then You Are Missing Cases of Glaucoma
- Lowering IOP is Beneficial for Patients with NTG

Predictors of Glaucoma Risk

- Pachymetry
- Corneal Hysteresis
- Tonography
- Diastolic BP
- Race
- Family History

Measuring IOP: Move Over Dr. Goldmann

CORNEAL HYSTERESIS:

The Newest Disruptive Technology

In Glaucoma

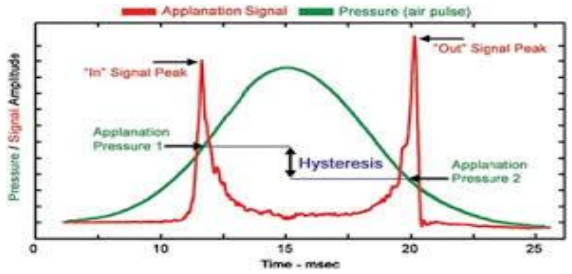
Reichert Ocular Response Analyzer® **G3:** Corneal Hysteresis (CH)

Corneal Hysteresis (**CH**), measured by the **Ocular Response Analyzer® G3**, is a result of a patented, non-contact, "*dynamic bi-directional applanation*" process.

- Rapid, gentle, in/out corneal deformation

Corneal Hysteresis reflects the ability of the cornea to *absorb and dissipate energy…*

- *"how good of a shock absorber is the cornea?"*
- A surrogate for structural characteristics related to the pathogenesis of glaucoma



Ocular Response Analyzer Signal

(Low) CH has been consistently shown to be *independently* associated with or **predictive of glaucoma development and rate of progression** and is more significant than other risk factors.

700 publications in the last 15 years

- **This measurement also enables the ORA G3 to provide a more accurate measure of IOP called IOPcc – closer to true IOP than GAT**

1. .

CH: Average Values in Normal Subjects

CH Values in Normals around the world	N	CH*
Brazil[1]	105	10.1 ± 1.8
UK[2]	272 pairs	10.2 ± 1.2
China[3]	125	10.9 ± 1.5
Japan[4]	204	10.2 ± 1.3
Spain[5]	88	10.8 ± 1.5
USA[6]	44	10.5 ± 1.2

*CH units are mmHg

1. Fontes BM J Refract Surg. 2008 Nov;24(9):941-5.
2. Carbonaro. The Heritability of Corneal Hysteresis and Ocular Pulse Amplitude A Twin Study doi:10.1016/j.ophtha.2008.02.011
3. Lam A. Et Al. Optom Vis Sci. 2007 Sep;84(9):909-14
4. Kamiya Et Al. J Refract Surg. 2009 Oct;25(10):888-93
5. Ortiz Et Al. J Cataract

Clinical Evidence – Study 1

Corneal Hysteresis found to be associated with progression

- The first observational study to investigate the relationship of Corneal Hysteresis to a variety of other parameters in a glaucoma population

- 230 POAG or suspected POAG patients were included in the study
  - POAG was defined by a reliable visual field that was abnormal according to OHTS criteria, with an optic nerve image, photo, or CDR thought to be consistent with the field damage by a fellowship-trained glaucoma specialist.
  - GAT, ORA, CCT and Axial Length measurements (IOL master) were recorded
  - Among persons with three or more reliable fields over three or more years, or with five reliable fields in less than three years, progression was defined as having achieved the OHTS standard of “conversion” (if previously normal), or (if previously damaged as evidenced by an abnormal GHT or PSD) having worsened by 1 dB or greater per year in either MD or PSD.
  - A stepwise model was not used nor were any hypotheses about interactions made.

POAG Primary Open Angle Glaucoma; GAT Goldmann Applanation Tonometry; IOP intraocular pressure; ence limit.

CCT Central Corneal Thickness; CH Corneal Hysteresis

Congdon NG et al. *Am J Ophthalmol.* 2006;141:868-875.

Clinical Evidence – Study 1

Corneal Hysteresis found to be associated with progression

	OR	LCL	UCL	*P*-value
Age per year <65	1.12	1.01	1.24	.03
Age per year >65	1.08	1.01	1.15	.02
GAT IOP per mmHg	1.22	0.95	1.58	.12
Treatment	1847.6	3.16	10^6	.02
IOP by treatment interaction	0.79	0.61	1.03	.08
CCT per 100 microns	1.65	0.66	0.98	.30
Years with glaucoma	1.00	0.96	1.04	.98
Baseline IOP	0.99	0.93	1.06	.79
CH per mmHg	0.81	0.66	0.98	**.03**

Conclusions: Corneal Hysteresis was the parameter most associated with progressive field worsening

GAT Goldmann Applanation Tonometry; IOP intraocular pressure; OR odds ratio; LCL lower confidence limit; UCL upper confidence limit.

CCT Central Corneal Thickness

Congdon NG et al. *Am J Ophthalmol*

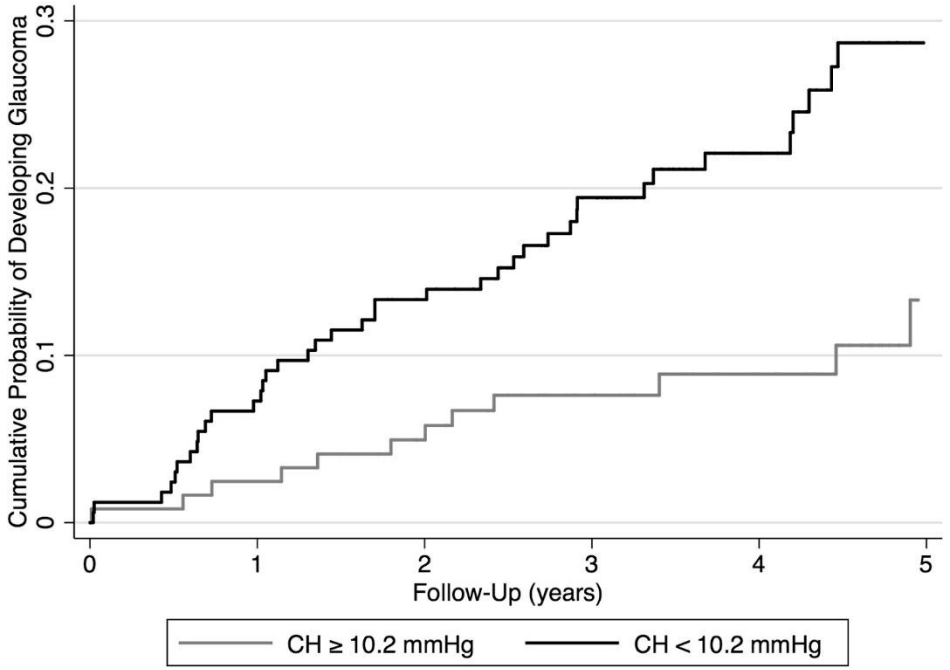
Corneal Hysteresis in Glaucoma

Predictive of conversion to Glaucoma in pre-perimetric Glaucoma Suspects

Purpose: To investigate the role of CH as a risk factor for **development** of glaucoma in a prospective longitudinal study.

Results: Fifty four (19%) of the 287 eyes developed repeatable visual field defects during a 4 year follow-up.

CH was *independently* predictive of conversion to glaucoma even when adjusted for age, IOP, and CCT.



Each 1mmHg lower CH was associated with an increase of 21% in the risk of developing glaucoma during follow up

A Prospective Longitudinal Study to Investigate Corneal Hysteresis as a Risk Factor for Predicting Development of Glaucoma
AJOPHT 10365 – in press
Author Block: Feilin Zhu , Alberto DinizFilho, Linda M. Zangwill , Felipe A. Medeiros

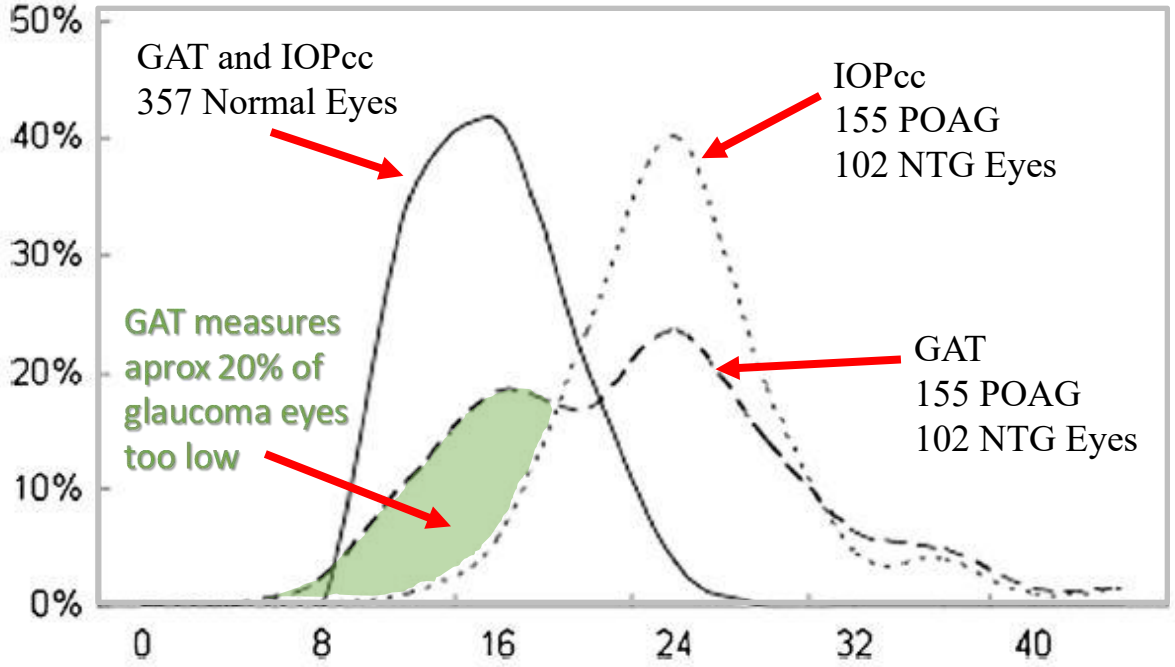
Corneal Compensated IOP

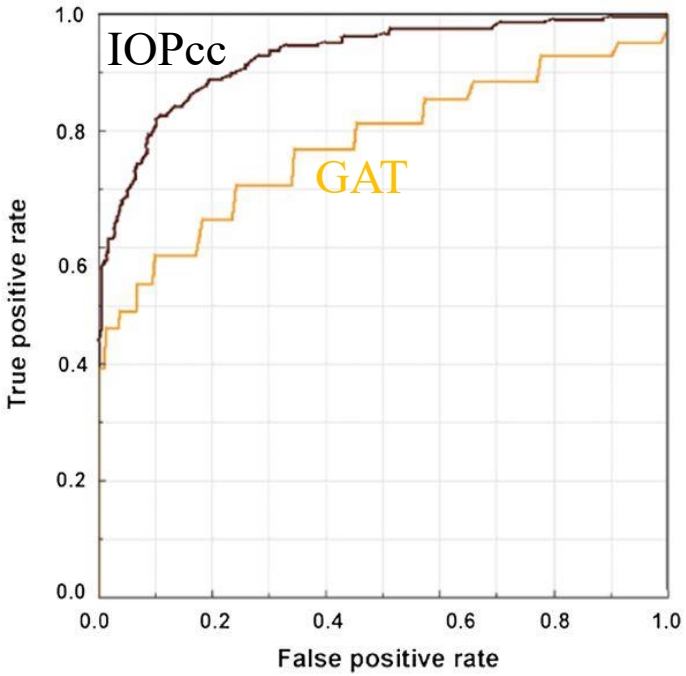
- Superior to Goldmann in all forms of post Refractive Surgery IOP measurements

IOPcc Key Benefit #2
IOPcc is superior for glaucoma risk assessment

IOPcc is clinically superior to GAT, other NCTs, and iCare because it is more associated with Glaucoma risk, status of glaucoma, and glaucoma progression

"the results of this study suggest that IOPcc may represent a superior test for the evaluation of glaucoma"





AUC .93 for IOPcc vs .78 for GAT

Not shown here from this study:

- **39%** of NTG eyes would be re-classified as POAG with IOPcc
- Average IOPcc was **5 mmHg higher** than GAT in NTG eyes

Goldmann applanation tonometry compared with corneal-compensated intraocular pressure in the evaluation of primary open-angle Glaucoma
Joshua R Ehrlich, Nathan M Radcliffe, and Mitsugu Shimmyo

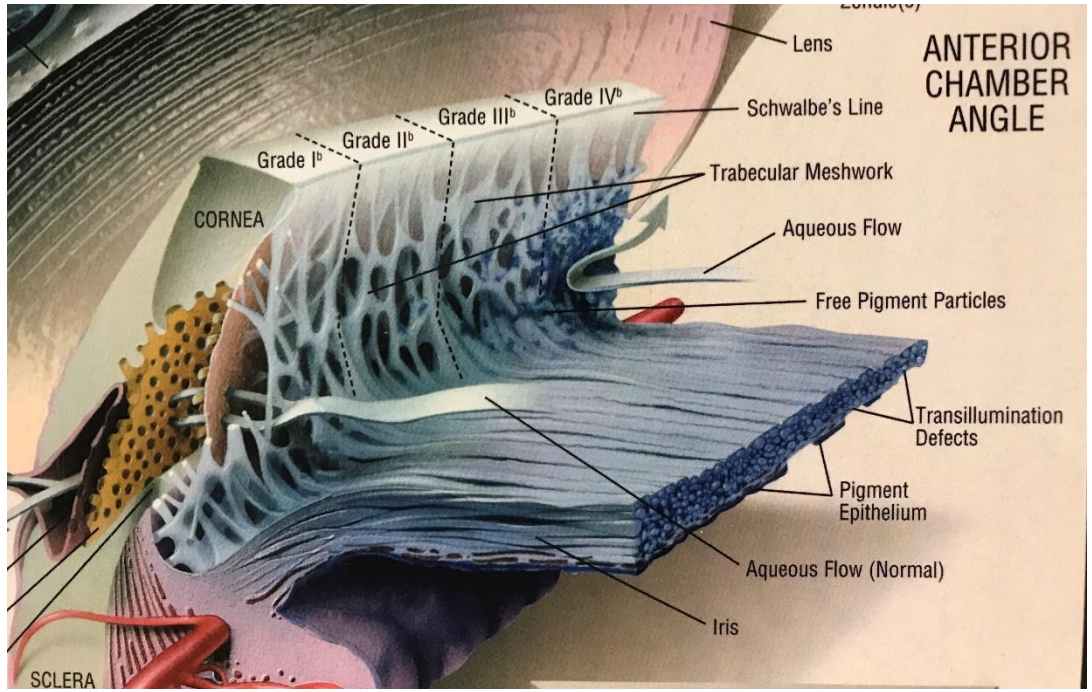
Tonography

Setting a Target Outflow Facility Value


Falck Medical
IOP
OPH
TON
?
FALCK MEDICAL

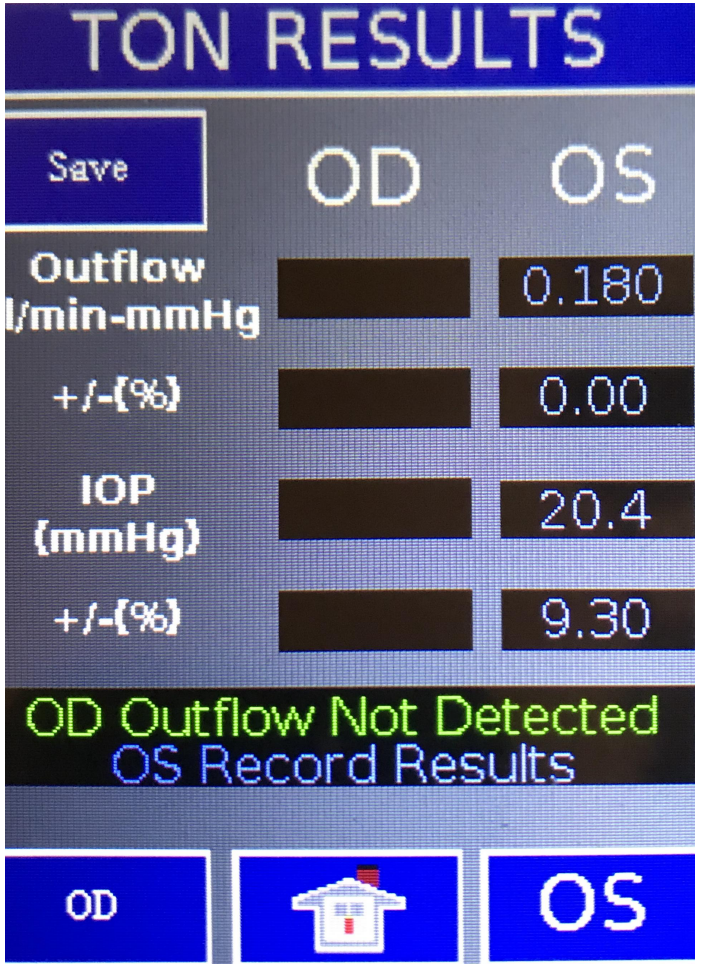
Aqueous Humor Dynamics

Aqueous Humor Outflow Pathway



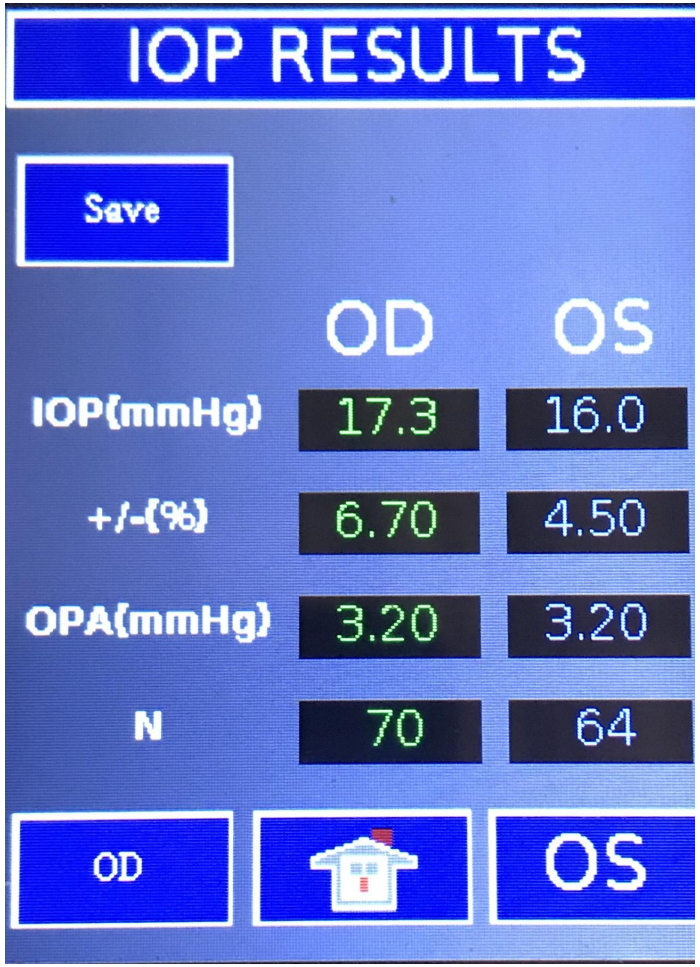
TONOGRAPHY

- ✓ Optical Aqueous Humor Outflow Measurement.
- ✓ Aqueous Outflow Decreased in Glaucoma.
- ✓ Decreased Outflow = Increased TM Resistance.
- ✓ Decreased Outflow = Increased IOP Fluctuation.
- ✓ Document Therapeutic Efficacy of Outflow Interventions.
- ✓ Document Need for Additional Intervention.
- ✓ Glaucoma risk assessment.



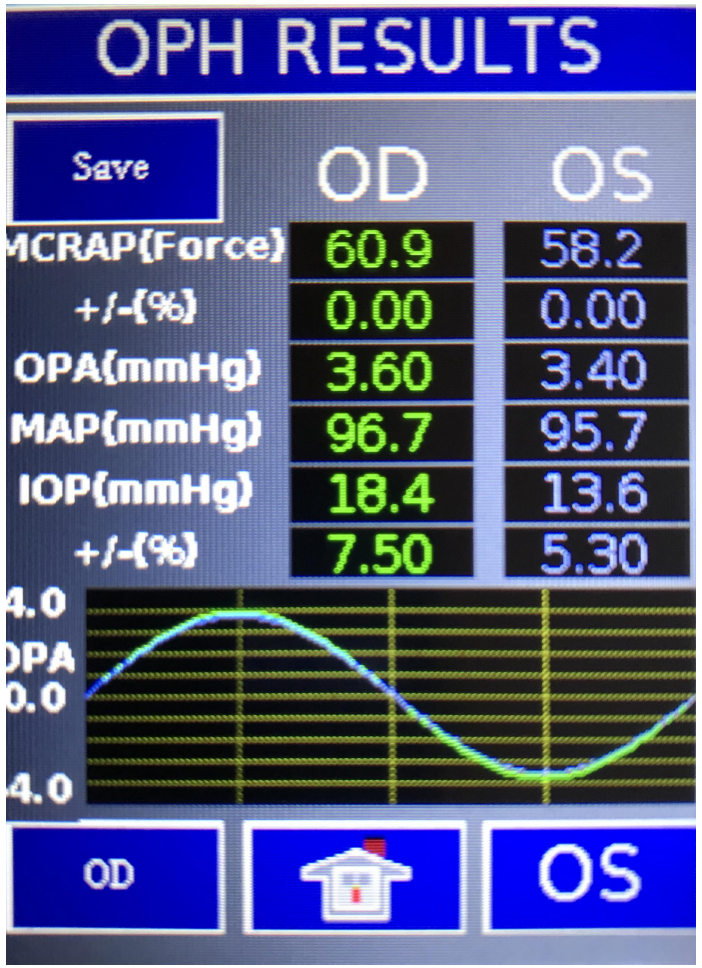
Intraocular Pressure

- ✓ Optical Applanation Measurement
- ✓ Compensates for Corneal Biomechanics
- ✓ Multiple Serial IOP Measurements – N Value
- ✓ Systolic and Diastolic IOP
- ✓ Average IOP Displayed
- ✓ IOP Variation with Cardiac Cycle - OPA
- ✓ Precision Displayed



OPHTHALMODYNAMOMETRY

- ✓ Mean Central Artery Pressure (MCRAP) measurement.
- ✓ Data Captured During Multiple Cardiac Cycles.
- ✓ Mean Arterial BP Displayed.
- ✓ MCRAP – IOP = True Ocular Perfusion Pressure (OPP).
- ✓ Reduced OPP is a risk factor for glaucoma progression.
- ✓ Abnormal OPH - Increased Risk of Stroke



Aqueous Humor Dynamics

- IOP is directly related to aqueous humor production and inversely related to aqueous humor outflow.
- The rate of aqueous humor production is not constant.
- The rate of aqueous humor outflow is constant.
- IOP varies throughout the day.
- The variability of aqueous humor production is the source of IOP variation.
- Using IOP alone can lead to the incorrect conclusion.
- Eyes with untreated glaucoma may have normal IOP when evaluated.
-

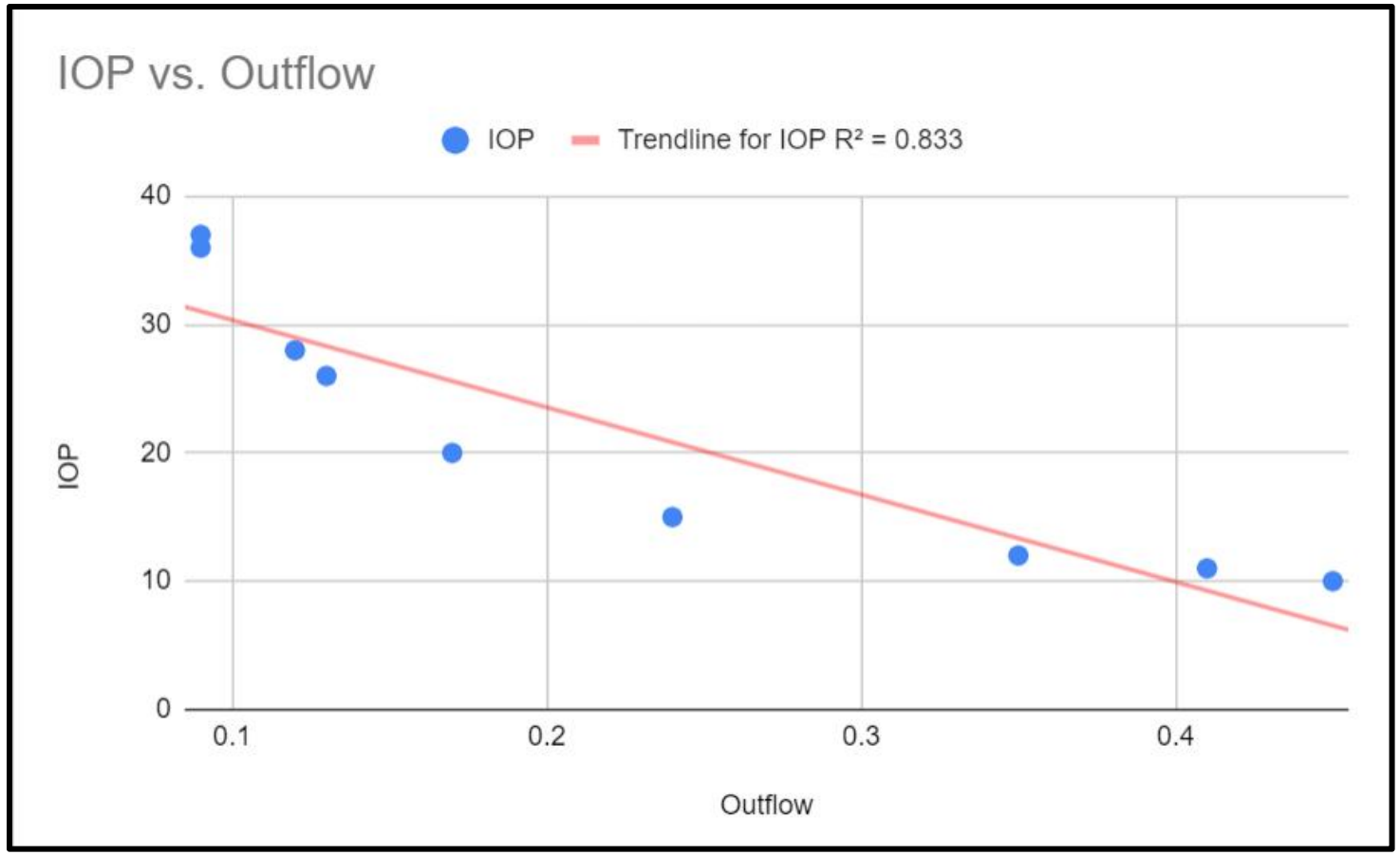
Why Measure Outflow Facility?

- Impaired Outflow Facility is the Primary Cause of Glaucoma
- Outflow Facility Measurements Predict IOP In and Out of the Office
- New Technology Available to Measure Outflow Facility - FMAT1 Tonography
- Outflow Facility Measurements Predict Risk

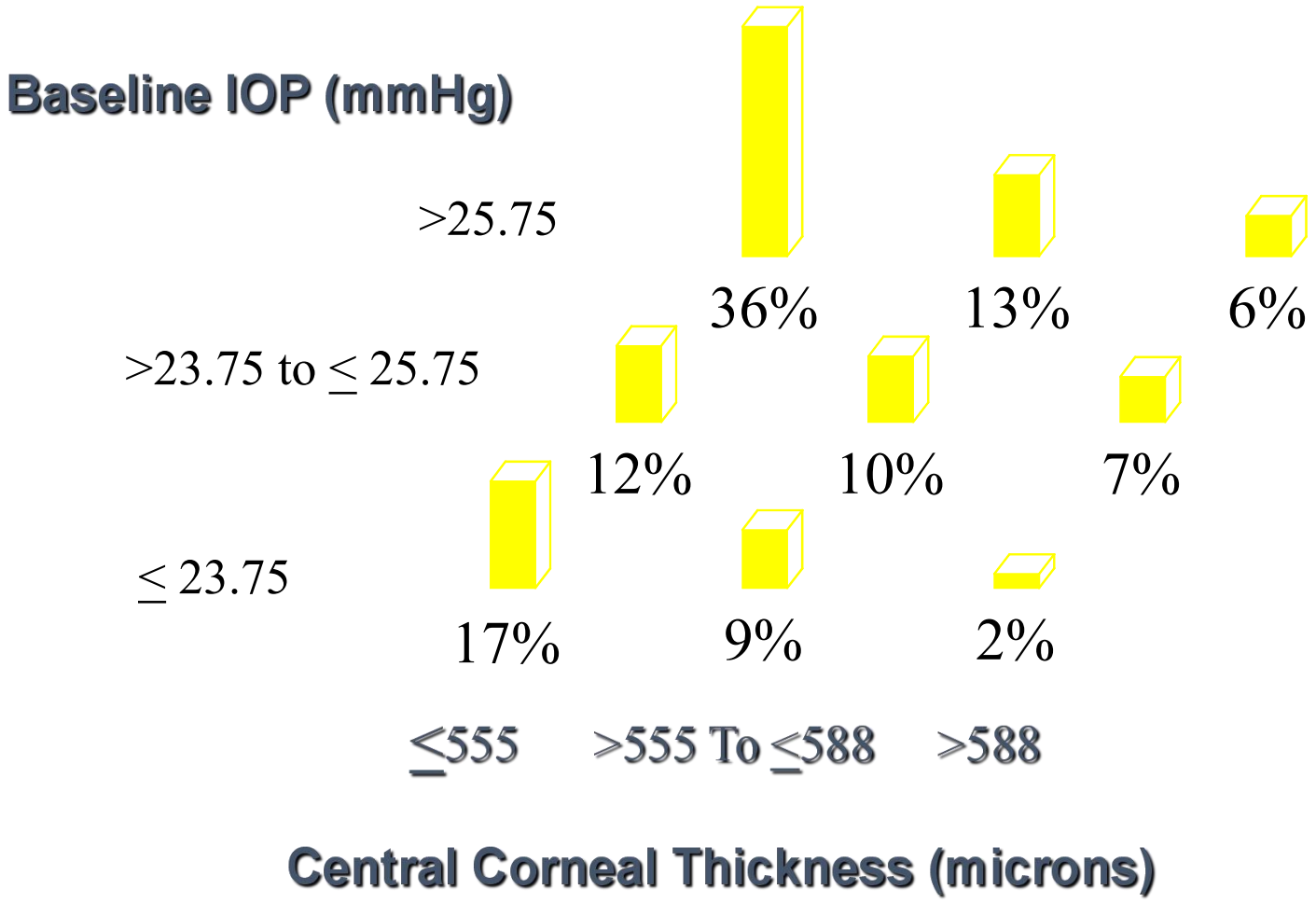
Reference: Chandler and Grant’s Glaucoma

Outflow Facility Measurements Predict IOP

- FMAT1 FDA Clinical Study Confirms
- IOP = (- 68)(Outflow) + 37, r^2= - 0.83

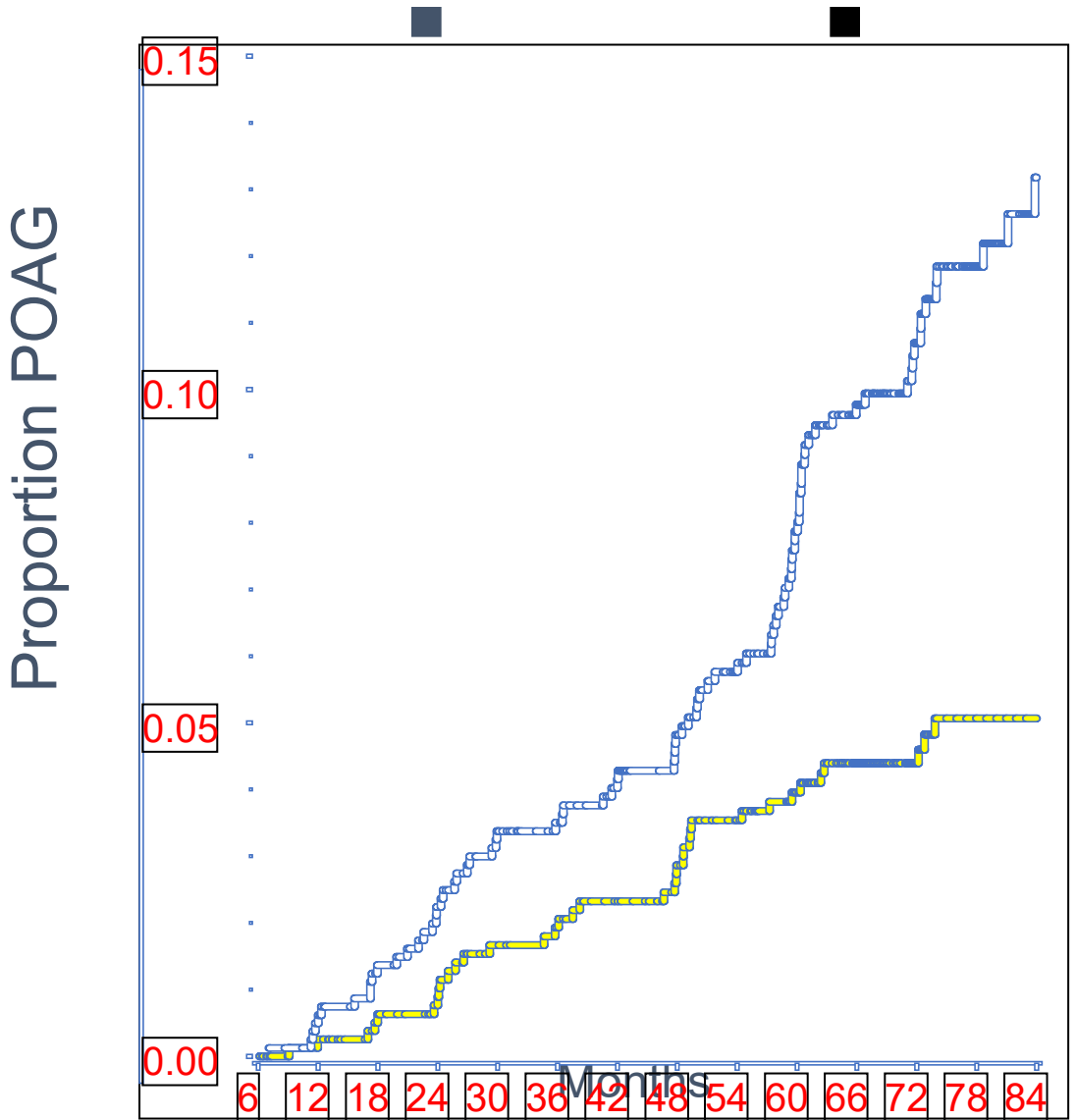


IOP/PACHYMETRY (OHTS)



OHTS Primary POAG Endpoints*

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



Observation

At 5 yrs, 4.4% of treated group and 9.5% observation group developed glaucoma

Medication

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

Collaborative Normal Tension Glaucoma Study

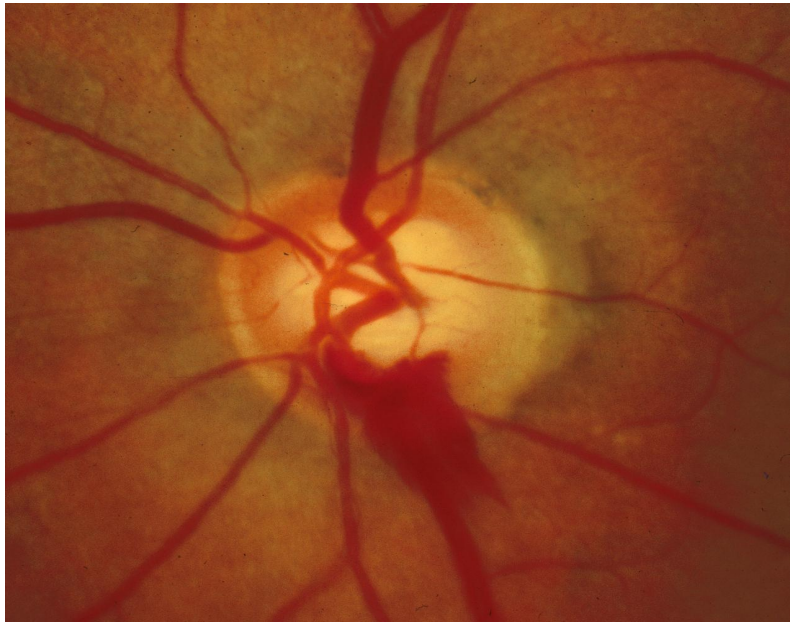
Methods One eye per each of 145 subjects with NTG was randomized either to 30% IOP reduction or to no treatment (control)

Survival analysis: time to visual field progression

- Findings At 5 years, treated patients showed overall survival of 80% compared with 40% in controls (P=.0018)
- The beneficial results of IOP reduction were found only when the impact of cataracts on visual field progression (caused mainly by filtration surgery) was removed
-

The Collaborative Normal-Tension Glaucoma Study Clinical Pearls

5. Disc hemorrhage is a strong, negative prognostic sign; other risk factors include migraine and female gender.



Early Manifest Glaucoma Trial

- Compared the effect of immediately lowering the IOP vs no treatment or later treatment, on the progression of newly detected open-angle glaucoma
- On average, tx reduced IOP by 5.1mm Hg or 25%

Heijl A. et al. *Arch Ophthalmol*. 2002;120:1268-1279

EMGT- Results

- In multivariate analyses, progression risk was halved by treatment
- Progression risk decreased by about 10% with each mm of HG of IOP reduction from baseline to the first follow-up visit

Leske MC et al. *Arch Ophthalmol.* 2003 Jan;121(1):48-56.

Collaborative Initial Glaucoma Treatment Study

- Clinical Results: Surgery vs. Medicine
  - VF loss did not differ over 5 years between treatment groups
  - VA was better for medically treated group over much of the study, but by 4 years, was no different than the surgical group
  - Number progressing in both groups was low (15%)

Ophthalmology 2001; 108: 1943-53

Advanced Glaucoma Intervention Study

- How effective is IOP lowering in preserving VF?
- Is there an “ideal” IOP that provides maximum benefit in reducing or eliminating pressure-related component of damage?

- *Am J Ophthalmol* 2000;130:429-440

AGIS 7 Results

- Patients with IOP<18 on 100% of follow-up exams over 6 years had mean change from baseline VF close to ZERO. (Mean IOP=12.3 over 6 years)
- Patients with IOP<18 on 50% of follow-up exams showed progression

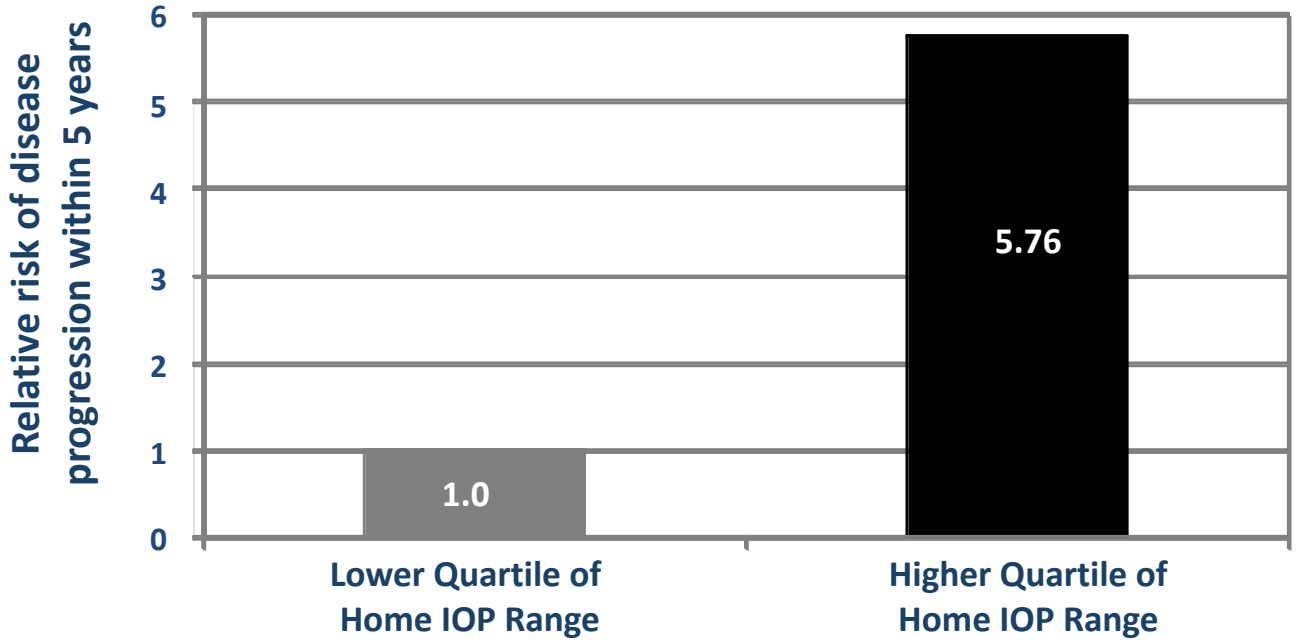
Aggressive IOP-lowering by any means is the best way to protect against further VF loss

Am J Ophthalmol 2000;130:429-440

Pathways to lower Intraocular Pressure

- Inflow
  - Alpha 2- agonists
  - B1 blockers
  - CAI
- Outflow
  - Alpha 2–agonists
  - Cholinergics
  - Prostaglandins/ Prostamindes

Diurnal Fluctuations Correlate with Visual Field Progression



Hazard ratio between higher quartile and lower quartile for "Range in Home IOP" was 5.7

Beta Blockers

- Beta receptor in the ciliary body epithelium
- Beta 1 receptors >> Beta 2 receptors in the eye
- Beta receptors stimulate productions of aqueous.
- Beta blockers suppress aqueous production

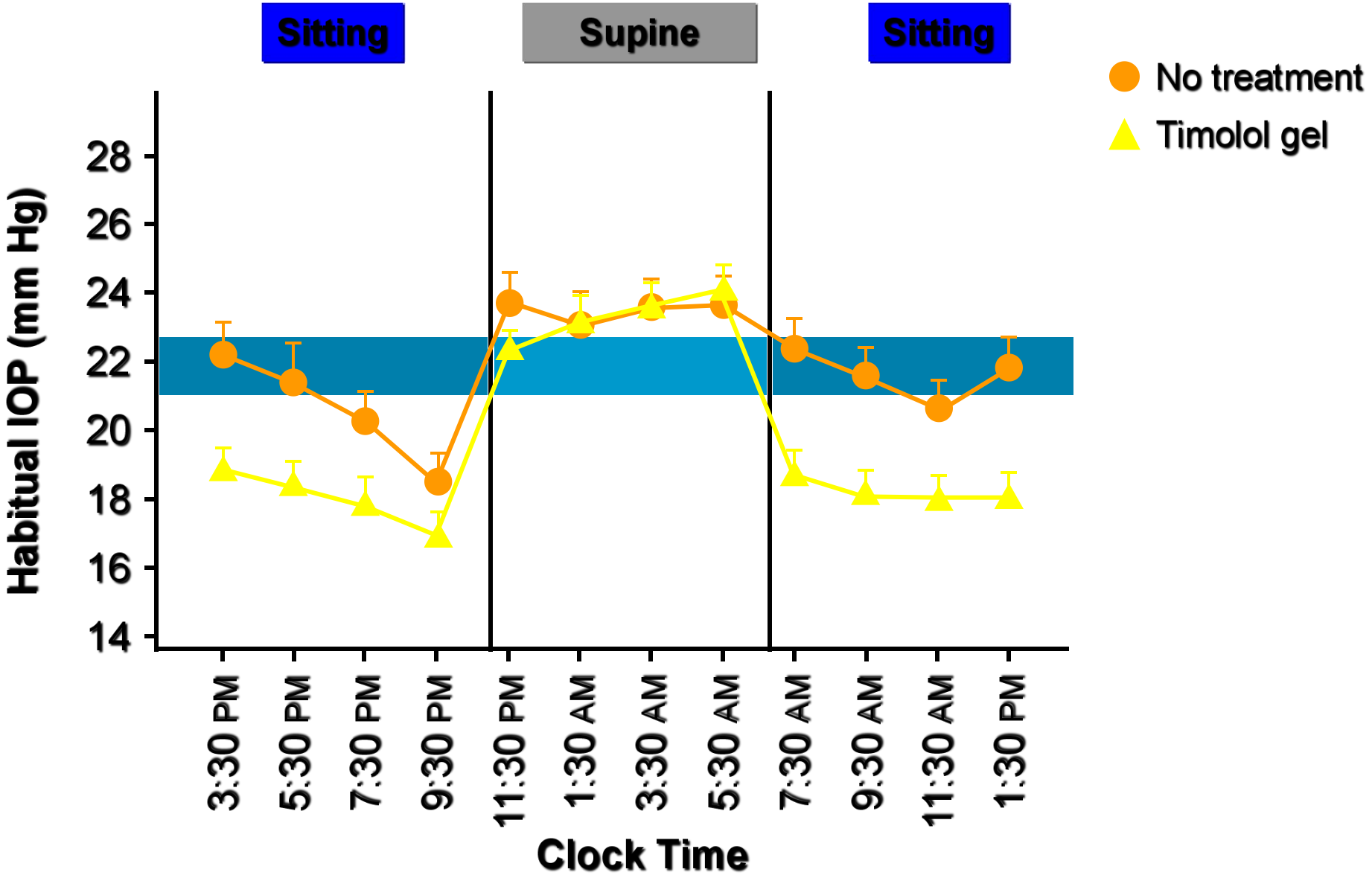
Timolol

- Equally effective in blacks and whites
- IOP decrease 30-60 min
- Long term drift
  - 47% decrease at 1 wk
  - 25% at 1 yr

Systemic

- Bradycardia
- Congestive heart failure
- Exacerbation of heart block
- Bronchospasm
- Mood change
- Impotence
- Lipid profile

Nocturnal and Diurnal Habitual IOP



Adapted from Liu, Kripke, Weinreb. *Am J Ophthalmol.* 2004;138:389-395.

Lama study (AJO 11/02)

- Conclusions:
  - ...identifies no scientific studies supporting the development of worsening claudication, depression, hypoglycemia, sexual dysfunction or impaired neuromuscular transmission
  - Recommends careful medical history and checking pulse rate and rhythm

Brimonidine 0.1% alphagan alpha-2

- Decrease aqueous production
- Also increase uveoscleral outflow (small amount)
- Not as effective as timolol but close
- May be neuroprotictive
- More effective than betaxalol or dorzolamide
- Can cause mild mydriasis

Side effects

- 10-30% dry mouth
- Malaise
- 10% allergy rate
- Avoid with MAO-A or MAO-B selective inhibitors
- Alphagan P 0.1%
  - Better tolerated

Carbonic Anhydrase Inhibitors

- Dorzolamide 2%
- Brinzolamide 1%
- Acetazolamide 125, 250, 500mg sequels
- Methazolamide 25, 50 mg
- Average Topical IOP reduction 20-25%

- Ocular side effects
- A. Burning/ Stinging 20-30%
- B. Corneal edema
- C. Blurred Vision 10-20%

Prostaglandins /Prostamides

- Different receptor sites DP,EP,IP
- Prostaglandins E and F most effective in lowering IOP
- They seem to facilitate aqueous outflow via the uveal scleral pathway

Traditional Prostaglandin Therapy

- Latanoprost 0.005% Xalatan
  - Prostaglandin F 2a analogue
  - Prodrug
- Travoprost 0.004% Travatan
  - Prostaglandin F 2a analogue
  - Prodrug
- Brimatoprost 0.03% Lumigan
  - Synthetic prostamide analog
  - Not a prodrug
- Tafluprost 0.0015% Zioptan
  - Prostaglandin F2a analogue
  - Unit dose
  - Preservative free

AJO 2003 May;135(5):688-703.

A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study

Rchard K Parrish [1], Paul Palmberg, Wang-Pui Sheu; XLT Study Group

8 A.M. IOP reduction (mm Hg) from baseline to week 12:

- Latanoprost: 8.2 ± 3.7
- Travoprost: 7.9 ± 3.4
- Bimatoprost: 8.1 ± 3.8

Latanoprost (Xalatan 0.005%)

- More effective than timolol
- Can be used as a 1st line drug
- Lowers IOP 33%(about 7-8 mmHg)
- Prodrug activated by esterase in the cornea
- Does not cause or reactivate HSV

Xalatan side effects

- 2% CME pseudophakic pt (reversible)
- 6% uveitis
- 7-16% hazel iris turn brown
- Hypertrichosis
- Periorbital Darkening

Travatan (Travoprost 0.004%)

- Lowers IOP 30-33%
- Contraindicated in pregnant woman
- Excellent responder rated in black pts
- No CME

Responder Rates in all Patients

- 56.3% for IOP 17 mm Hg for Travatan
- 49% for Xalatan
- 39% for timolol

Bimatoprost (Lumigan 0.03%)

- Lowers IOP 30-33%
- Favorable lowering of IOP with lumigan vs xalatan
- Side effects
- 15-45% hyperemia
- 15% ocular pruritis
- 45% Eyelash growth
- CME rare
- 0.01% shows significantly less hyperemia

New Age PGA's

- Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is a new combination drug product and has a white cap
- Rocklatan® is available in a 1-month supply (2.5 mL)
- Protect from light.
- Must remain refrigerated

RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% OCULAR ADVERSE EVENT PROFILE

PREFERRED TERM (with Incidence ≥5% [pooled safety population[a]])	RHOPRESSA® 0.02% QD (N=805) n (%)	TIMOLOL 0.5% BID (N=816) n (%)
Eye Disorders		
Conjunctival hyperemia	428 (53.2)	85 (10.4)
Cornea verticillata (corneal deposits)	162 (20.1)	2 (0.2)
Conjunctival hemorrhage	137 (17.0)	15 (1.8)
Vision blurred	60 (7.5)	12 (1.5)
Lacrimation increased	53 (6.6)	5 (0.6)
Erythema of eyelid	52 (6.5)	4 (0.5)
Visual acuity reduced	44 (5.5)	13 (1.6)
General Disorders and Administration Site Conditions		
Instillation site pain	158 (19.6)	175 (21.4)
Instillation site erythema	74 (9.2)	13 (1.6)
Investigations		
Vital dye staining cornea present	65 (8.1)	57 (7.0)

[a]Includes ROCKET 1, ROCKET 2, and ROCKET 4.

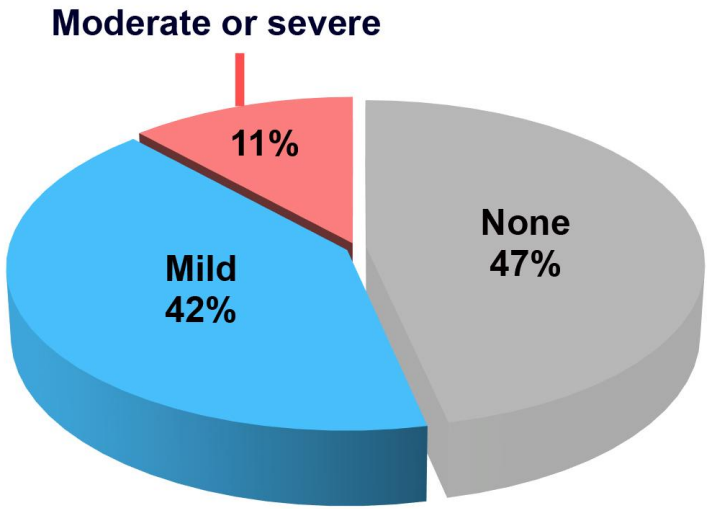
1. Data on file, Aerie Pharmaceuticals, Inc.

VISIONaerie science

CONJUNCTIVAL HYPEREMIA IN THE POOLED ROCKET STUDIES WAS REPORTED AS MILD BY THE PHYSICIANS UPON BIOMICROSCOPY

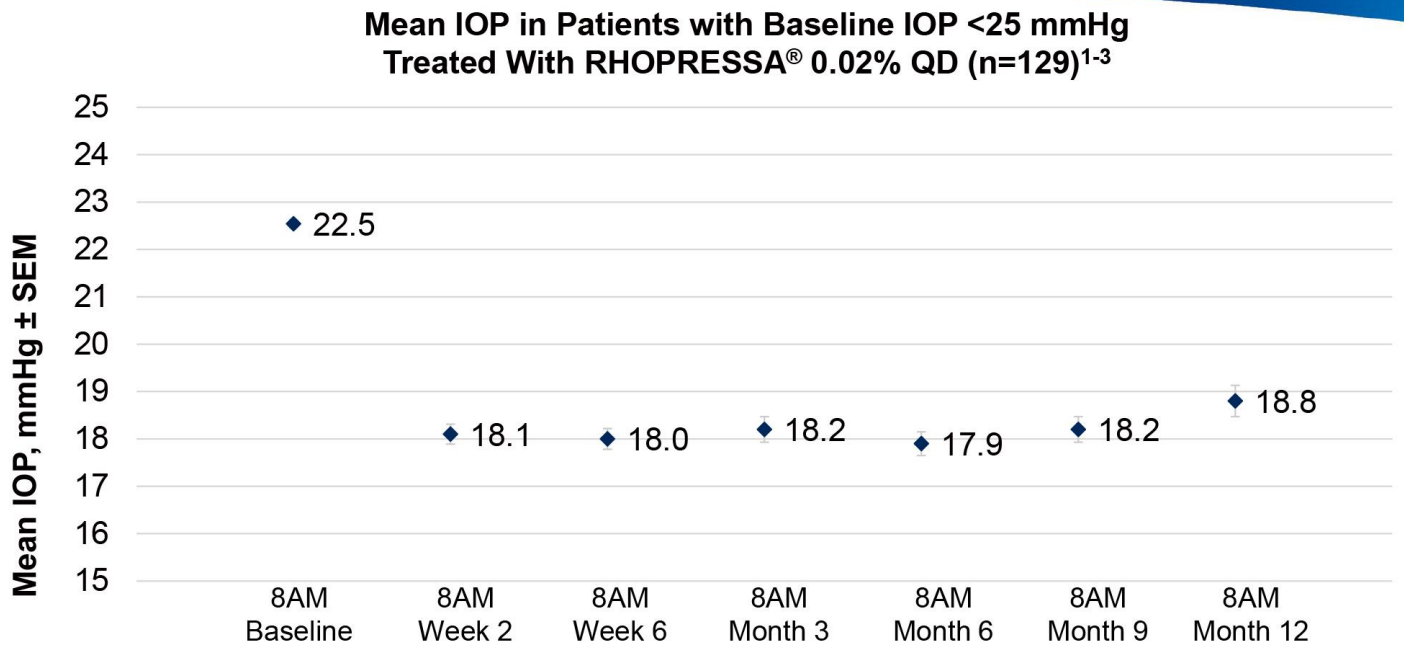
- Hyperemia may begin by the second week of treatment in patients treated with RHOPRESSA® (netarsudil ophthalmic solution) 0.02% QD[1]
- In approximately 9 out of 10 patients, either no hyperemia or mild hyperemia was reported[2]
- Severity did not increase with continued dosing[1]
- Hyperemia was observed by biomicroscopy at baseline in ~15%-20% of patients[1]

Grading of Conjunctival Hyperemia Adverse Events in Patients Treated With RHOPRESSA® 0.02% QD (N=805)[2]



1. Serle et al. *Am J Ophthalmol*. 2018;186;116-127. 2. Data on file, Aerie Pharmaceuticals, Inc.

RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% MAINTAINED EFFICACY THROUGH 1 YEAR IN THE ROCKET 2 TRIAL



- IOP was collected at 8 AM only at months 6, 9, and 12 as a safety measure

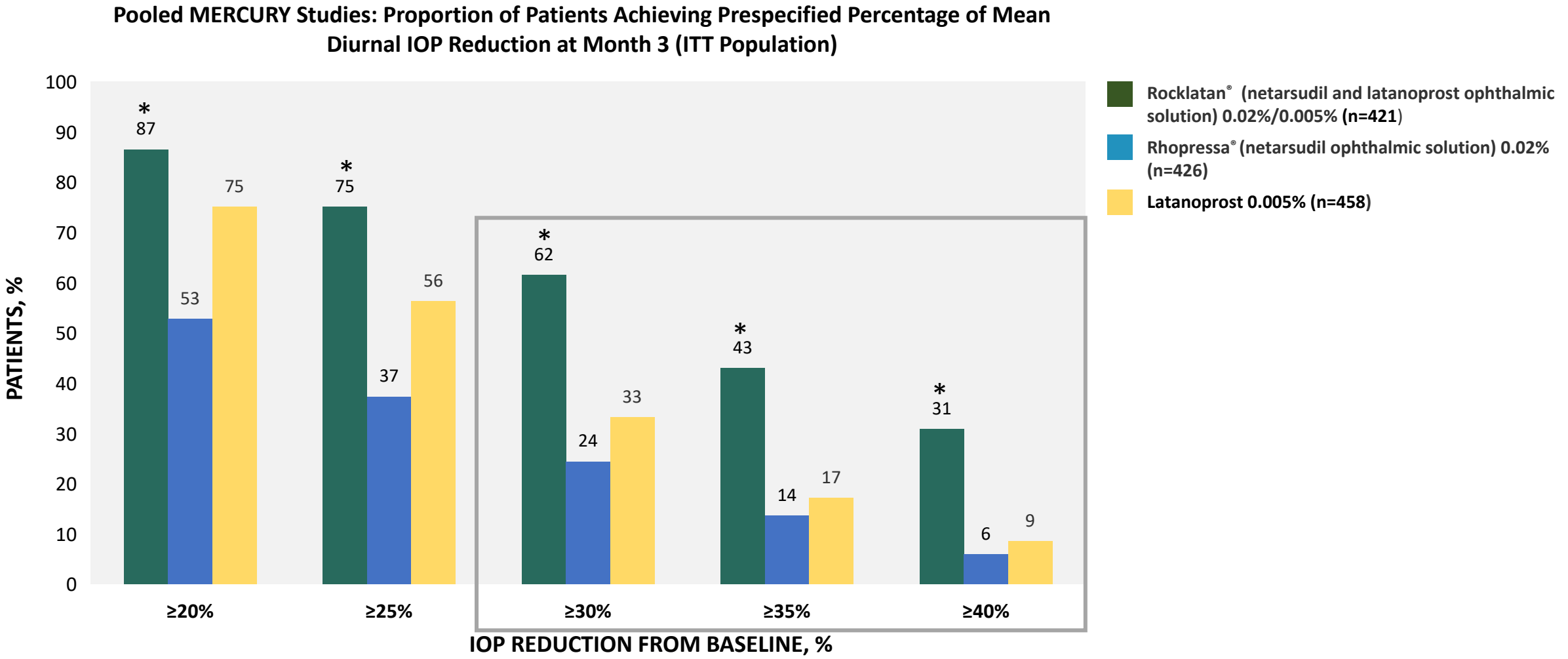
For important safety information refer to the RHOPRESSA® Prescribing Information at the end of this presentation or at www.RHOPRESSA.com.

IOP, intraocular pressure; QD, once daily; SEM, standard error of the mean.

1. Serle et al. Abstract accepted at Association for Research in Vision and Ophthalmology 2018 annual meeting. 2. Serle et al. *Am J Ophthalmol.* 2018;186;116-127. 3. Data on file, Aerie Pharmaceuticals Inc.

VISIONaerie science

Over 60% of Rocklatan® Patients Achieved ≥30% Mean IOP Reduction at 3 Months[1]



*P<0.0001 vs Rhopressa® and latanoprost. ITT, intent-to-treat

1.Data on file, Aerie Pharmaceuticals, Inc.

VYZULTA®
(latanoprostene bunod ophthalmic solution), 0.024%

VYZULTA® is the **only nitric oxide-releasing agent** that targets both the trabecular meshwork and the uveoscleral pathway to reduce IOP in patients with open-angle glaucoma and ocular hypertension

IOP, intraocular pressure.

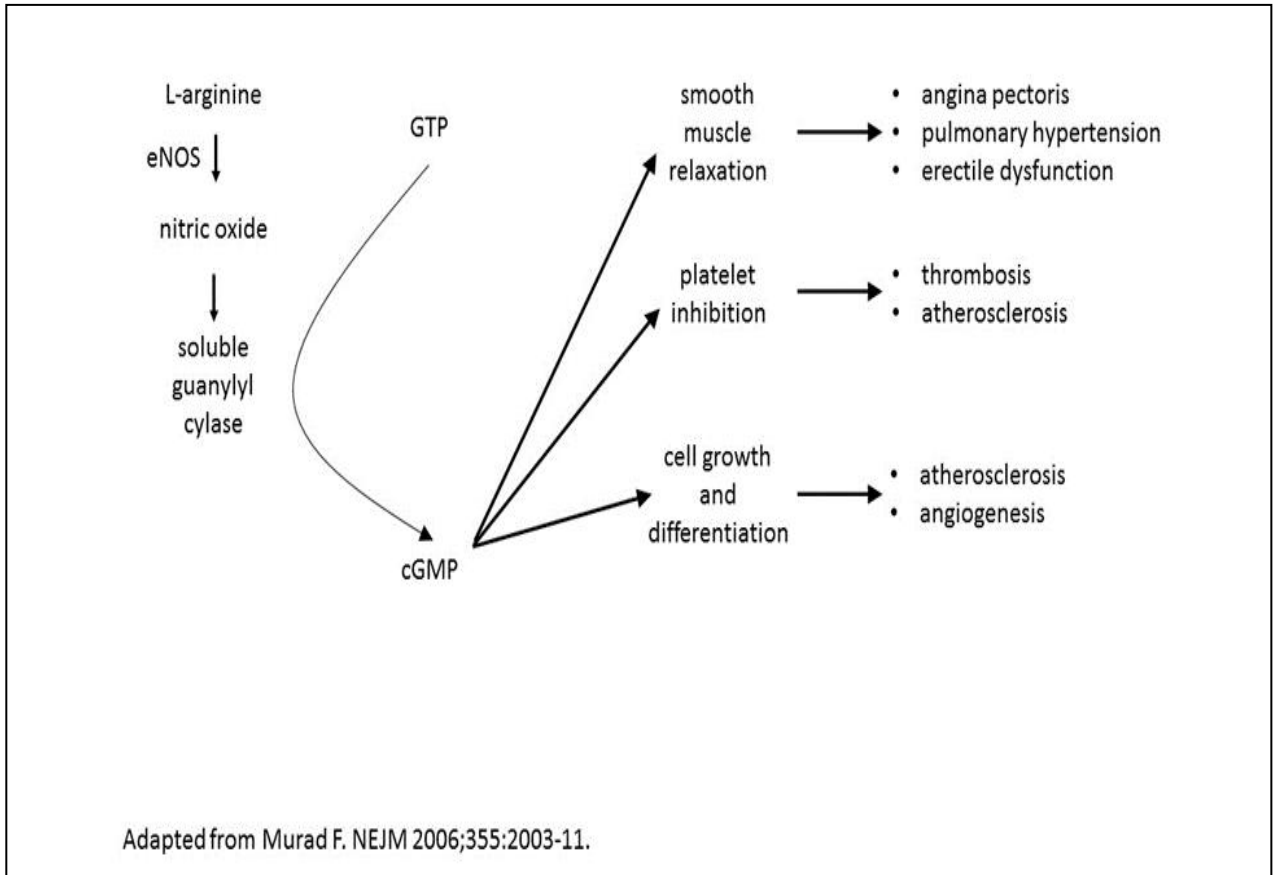
VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2019.

Nitric Oxide and Glaucoma

- **Patients with primary open-angle glaucoma (POAG) have lower levels of NO synthase activity in the trabecular meshwork (TM), Schlemm's canal, and ciliary muscle[1]**
- **NO donors lower IOP in normal and POAG eyes**
- **A major site of action for NO donors is the TM**
  - **NO relaxes the TM and ciliary muscle**
  - **NO donors increase outflow facility in anterior segments, mediated by a decrease in TM cell volume**
  - **Endothelial NO synthase (eNOS) overexpression increases conventional outflow and lowers IOP in a mouse eye model**

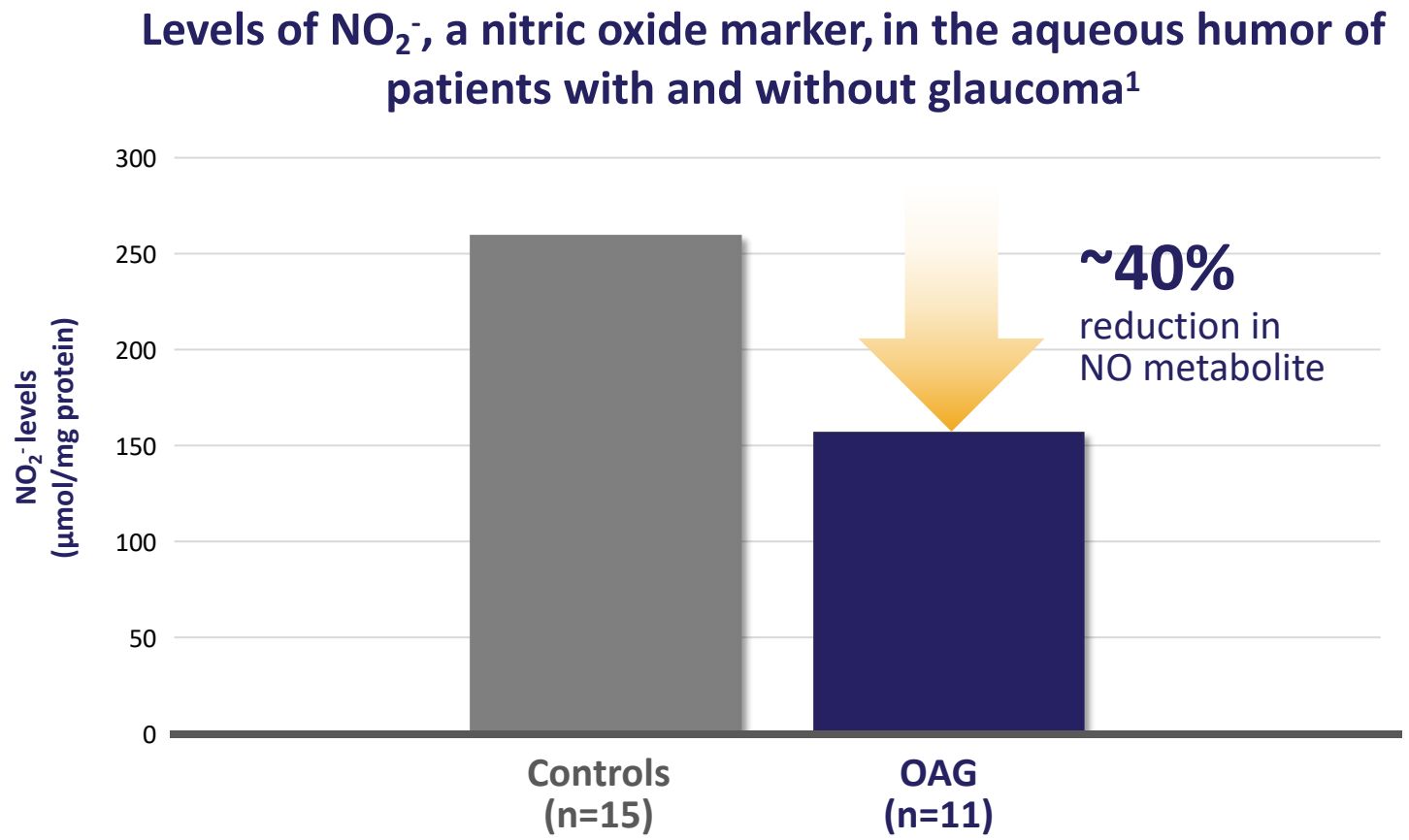
Latanoprostene Bunod: NO-Donating Latanoprost

- NO plays key roles in both health and disease throughout the body, including the eye



Adapted from Murad F. NEJM 2006;355:2003-11.

Nitric Oxide Has Been Shown to Be Up to 40% Deficient in Glaucomatous Eyes

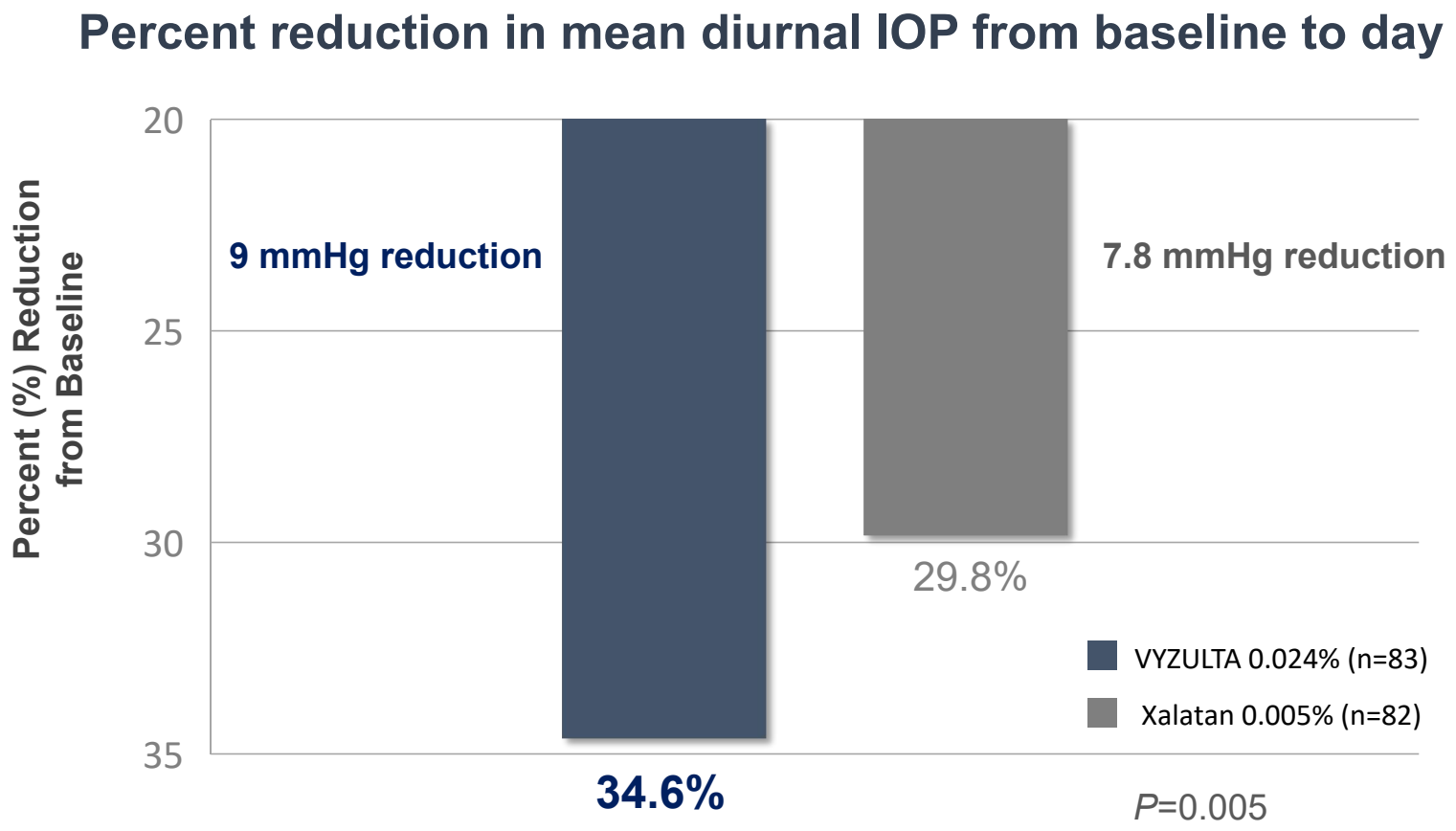


Nitric oxide deficiency may play a role in trabecular contraction and **elevated IOP**[2]

IOP, intraocular pressure; OAG, open-angle gluacoma.

1. Galassi F et al. *Br J Ophthalmol*. 2004;88(6):757-760. doi:10.1136/bjo.2003.028357 **2.** Nathanson JA, McKee M. *Invest Ophthalmol Vis Sci*. 1995;36(9):1765-1773.

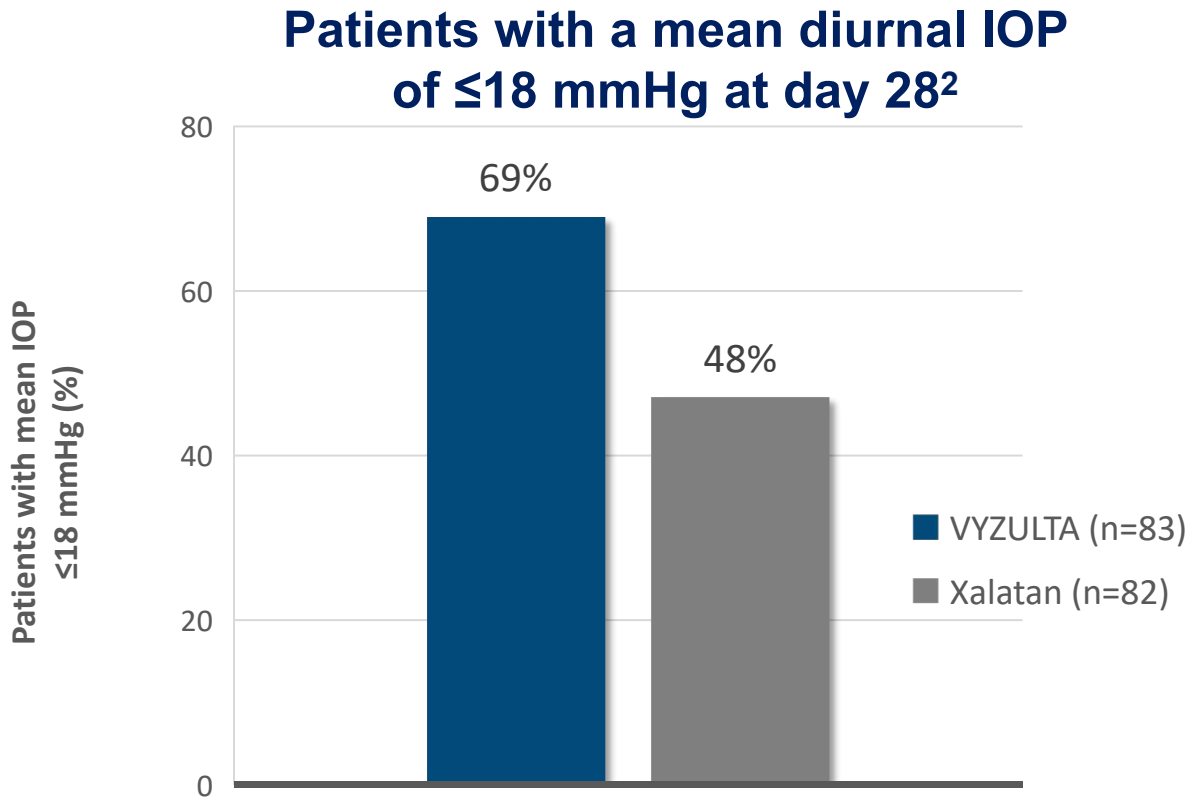
VYZULTA® Achieved a Significantly Greater IOP Reduction vs Xalatan (latanoprost 0.005%)



1. Weinreb RN et al. *Br J Ophthalmol*. 2015;99(6):738-745.

With VYZULTA®, More Patients Achieved An IOP of ≤18 mmHg Than With Xalatan®

According to the AGIS, an IOP of <18 mmHg significantly reduces visual field loss[1]

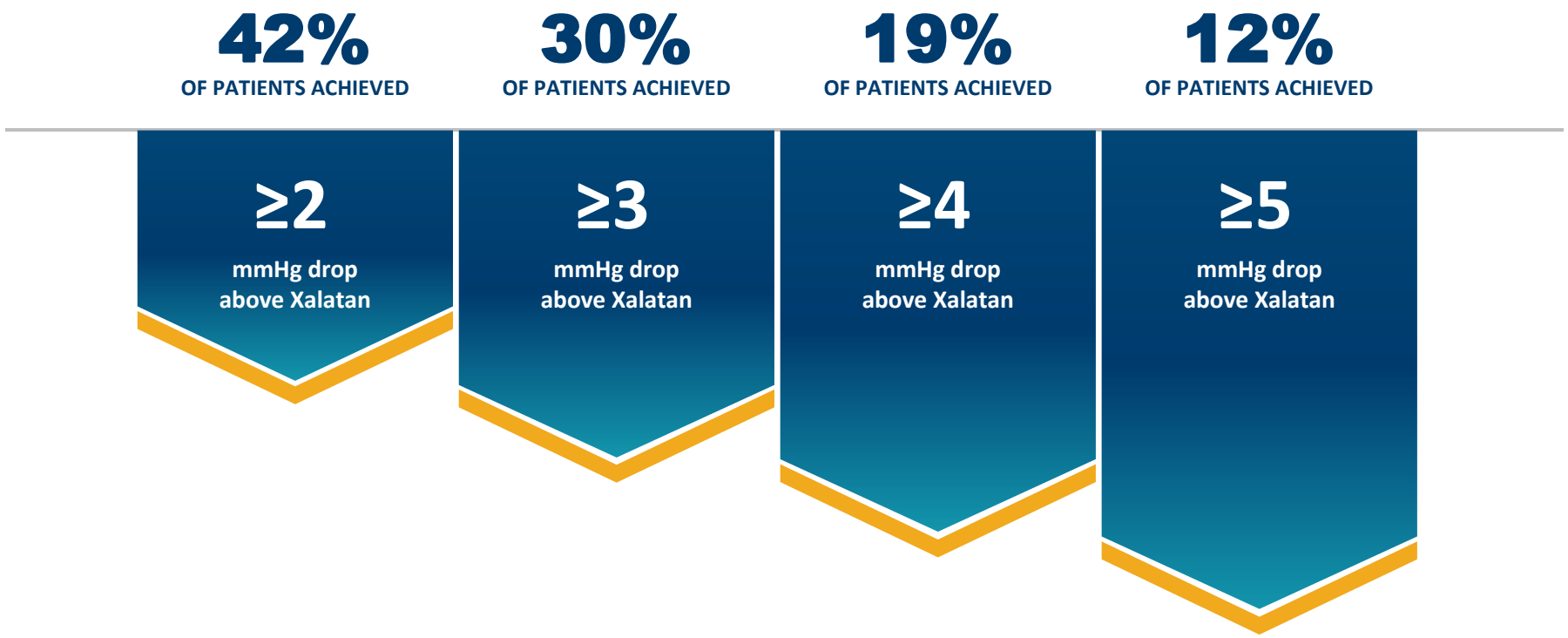


AGIS, Advanced Glaucoma Intervention Study; IOP, intraocular pressure.

1. AGIS Investigators. *Am J Ophthalmol*. 2000;130(4):429-440. doi:10.1016/s0002-9394(00)00538-9 **2.** Weinreb RN et al. *Br J Ophthalmol*. 2015;99(6):738-745. doi:10.1136/bjophthalmol-2014-305908

VYZULTA® Delivered Greater IOP Reductions Than Xalatan[1,2]

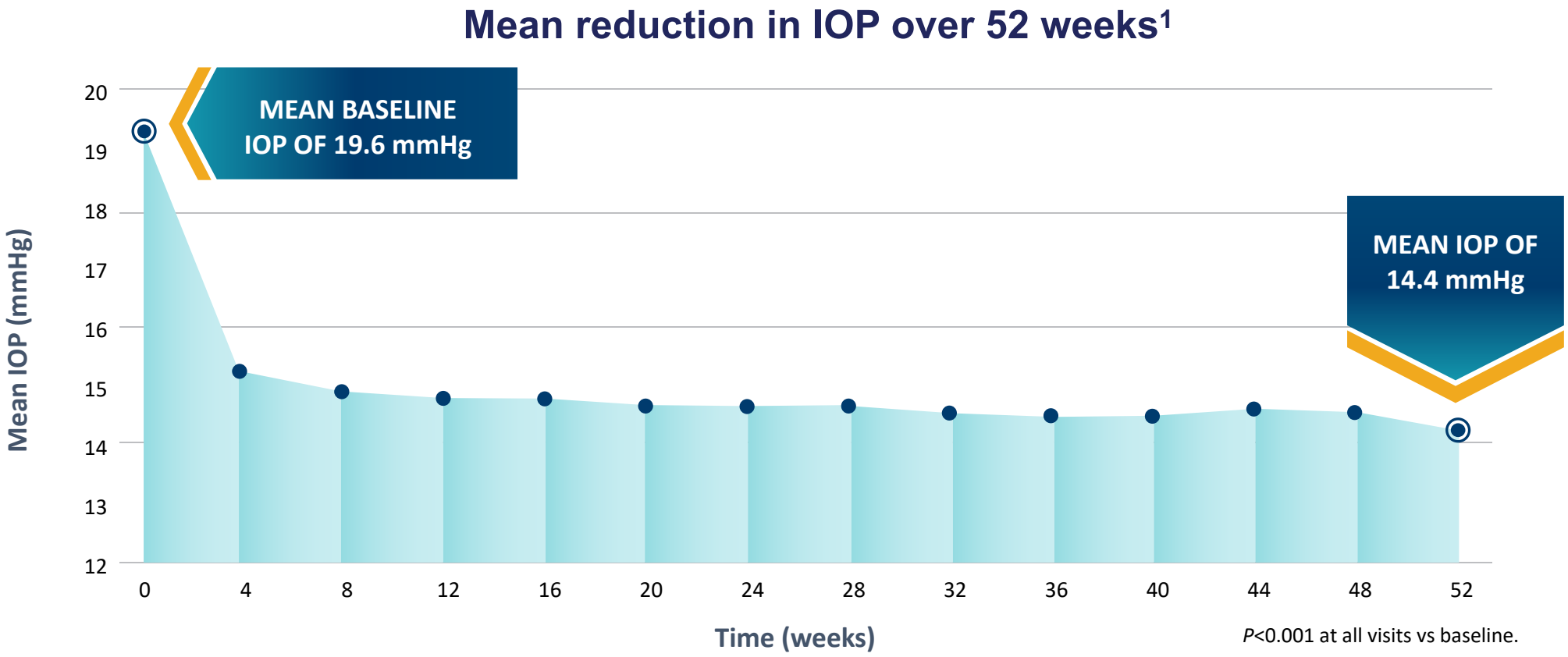
Percent of patients treated with VYZULTA who achieved greater IOP reductions than Xalatan*



*Post hoc analysis; Xalatan 0.005%, mean diurnal IOP reduction of 7.8 mmHg at Day 28.

1. Weinreb RN, et al. *Br J Ophthalmol*. 2015;99(6):738-745.

VYZULTA® Resulted in Significant Long-Term Reductions in IOP

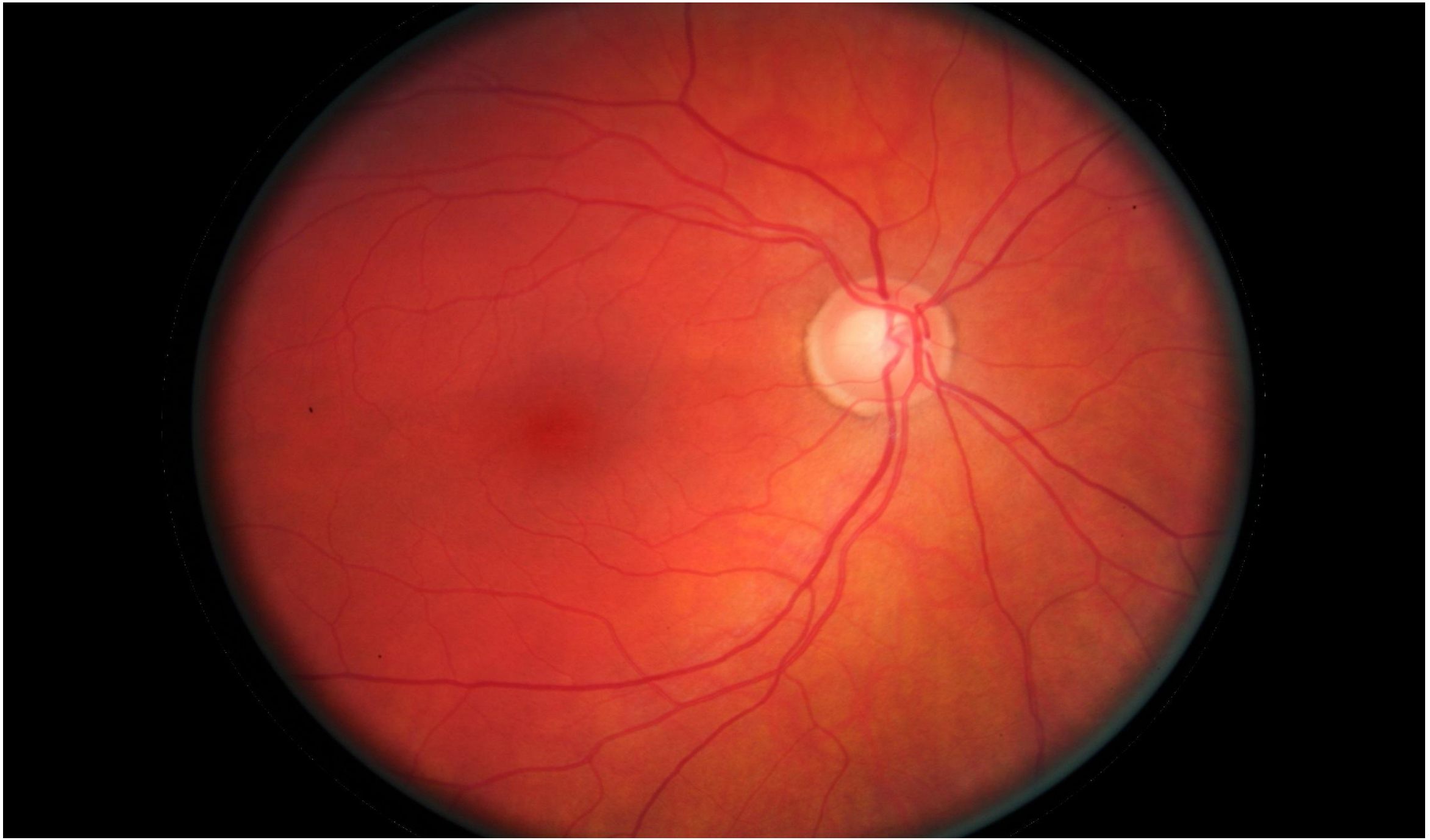


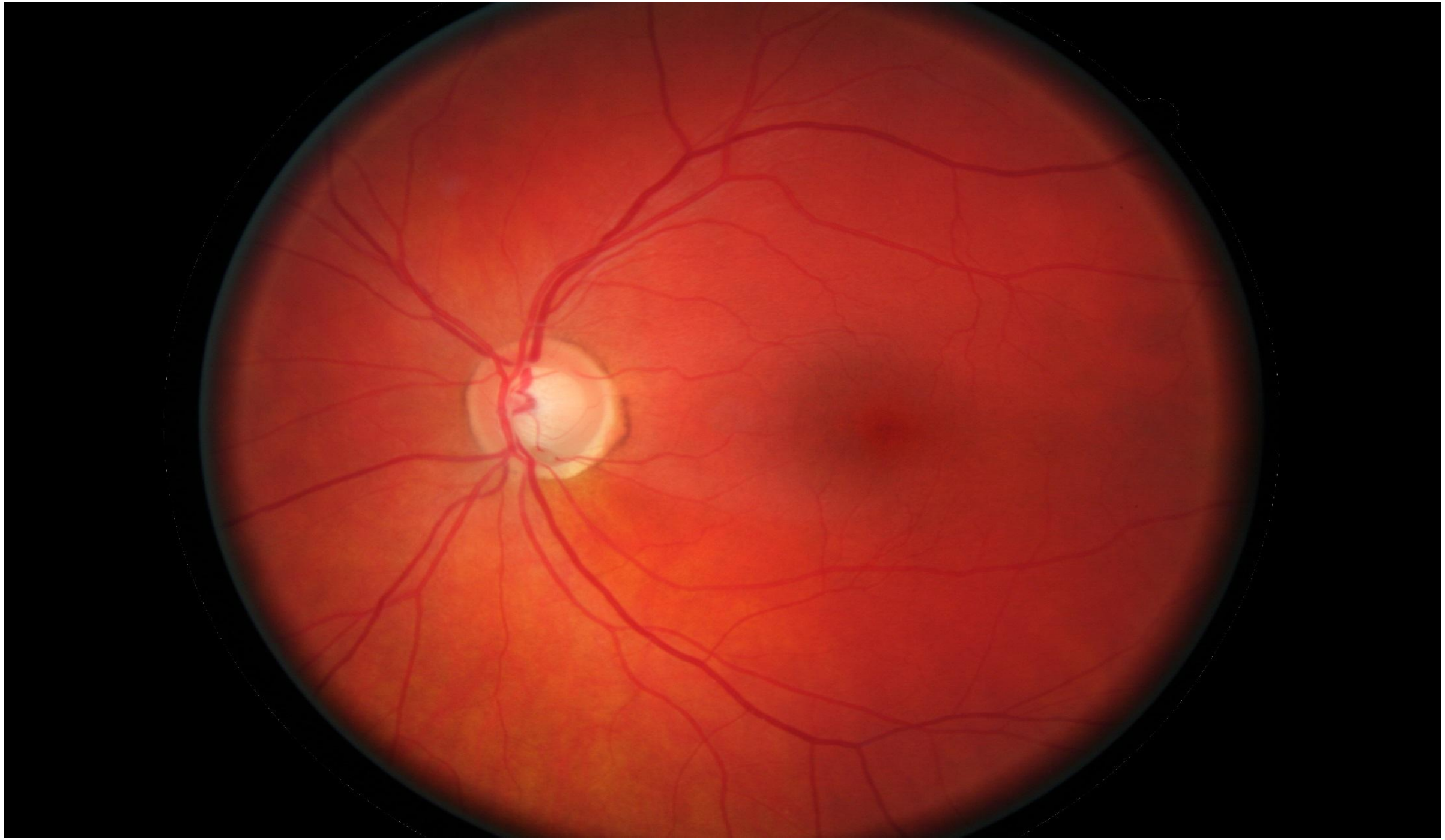
At 52 weeks, 69% of patients had an IOP of ≤15 mmHg[2]

1. Kawase K et al. *Adv Ther*. 2016;33(9):1612-1627. doi:10.1007/s12325-016-0385-7

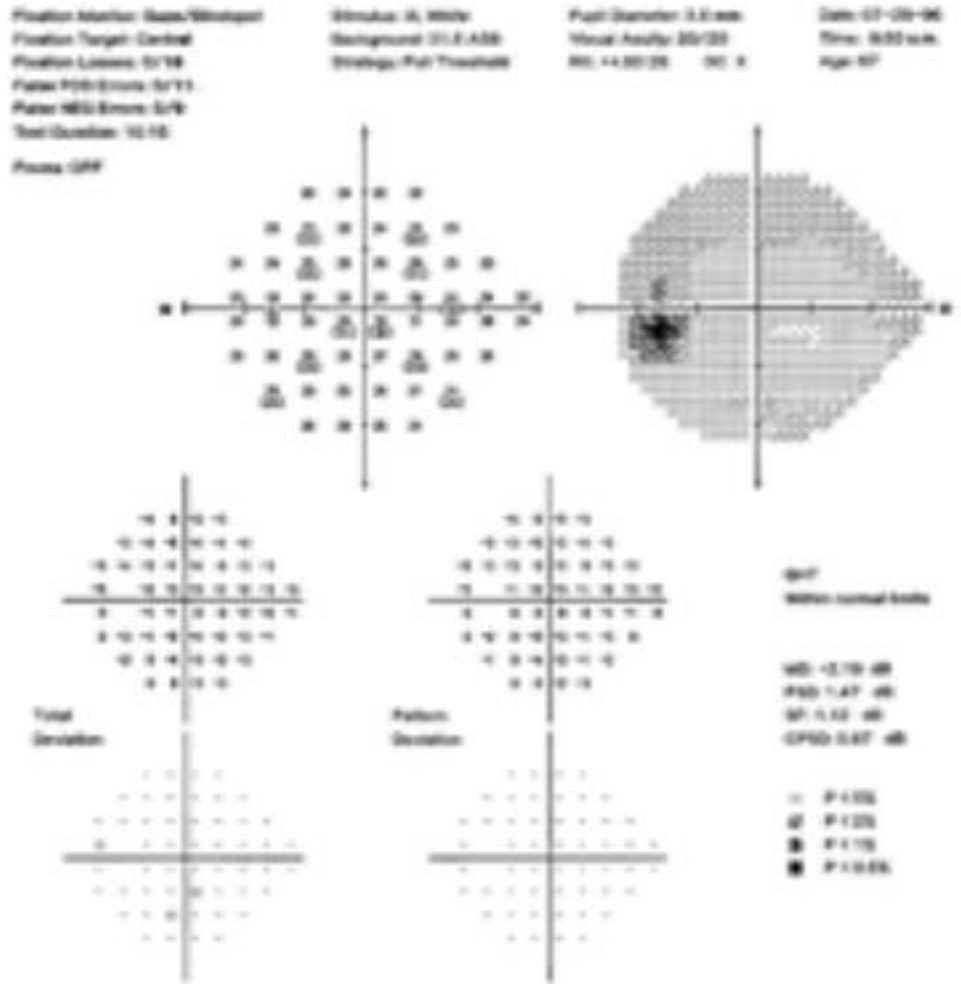
Case Three: How Low Can You Go!

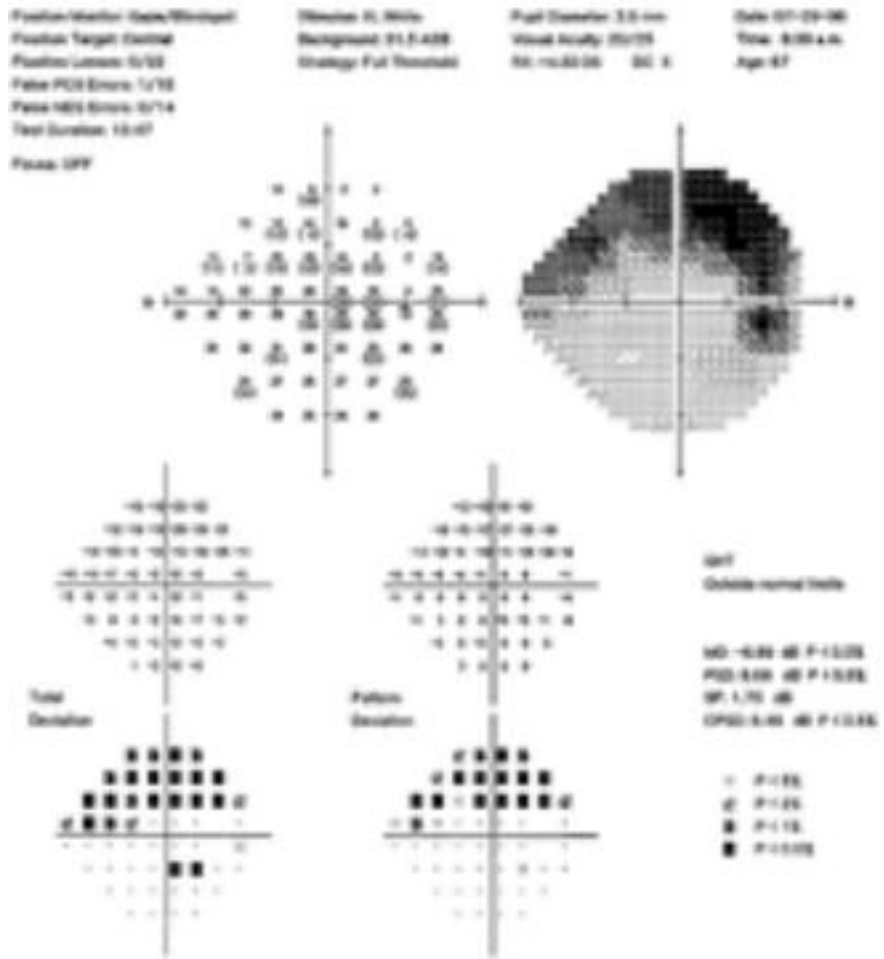
- SM a 40 y/o white female was referred for evaluation of glaucoma. Current Tx was Latanoprost and Alphagan.
- VA 20/20 OD/OS
- Ta 17/16 @ 10
- SLE: wnl
- DFE: 0.7 OD / 0.9 OS
- VF: Early near fixation loss OS
- Gonioscopy: CB 360 OU
- Medical Hx: LBP (100/65), pulse 54, Raynaud's, Migraine HA
- Family Hx: Negative
- Treatment ?





Visual Field Loss

- 



How Low can You Go?

- Meds: Vyzulta, Alphagan P
- Ta: 12/13 mmHg
- VF: Stable x 6 months

Nocturnal Hypotension: It's role in Visual Field Progression

- Graham SL, Drance S: Surv Ophthalmol Jun 1999
- 84 patients 24 hour ambulatory BP
- Nocturnal BP variables were lower in patients with progressive VF loss
- Patients with > nocturnal dips were more likely to show VF loss even with good IOP control
- Increased risk of disc hem's

How Low Can You Go?

3 months f/u

- Ta: 10/11 @ 2:00
- VF: stable 10-2
- Meds: no change
- ONH:

- Treatment?

NORMAL TENSION: ABNORMAL RESULTS

- ANDERSON et al AJO
  - EXAMINED NTG'S FOR MULTIPLE VARIABLES (AGE, GENDER,BP AND MIGRAINES)
  - MIGRAINES,DISC HEM'S MOST NOTABLE RISK FOR PROGRESSION
  - AGE , RACE NEXT
  - 230 PATIENTS/NTG/IOP< 20mm Hg

NTG

- 99 WOMEN/61 MEN
- 23 WOMEN WITH H/O MIGRAINES
- 2 MEN
- WOMEN WITH MIGRAINES HAD FASTEST RATE OF PROGRESSION

Durysta

Durysta

- Bimatoprost is a prostamide that has been shown to reduce IOP when administered topically
- A biodegradable implant has been developed
- The implant is designed to be placed intracamerally in the eye and provide slow release of bimatoprost over time

Gonioscopic photographs of bimatoprost sustained-release implant 10 µg in the anterior chamber of an eye of a representative patient diagnosed with open-angle glaucoma

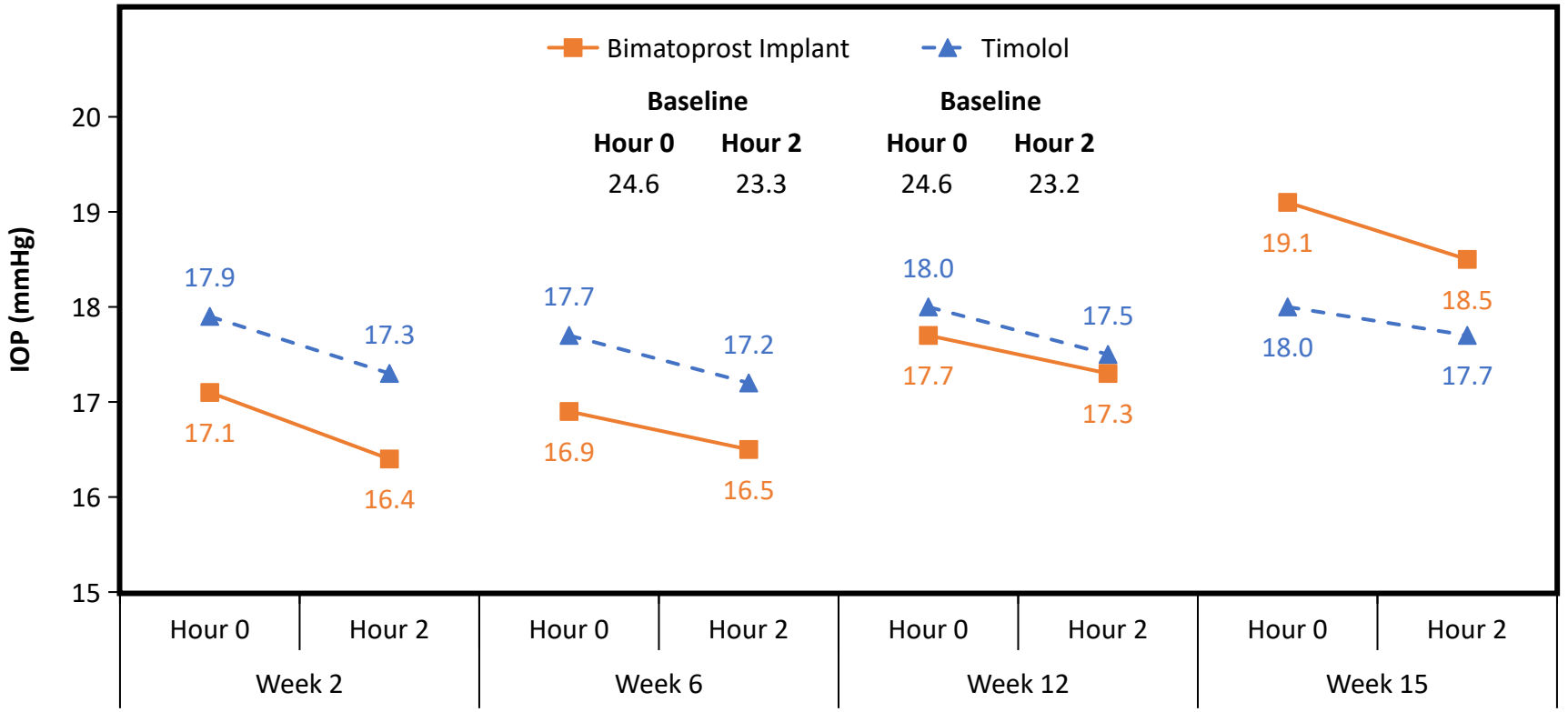
IOP = intraocular pressure

Lewis R, et al. *Am J Ophthalmol* 2017;175:137-147.

Mean IOP by Treatment Group and Treatment Difference in Mean IOP

ARTEMIS Study 1

Primary Endpoint



Bimatoprost Implant vs. Timolol (95% CI)				
Hour 0	-0.8 (-1.47, -0.14)	-0.8 (-1.47, -0.21)	-0.3 (-1.09, 0.43)	1.1 (0.22, 1.89)
Hour 2	-0.9 (-1.50, -0.31)	-0.7 (-1.27, -0.04)	-0.2 (-0.90, 0.46)	0.9 (0.10, 1.64)

1. DURYSTA™ [package insert]. Irvine, CA: Allergan USA, Inc., March 2020.

THE LANCET
THE “LIGHT” STUDY

VOLUME 393, ISSUE 10180, P1505-1516, APRIL 13, 2019

- **Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial**
- Gus Gazzard, FRCOphth
- Evgenia Konstantakopoulou, PhD
- Prof David Garway-Heath, MD
- Anurag Garg, FRCOphth
- Victoria Vickerstaff, MSc
- Rachael Hunter, MSc
- et al.

Trans Am Ophthalmol Soc. 2009 Dec; 107: 167–181.
PMCID: PMC2814574
PMID: 20126493

From The Bedside to the Bench and Back Again: Predicting and Improving the Outcomes of SLT Glaucoma Therapy

Jorge A. Alvarado, MD,* Rumiko Iguchi, MS, Richard Juster, PhD, Julie A. Chen, MD, and Amde Selassie Shifera, MD

IOP DIFFERENCE (MM HG) BETWEEN CONDITIONS

IOP, intraocular pressure; N, number; SD, standard deviation; PGA, prostaglandin analogue; SLT, selective laser trabeculoplasty.
*All *P* values are for the paired *t* statistic and are 2-sided.

N EYES = 24	**A. MEAN % DIFFERENCE (SD)**	**B. MEAN % DIFFERENCE (SD)**
IOP_{PGA}-$IOP_{BASELINE}$	−5.58 (2.38); *P* < .001*	−25.37% (8.86); *P* < .001
IOP_{SLT}-$IOP_{BASELINE}$	−6.60 (2.44); *P* < .001	−29.93% (7.05); *P* < .001
IOP_{SLT}-IOP_{PGA}	−1.02 (1.81); *P* = .011	−5.33% (11.39); *P* = .031

LIGHT Study

- Methods

  Observer-masked, randomized controlled trial treatment-naive patients with open angle glaucoma or ocular hypertension and no ocular comorbidities were recruited between 2012 and 2014 at six UK hospitals.

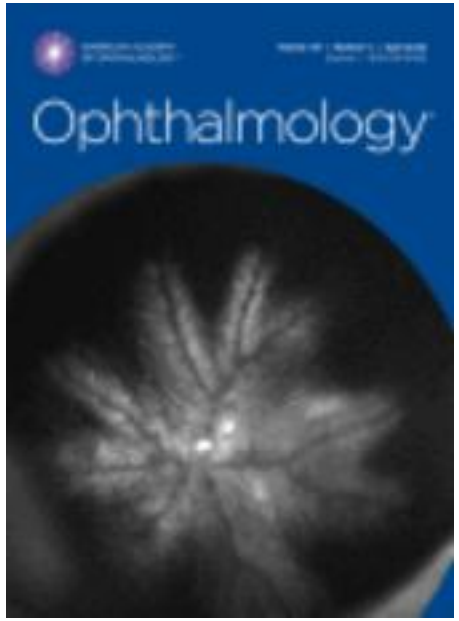
- Randomly allocated (web-based randomization) to initial selective laser trabeculoplasty or to eye drops. An objective target intraocular pressure was set according to glaucoma severity.
- The primary outcome was health-related quality of life (HRQoL) at 3 years (assessed by EQ-5D). Secondary outcomes were cost and cost-effectiveness, disease-specific HRQoL, clinical effectiveness, and safety.
- Analysis was by intention to treat. This study is registered at controlled-trials.com (ISRCTN32038223).

LIGHT Study

- Standardization of laser delivery was achieved by protocol-defined settings and clinical endpoints.[14]
- Selective laser trabeculoplasty was delivered to 360° of the trabecular meshwork. 100 non-overlapping shots (25 per quadrant) were used, with the laser energy varied from 0·3 to 1·4 mJ by the clinician, using an appropriate laser gonioscopy lens.
- One re-treatment with selective laser trabeculoplasty was allowed, provided there had been a reduction in intraocular pressure after the initial treatment; the next escalation was medical therapy.
- Significant complications of selective laser trabeculoplasty (eg, a spike in intraocular pressure) precluded repetition of selective laser trabeculoplasty.

LIGHT Study

- 718 patients enrolled, 356 were randomized to the selective laser trabeculoplasty and 362 to the eye drops group. 652 (91%) returned the primary outcome questionnaire at 36 months.
- Average EQ-5D score was 0·89 (SD 0·18) in the selective laser trabeculoplasty group versus 0·90 (SD 0·16) in the eye drops group, with no significant difference (difference 0·01, 95% CI −0·01 to 0·03; p=0·23).
- At 36 months, 74·2% (95% CI 69·3–78·6) of patients in the selective laser trabeculoplasty group required no drops to maintain intraocular pressure at target.
- Eyes of patients in the selective laser trabeculoplasty group were within target intraocular pressure at more visits (93·0%) than in the eye drops group (91·3%), with glaucoma surgery to lower intraocular pressure required in none versus 11 patients.
- Over 36 months, from a cost perspective, there was a 97% probability of selective laser trabeculoplasty as first treatment being more cost-effective than eye drops.



Efficacy of Repeat Selective Laser Trabeculoplasty in Medication-Naive Open-Angle Glaucoma and Ocular Hypertension during the LiGHT Trial

Anurag Garg FRCOphth;[1] Victoria Vickerstaff MSc[2,3] Neil Nathwani BSc[1] David Garway-Heath MD[1] Evgenia Konstantakopoulou PhD[1] Gareth Ambler PhD[4] Catey Bunce DSc[1,5,6] Richard Wormald FRCOphth[1,6] Keith Barton FRCS Gus Gazzard MD[1,7]

Repeat SLT

- Results
- A total of 115 eyes of 90 patients received repeat SLT during the first 18 months of the trial. Pretreatment IOP before initial SLT was significantly higher than before retreatment IOP of repeat SLT (mean difference, 3.4 mmHg; 95% confidence interval [CI], 2.6–4.3 mmHg; $P < 0.001$).
- Absolute IOP reduction at 2 months was greater after initial SLT compared with repeat SLT (mean difference, 1.0 mmHg; 95% CI, 0.2–1.8 mmHg; $P = 0.02$).
- Adjusted absolute IOP reduction at 2 months (adjusting for IOP before initial or repeat laser) was greater after repeat SLT (adjusted mean difference, −1.1 mmHg, 95% CI, −1.7 to −0.5 mmHg; $P = 0.001$).
- A total of 34 eyes were early failures (retreatment 2 months after initial SLT) versus 81 later failures (retreatment >2 months after initial SLT). No significant difference in early absolute IOP reduction at 2 months after repeat SLT was noted between early and later failures (mean difference, 0.3 mmHg; 95% CI, −1.1 to 1.8 mmHg; $P = 0.655$).
- Repeat SLT maintained drop-free IOP control in 67% of 115 eyes at 18 months, with no clinically relevant adverse events.