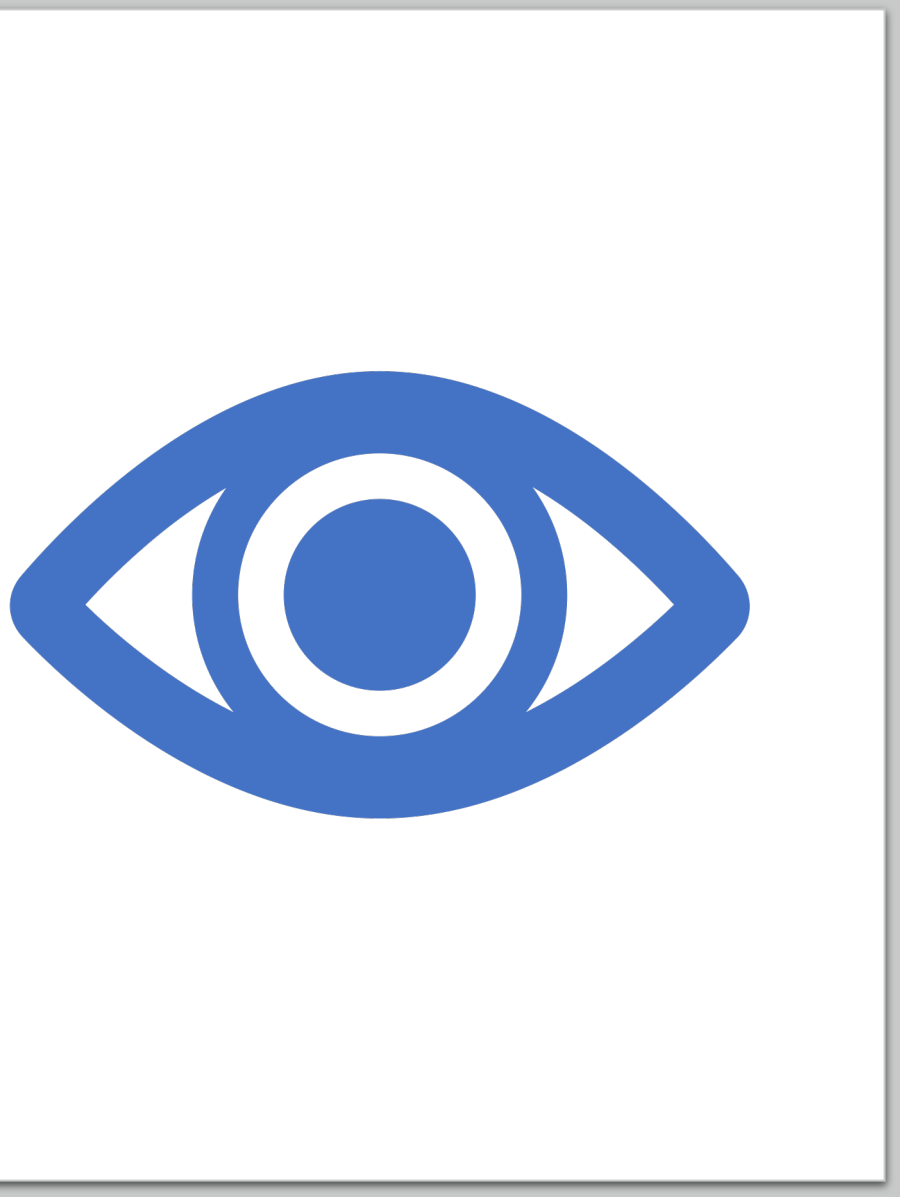


Roadmap For Medical Management of Glaucoma

Eric E Schmidt, OD, FAAO

Omni Eye Specialists

KeplrVision

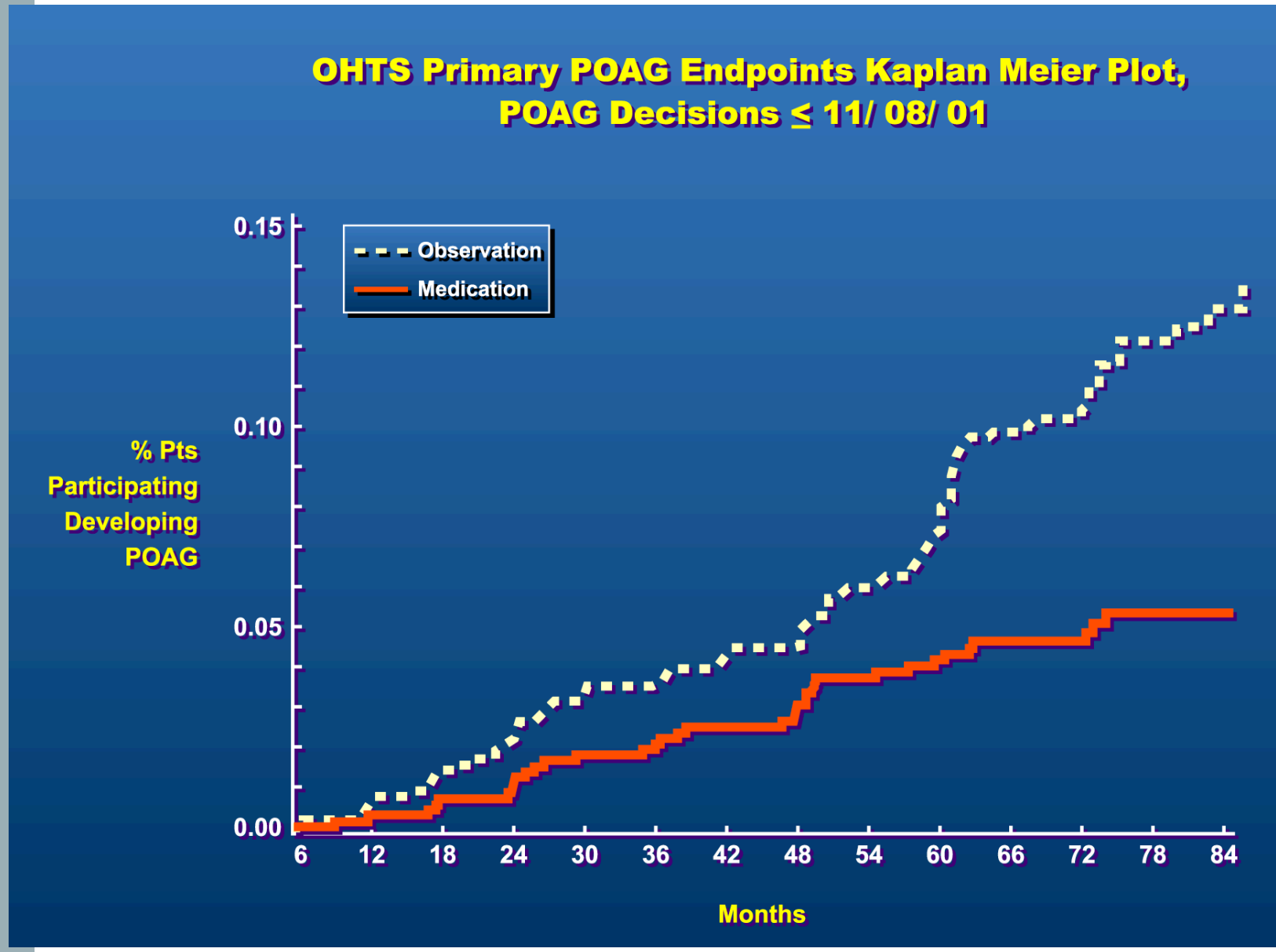
Wilmington, NC

Disclosures For Dr. Schmidt

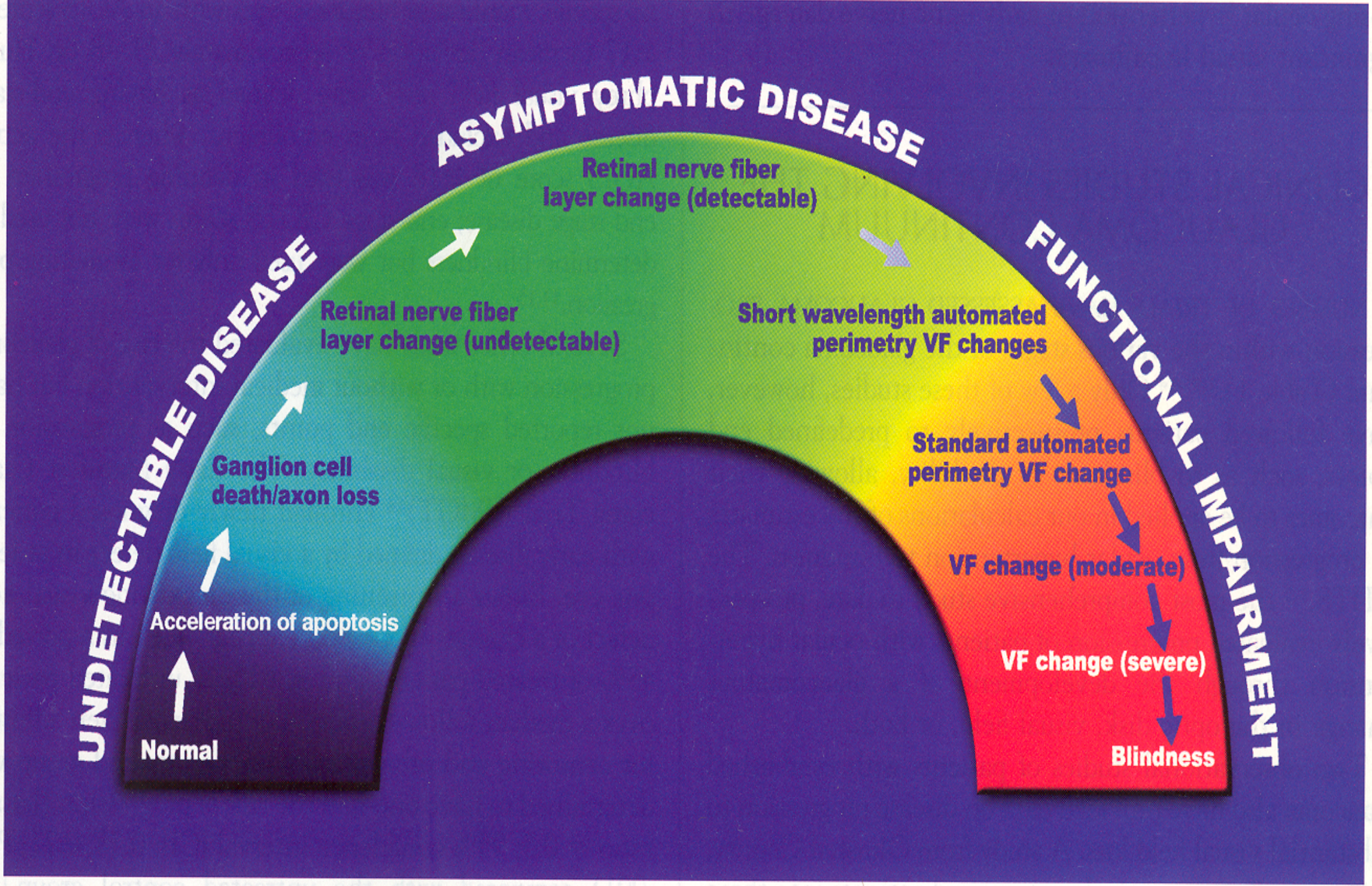
- Dr Schmidt is a consultant or advisor for:
  - Allergan
  - Aerie Pharmaceuticals
  - Ivantis
  - Carl Zeiss Meditec
  - Kala Pharmaceuticals
  - Tarsus
  - Visus

OCULAR HYPERTENSION TREATMENT STUDY*

Cumulative Probability of Developing Primary Open Angle Glaucoma



*Michael A. Kass, Dale K. Heuer, et al., Archives of Ophthalmology, Vol. 120, June 2002, 701-703


UNDETECTABLE DISEASE
ASYMPTOMATIC DISEASE
FUNCTIONAL IMPAIRMENT
Normal
Acceleration of apoptosis
Ganglion cell death/axon loss
Retinal nerve fiber layer change (undetectable)
Retinal nerve fiber layer change (detectable)
Short wavelength automated perimetry VF changes
Standard automated perimetry VF change
VF change (moderate)
VF change (severe)
Blindness

THE LATEST OHTS DATA

- Just released data

- Recommended patience before initiating therapy
- Don't rush to treatment judgement
- Treat them as glaucoma patients but without treatment

- Oh Really?!?!?!

EARLY MANIFEST GLAUCOMA TRIAL

- Compared progression rates between immediate treatment vs no or deferred treatment
- Immediate treatment group progressed at 45% rate
- Observed group progressed at 62% rate
- Average rate of IOP reduction was 25%

- Showed a definite benefit to early treatment
- Why the high progression rate?

EMGT Conclusions

Reducing IOP (by 25%) prevents or slows VF defect and progression

For each 1mm of IOP reduction there is a 10% lower risk of VF loss

Study design and outcome show that these results are only due to IOP reduction (non IOP related factors showed difference between the 2 groups)

Tx effect was equal across age and glaucoma categories

Eric's spin on the EMGT

1-2 extra mm Hg may indeed be important- especially in advanced cases.

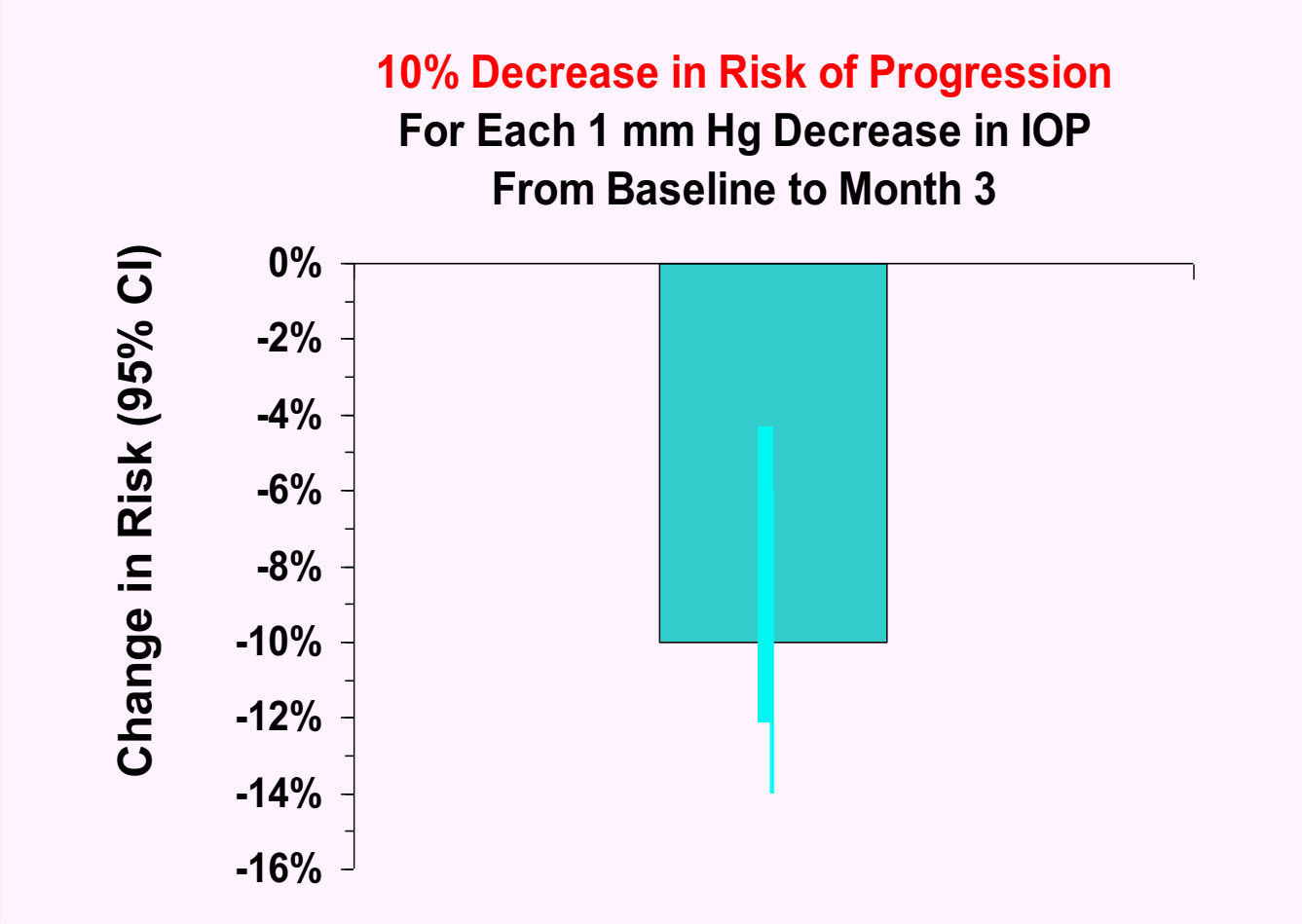
For those pxs who need treatment, AGGRESSIVE therapy is warranted

It is DEFINITELY better to treat early than late

You SHOULD NOT WAIT until the VF defects arise before therapy is initiated

The benefit of treatment does last throughout the lifetime of the px – just remember the risk/benefit

EMGT: EVERY MM HG OF IOP LOWERING MATTERS



Leske et al. *Arch Ophthalmol.* 2003.

WHAT PERCENT OF PATIENTS REALLY PROGRESS?

Rough Rule of Thumb:

- 40 % never have meaningful progression
- 50 % have insidious progression
- 10 % progress quickly
  - (These folks need surgery)

Meaning – ODs should treat 90% of G pxs!!

20 YEAR OHTS DATA

- 1 in 4 progresses WITHOUT TREATMENT!!

INITIAL MEDICAL MANAGEMENT OF OAG

- Before starting therapy
  - obtain several IOP readings
    - Not necessarily on same day. Better over 2-3 days at different times
    - need detailed pretreatment information
      - medical and ocular
  - grade severity of glaucoma
    - based upon nerve appearance, fields and highest IOP

WHAT IS THE GOAL OF TREATMENT

- At least 30% reduction
  - Can one medicine do this??
- Monitor to see if 30% is enough
  - Is there progression at 6 mos, 1 year??
- How do we tell if there is progression?
  - Visual Field
  - IOP drift
  - OCT

TREATMENT GOALS OF GLAUCOMA

- **Maximum IOP reduction**—achieve lower IOP to help preserve sight; historically physicians tried to achieve pressures below 20 mm Hg
- **Maintaining low IOP over 24 hours**—avoid pressure spikes associated with visual field progression
- **Ease of use**—patient compliance is best with simple, easy-to-use medication regimen (typical glaucoma patient uses at least 3 other systemic medicines); monotherapy is preferred
- **Safety**—minimize systemic safety issues

Gottfredsdottir et al. *J Glaucoma*. 1997.

TREATMENT RECOMMENDATIONS

- Minimum initial target IOP reduction of 25% recommended for glaucoma patients
- More aggressive initial target IOP reductions of 30% or 35% recommended for most patients: especially those at higher risk
- Target IOP must be DYNAMIC, re-evaluated periodically, and lowered if patient progresses despite meeting the initial target IOP
  - Re-evaluate and adjust patient's target IOP at least every 5 years, and in light of newest information

Delphi Panel 2003

The Delphi Panel. PDR. 2003.

"NEW" GOAL OF TREATMENT IN GLAUCOMA

1. Low and *Stable* IOP
2. Minimize the diurnal curve
3. Prevent IOP peaks
4. Enhance Compliance

CHOOSING A TARGET IOP - GENERAL RULE #1

- 30% decrease as an initial target
- Target decrease from highest untreated IOP
- CIGTS, OHTS

TARGET IOP RULE #2

Mild glaucoma – decrease IOP 30%

Moderate glaucoma – decrease IOP 40%

Severe glaucoma – decrease IOP 50% (at least)

WHEN SHOULD TARGET IOP BE CHANGED?

- VF progression (even at target IOP)
- Neuroretinal rim recession
- Parametric changes
- Disk Hemorrhages
- Long term stability – even if on multiple meds

IMPORTANCE OF IOP STABILITY

IOP variation is a risk factor for VF loss in glaucoma

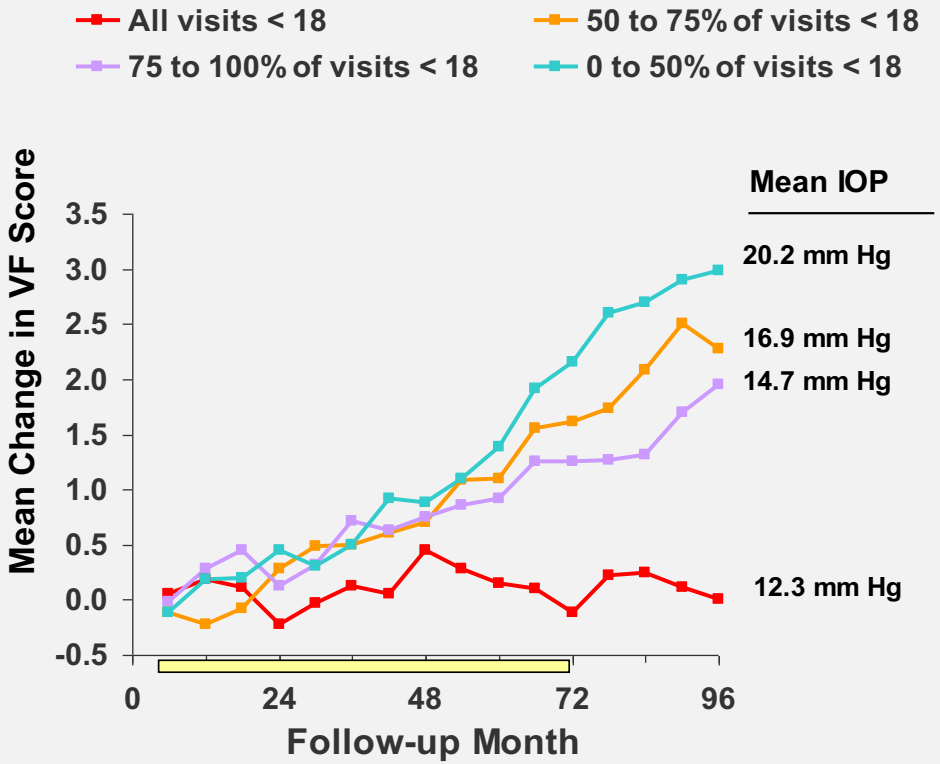
VF protected best when pressures are consistently kept under 18 mm Hg

Wide swings in IOP during the day or from visit to visit should be avoided

Stabilizing IOP is vital

AGIS: NEED TO MAINTAIN LOW IOP OVER TIME

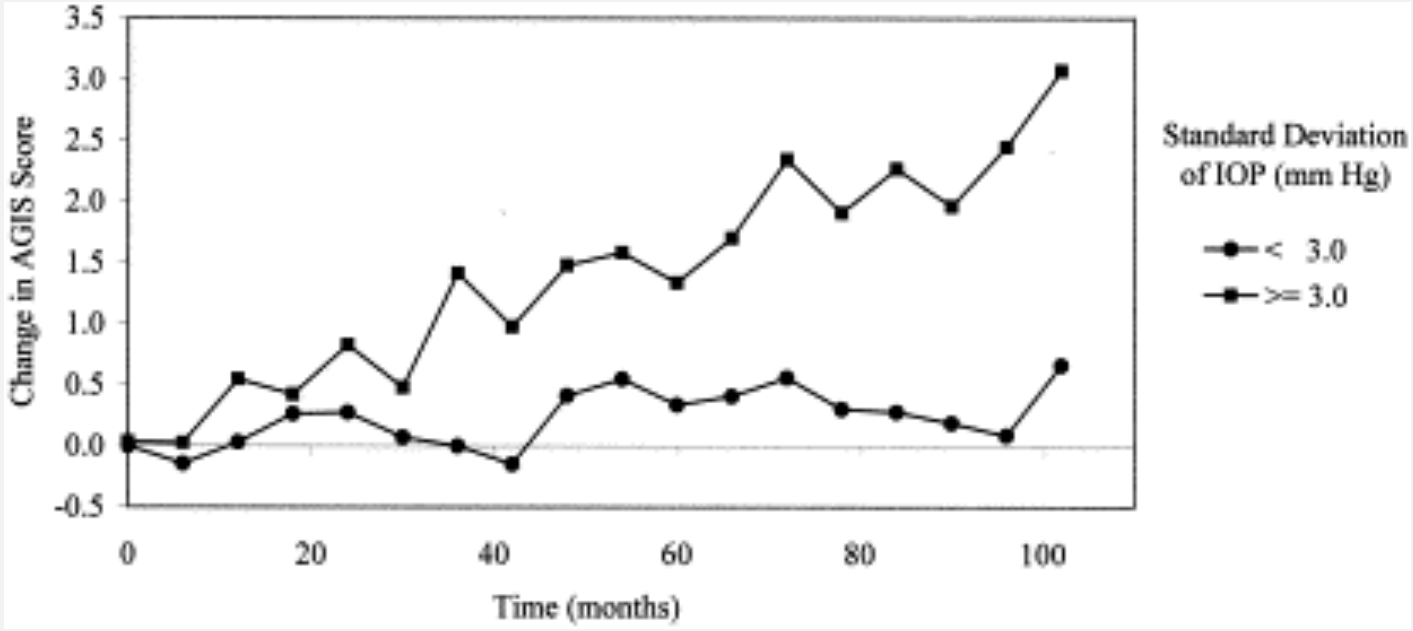
- Target IOP <18 mm Hg
- 100% of visits <18 mm Hg: on average no loss in VF
- Any visits with IOP target not met: on average significant VF loss
  - 2-unit loss in VF over 7 years when target met at <75% of visits



CONCLUSION: Progression is minimized when IOP is kept consistently low (<18 mm Hg)

AGIS:7. *Am J Ophthalmol.* 2000.

AGIS: PATIENTS WITH SMALL IOP VARIATION HAD STABLE FIELDS



- Eyes with variation < 3 mm Hg: no average progression
- Eyes with variation ≥ 3 mm Hg: on average, significant progression

Nouri-Mahdavi et al. *Ophthalmology.* 2004.

The Glaucoma Treatment Universe 2021

- Prostaglandins
- Alpha –agonist
- ROCK-Inhibitors
- CAI
- Combo drugs
- Beta blockers
- Surgical Intervention
- MIGS
- SLT
- Trabeculectomy
- Cataract Extraction
- Nutrition issues

Prostaglandins

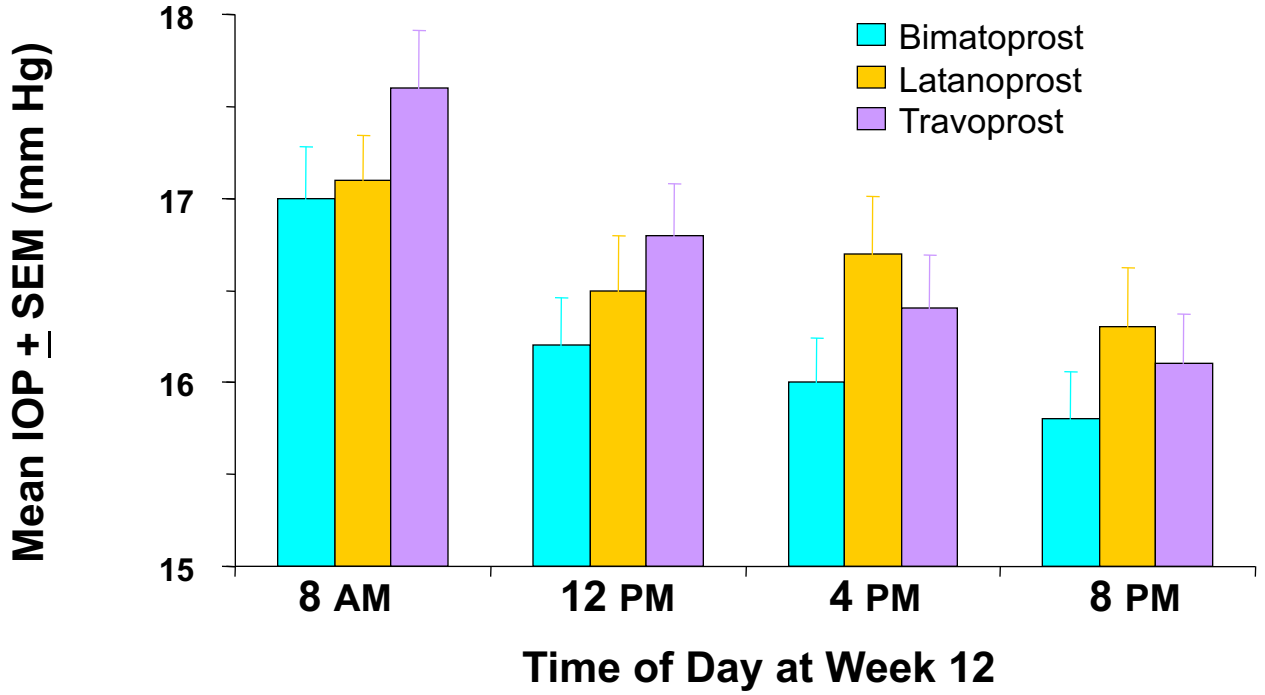
- Average drop in IOP - 34%
- All decrease IOP by increasing uveoscleral outflow
- All are effective at squashing the diurnal curve
- They have either no effect or a positive effect on retinal perfusion
- But does 1 work better than the others?

Prostaglandin Side Effects

- Hyperemia is the main adverse event – 33-50% of the time
  - But consider this…

- Conjunctival hyperemia: Severe hyperemia
  - Lumigan 3.5%
  - Travatan 1.5%
  - Xalatan <1%
  - Vyzulta??
- Is this a transient phenomenon?
- Is it an allergic conjunctivitis?
- Is it worth stopping the drop?

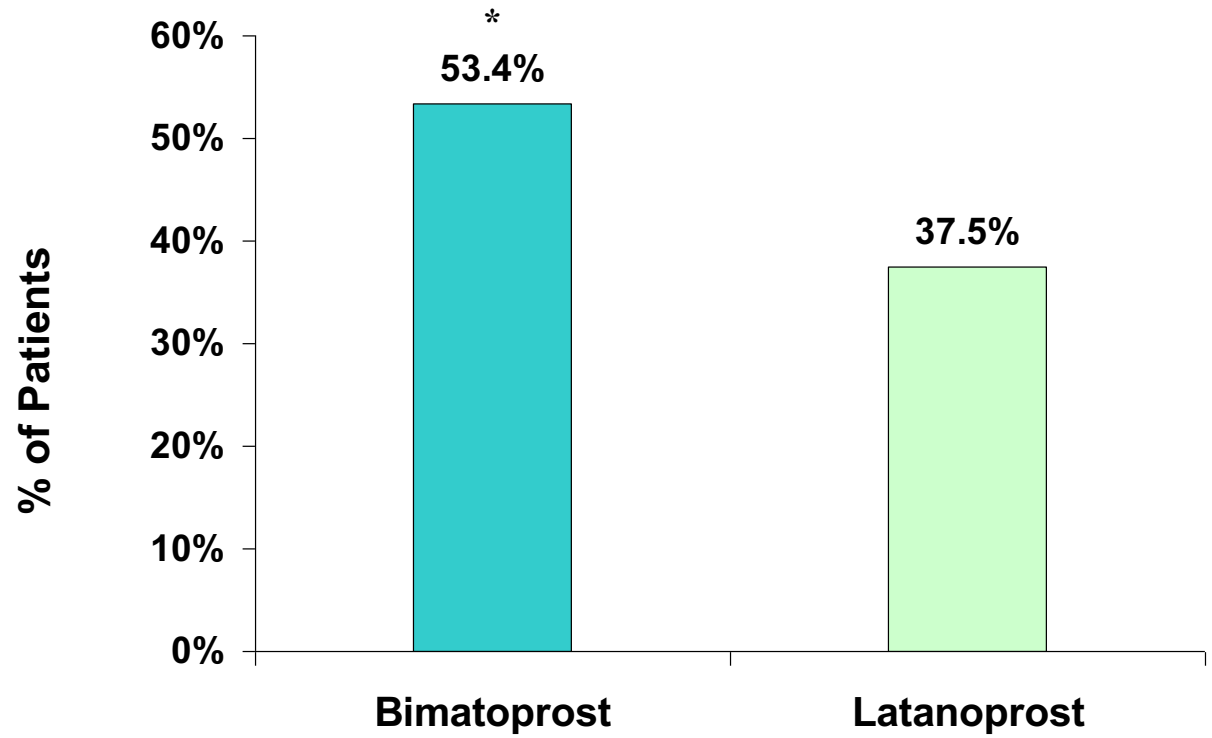
XLT Study:
Mean IOP at Week 12



- Study population: previously treated patients
  - Approximately 50% on latanoprost at screening
- Consistently lower mean IOP with bimatoprost*

**Statistical analysis not reported*

Patients Consistently Achieving a Mean Diurnal IOP <18 mm Hg At Every Visit Through 6 Months



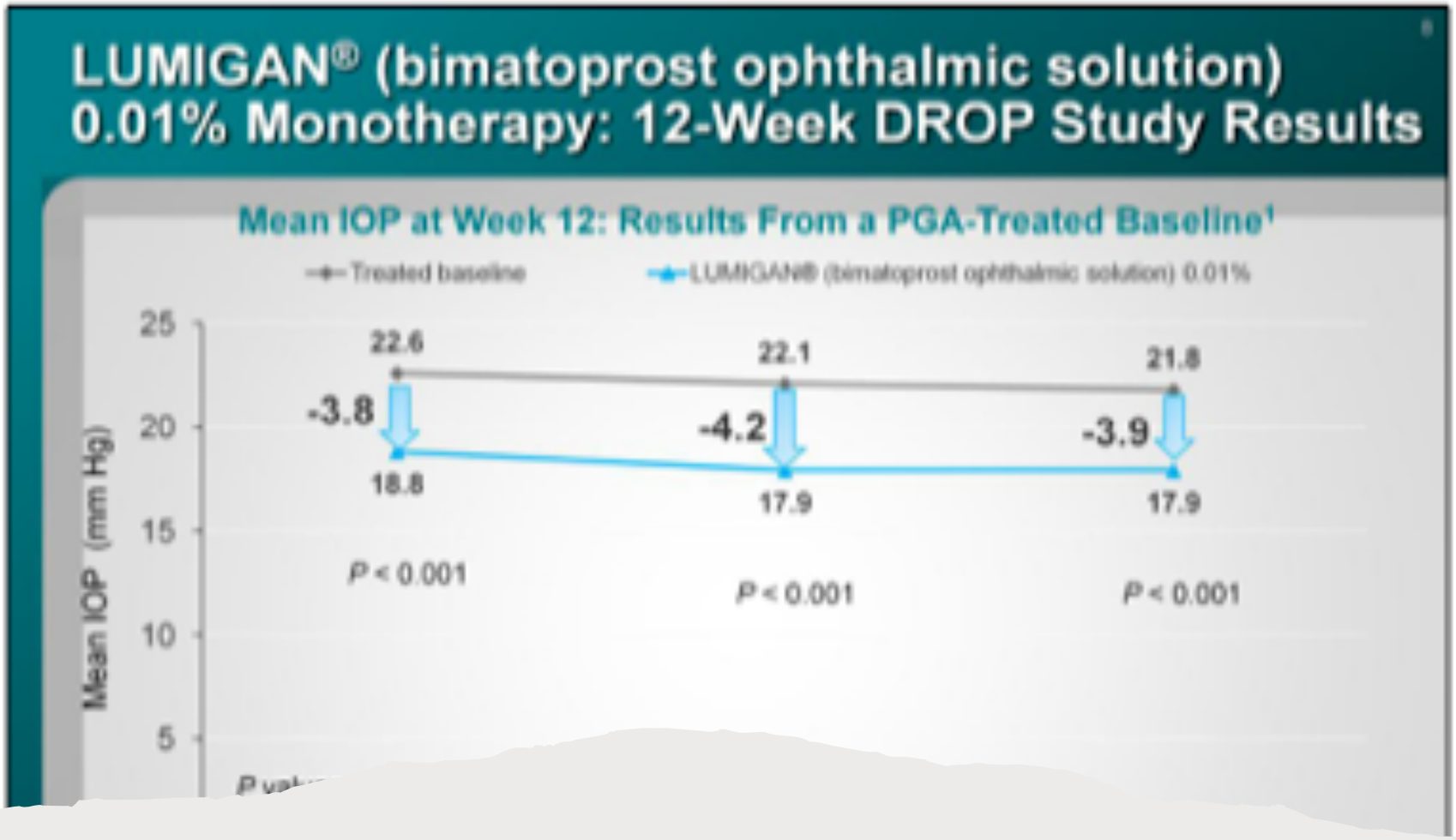
*P = .010

Choplin et al. IGS. 2005

Regarding Prostaglandins:

- Generally the 1st line of treatment
- There are interindividual differences in efficacy
- Are there racial differences?
- If at first one fails; try, try , try again (with another prostaglandin)

- Why wouldn't you use a prostaglandin 1st?



Myers Study 2014

ROCK Inhibitors- Rhopressa

- New class of drugs – Rho-kinase inhibitor
- MOA – “Triple Action”
- - relaxes trabecular meshwork similar to pilocarpine (enhances outflow)
- - lowers episcleral venous pressure
- - blocks fibrotic response at t.m.(increases perfusion)
- QD dosing
- Looks especially effective at IOP 25 mmHg or less

What Do We Know About Rhopessa (netarsudil 0.02%)

- Rhopressa QD is non-inferior to timolol 0.5% BID in lowering IOP
- Expected IOP reduction 3.7 -7.0mm Hg
- Rhopressa seems to better at lowering IOP (as compared to itself) in pressures < 25mm Hg
- IOP lowering effect is maintained over 12 months
- Was given a broad label by FDA

Rhopressa – Adverse Effects

- Generally well tolerated

- Conjunctival hyperemia – 53%
  - Did not worsen with time
  - Mild-36.8%, moderate – 10.5%, severe -0.6%
  - D/C rate due to redness -~3%
- Corneal verticillata – 18%
- Conjunctival hemorrhage – 15%
  - All are transient and considered mild

M.O.S.T. Study

- Real World Open Label Phase 4 Study
- ASCRS 2020
- To determine efficacy of Rhopressa as an adjunct med
- Investigator’s Choice – Rhopressa + any other agent
- 24.4% African-American participants

M.O.S.T. Results

Rhopressa + PGA - IOP 21.1> 16.9 mmHg (20% reduction)

Rhopressa + 2 meds – 20.6 > 16.6 mmHg (20% reduction)

Notice the low baseline IOP

More M.O.S.T. Results

- % of pxs less than < 18mm Hg
  - <18mm -72.7 % (from 34.4%)
  - <17mm- 65% (from 25.2%)
  - <15mm -40.6% (from 15.9%)
  - <14mm- 30.1% (from 11.3%)

- 2/3 of all patients achieved IOP < 17mm Hg

M.O.S.T. Tolerability rates

Hyperemia – 20.* %

D/C rate – hyperemia 3.4%

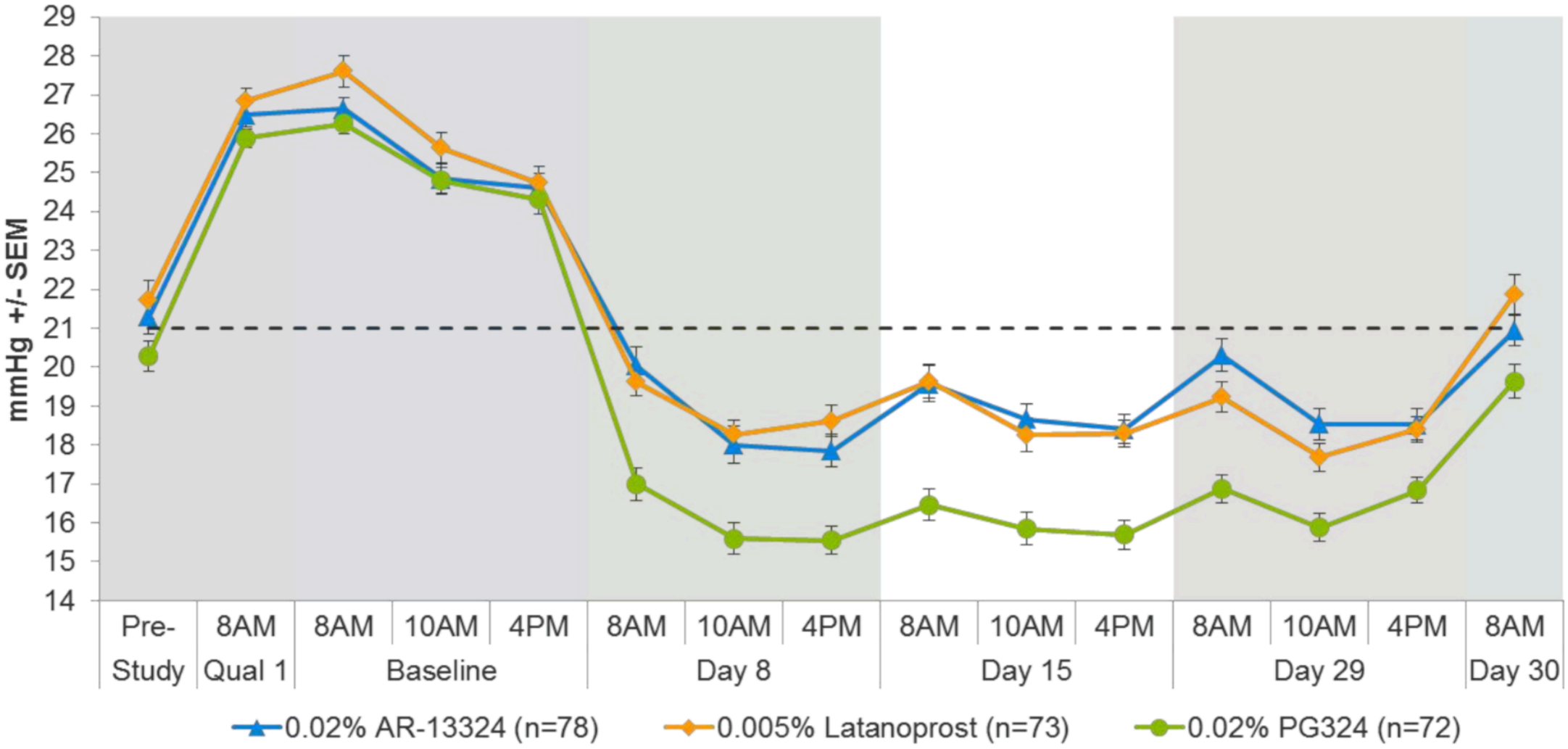
Tolerability rating

- 67.8-73.1% good or decent (physician response)
- 65-78% good or decent (Patient response)

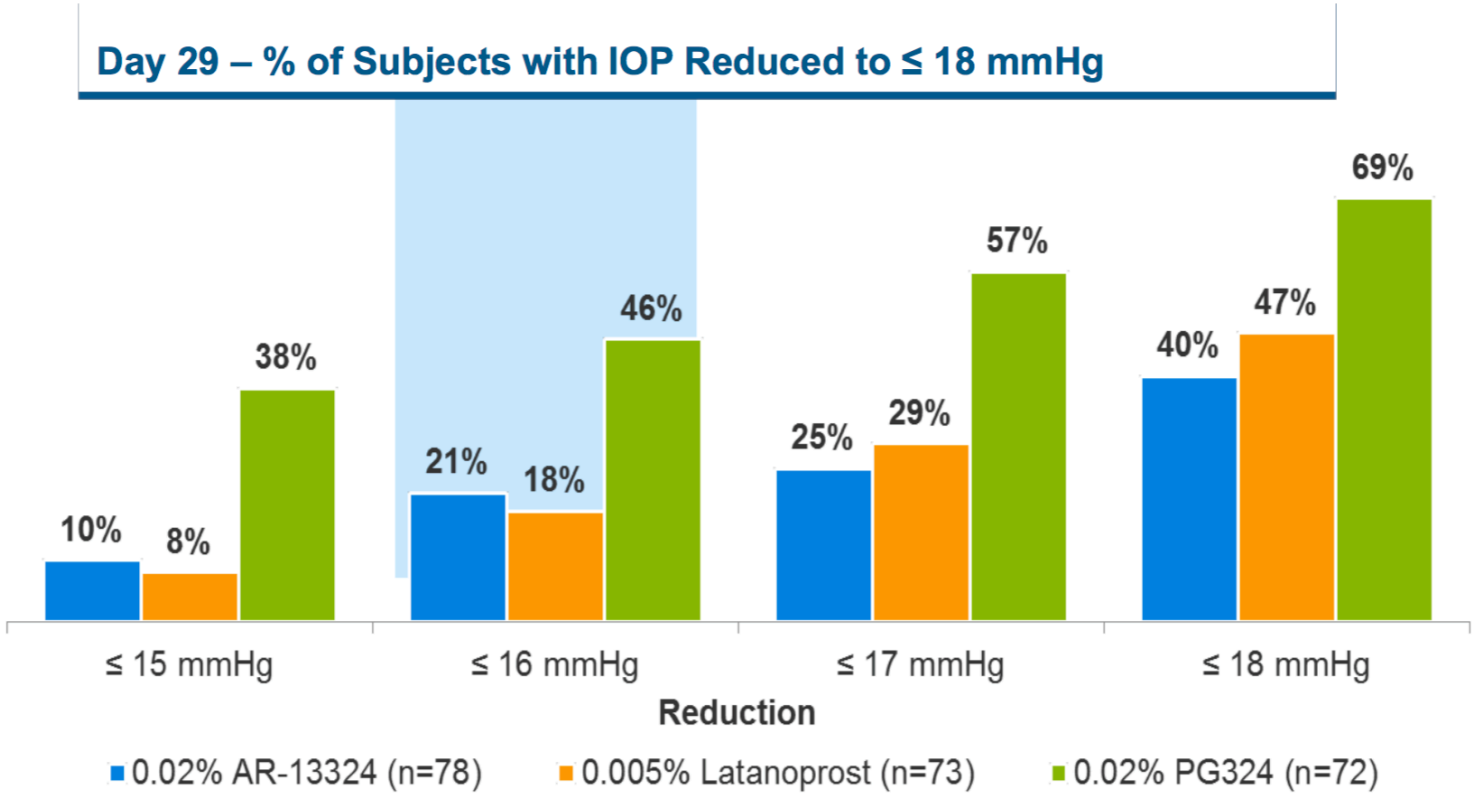
Roclatan – Aerie

- Fixed Combination drug – Rhopressa + latanoprost
- QD dosing
- “Quadruple acting” MOA – (adds increased uveoscleral outflow)
- IOP lowering better than either of its components
- Potential to be very effective – lowered IOP an additional 2-3 mm compared to Rhopressa (and other PGAs)

Mean IOP at Each Time Point (Primary Efficacy Measure)

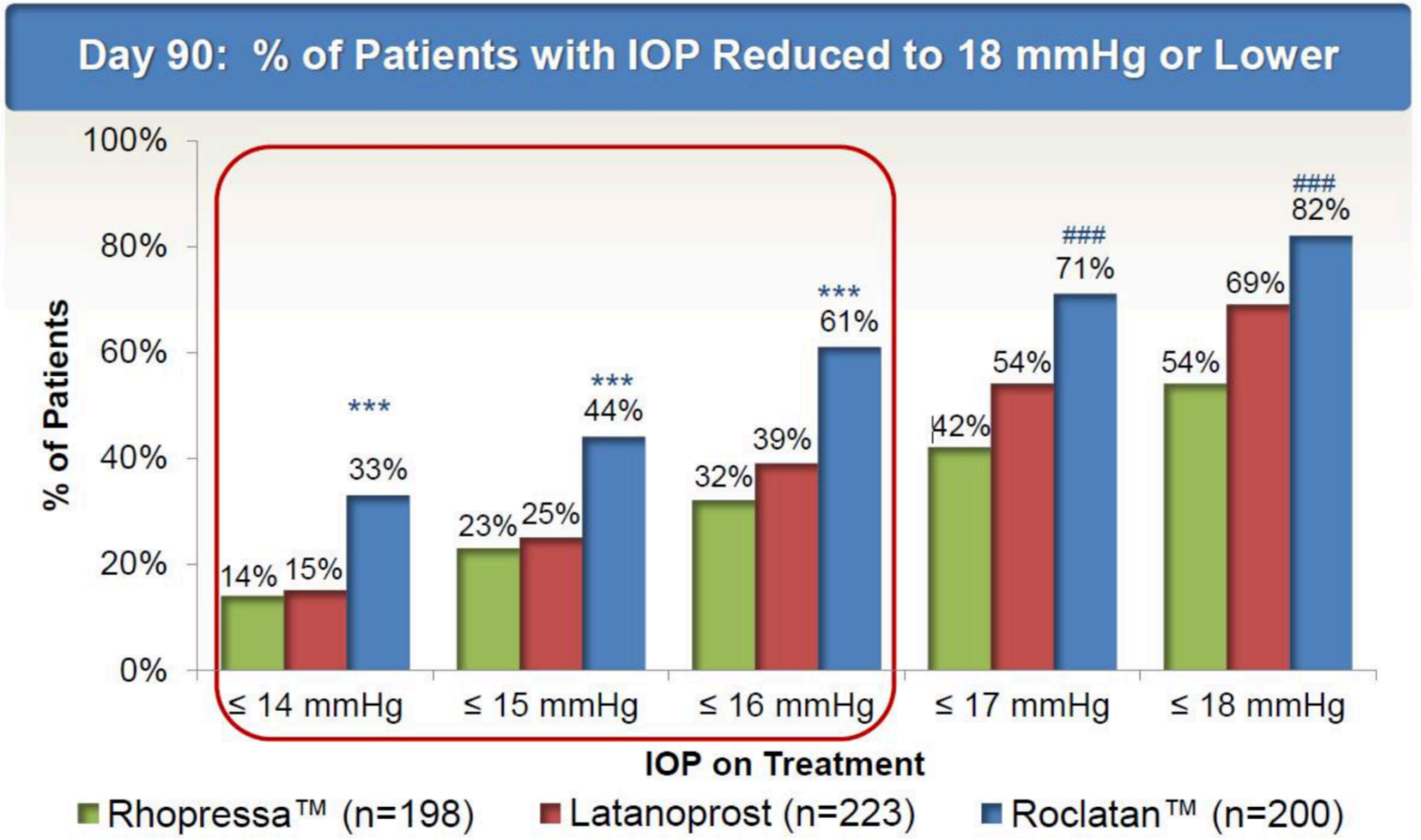


Roclatan
Phase 2b Responder Analysis



Source: Bacharach J, Levy B, Ramirez N, Kopczynski CC, Novack GD for the PG324-CS201 Study Group. Evaluation of PG-324, a fixed dose combination of AR-13324 and latanoprost, in patients with elevated intraocular pressure in a double-masked, randomized, controlled study. American Glaucoma Society 2015 (in press).

Roclatan™ Phase 3 Responder Analysis



***p<0.0001 vs Latanoprost and Rhopressa™
###p<0.0001 vs Rhopressa™, p<0.05 vs Latanoprost

Newest Rocklatan Data

- 1400 pxs
- Rocklatan vs Rhopressa vs Latanoprost
  - 60% achieved >30% reduction in IOP
  - 1/3 achieved > 40% reduction in IOP
  - CIGTS showed 38% drop to STOP VFG progression
  - 75% achieved <18mm Hg
  - 1/3 achieved 14mm or less
  - On average 3.2 mm lower IOP than either latanoprost or Rhopressa

Newest side effect data

- No tachyphylaxis at 12 months
- No unexpected A.E.
- Very few serious A.E.- majority are mild

- 58% hyperemia but 5% d/c rate
- 20% Instillation pain – 0% d/c
- 10% subconj heme – 0% d/c

Combo Drugs

- Are they the best “2nd Choice?”
- Can we use them as solo agents?
- What can we expect of them?

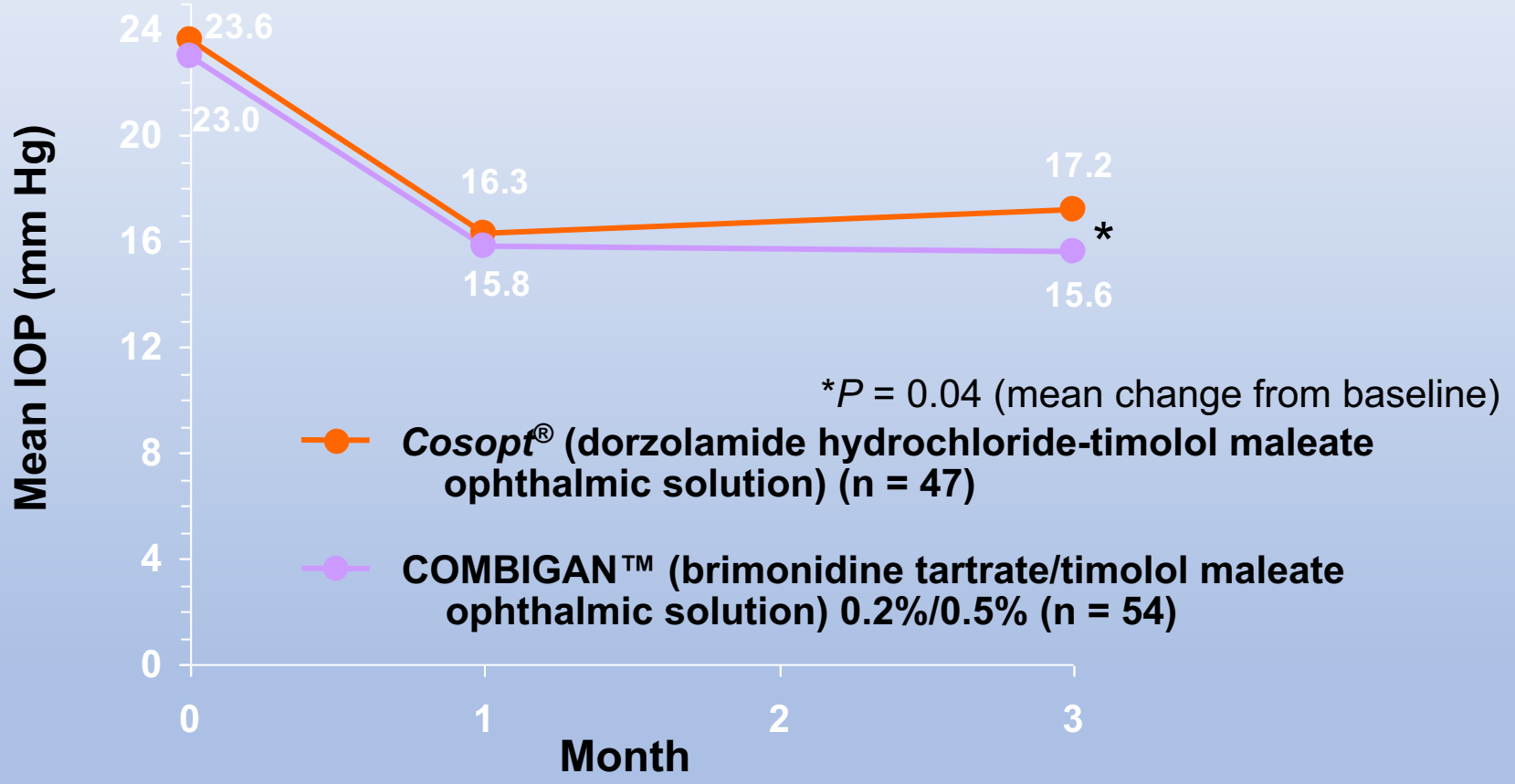
COMBIGAN™ and *Cosopt*®

- Randomized, investigator-masked, 3-month, parallel comparison
- Pooled data from 2 studies at 10 sites with identical protocols (Canada)
- Patients with OAG/OHT requiring additional IOP lowering
- Two subgroups
  - Monotherapy: COMBIGAN™(brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% (n = 54) and *Cosopt*® (dorzolamide hydrochloride-timolol maleate ophthalmic solution) (n = 47)
  - Adjunctive: COMBIGAN™ added to PGA (n = 37) and *Cosopt*® added to PGA (n = 42)
- IOP 2 hours after morning dose
  - Visits at baseline, 1 month, and 3 months

PGA = prostaglandin analogue

[1]Nixon and Hollander. AAO. 2007; [2]Data on file, Allergan, Inc.

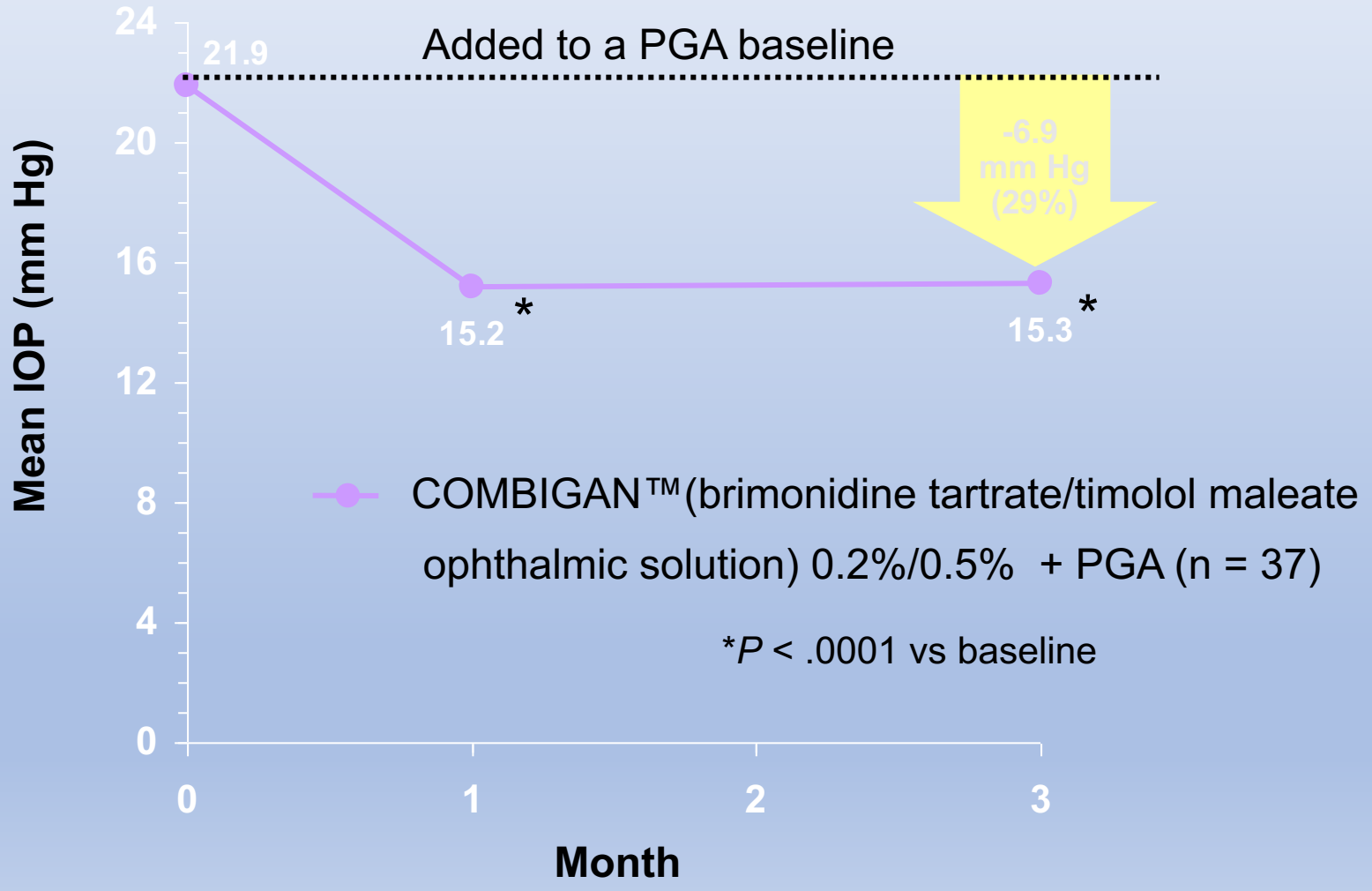
COMBIGAN™ and *Cosopt*® as Monotherapy: Mean IOP



- Mean IOP reductions from baseline at month 3 were 7.7 mm Hg with COMBIGAN™ and 6.7 mm Hg with *Cosopt*® (*P* = .040)

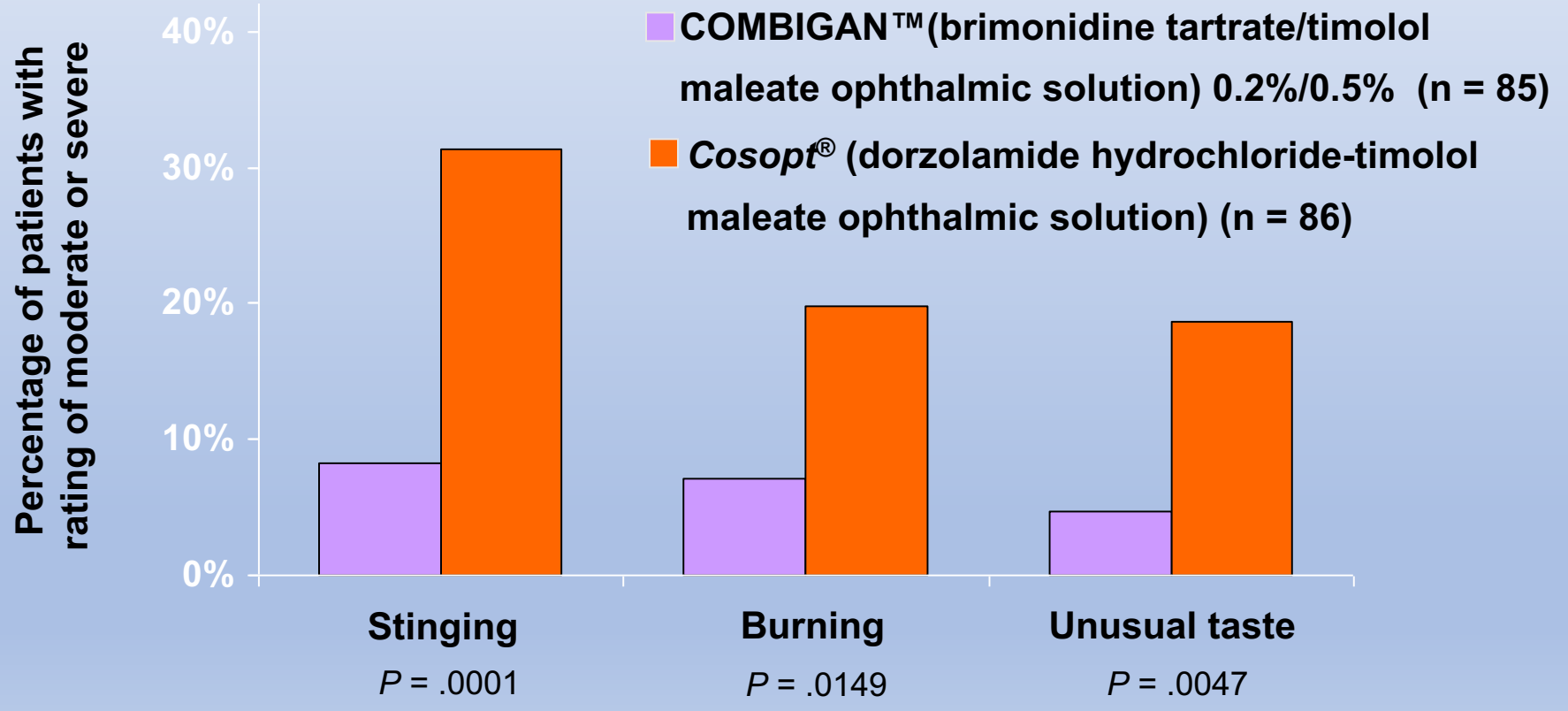
[1]Nixon and Hollander. AAO. 2007; [2]Data on file, Allergan, Inc.

COMBIGAN™ in Adjunctive Therapy With a PGA: Mean IOP



[1]Nixon and Hollander. [2]AAO, 2007. Data on file, Allergan, Inc.

COMBIGAN™ and *Cosopt*® Tolerability and Comfort



[1]Nixon and Hollander. [2]AAO, 2007. Data on file, Allergan, Inc.

Combination Drug #3

- Cosopt PF
  - Preservative free
  - Unit dosage vial
  - Able to lower IOP as good as preserved, branded Cosopt
  - BID
  - So???

Combination Drug #4

- Simbrinza (Alcon)
  - Brinzolamide 1.0%/Brimonidine 0.2%
  - TID Dosing
  - Approved for adjunctive therapy
  - Adjunctive to what??

Simbrinza

- 5-9 mm Hg IOP reduction
- Baseline IOP – 22 -36mm Hg
- 21- 35% IOP reduction
- TID dosing

Simbrinza

- Compared to Azopt head-to –head
- Compared to Brimonidine 0.2% head- to – head

- Statistically superior to either of the components in lowering IOP 2 3 mths
- At all time points

Simbrinza – Safety data

- Side effects are similar to each of the component drugs
- D/C rate – 11%
- 3-5% incidence rate of:
  - Blurred vision
  - Ocular irritation
  - Bad taste
  - Dry mouth
  - Ocular allergy

What About …

- Beta Blockers?
- CAI?
- Alpha Agonists?

Beta-blocker debate

- Are they still useful?
- As initial therapy?
- QD or BID?
- 0.25% or 0.5%?
- Gel or drop?
- Monocular therapy?
- How bad are the side effects really?
- Do systemic beta-blockers affect the efficacy of the drops?

- Tell me something good about beta-blockers!

Adrenergic Agonists

- Dual mechanism of action
  1. Reduce aqueous production
  2. Enhance outflow mechanisms
- 22-28% IOP reduction
- Short duration of action
- TID dosage
- Avoid in kids

CAI make wonderful partners

- Feldman, et al 2006 –
- 1.5-1.8 mm lower IOP as compared to brimonidine 0.15% when added to travaprost
- This significance was present at all time points
- BID dosing

Companion study #2

- When compared to brimonidine 2% adding them to Travaprost...
- IOP lowered by 13% w/ brimonidine
- IOP lowered by 23% w/ brinzolamide

Companion study #3

- Stewart et al, 2006
- Compared to timolol 0.5% as additive to travaprost
- No difference at all between the 2 drugs
- CAI is effective at controlling night IOP spikes (TID?)

So A Patient Has Mild POAG, Tmax 26…

What is your first choice of therapy?

So, a patient on latanoprost needs 4 more mm of IOP reduction- do you…

- Add Rhopressa?
- Switch to Rocklatan??
- Add a combo drop??
- Switch to a combo drop??
- Add a different single agent?
- SLT??

So A Patient has moderate glaucoma, Highest IOP - 21

- What Is Your first Step???
- What is Your Second Step??
- Then What??

How do you decide?

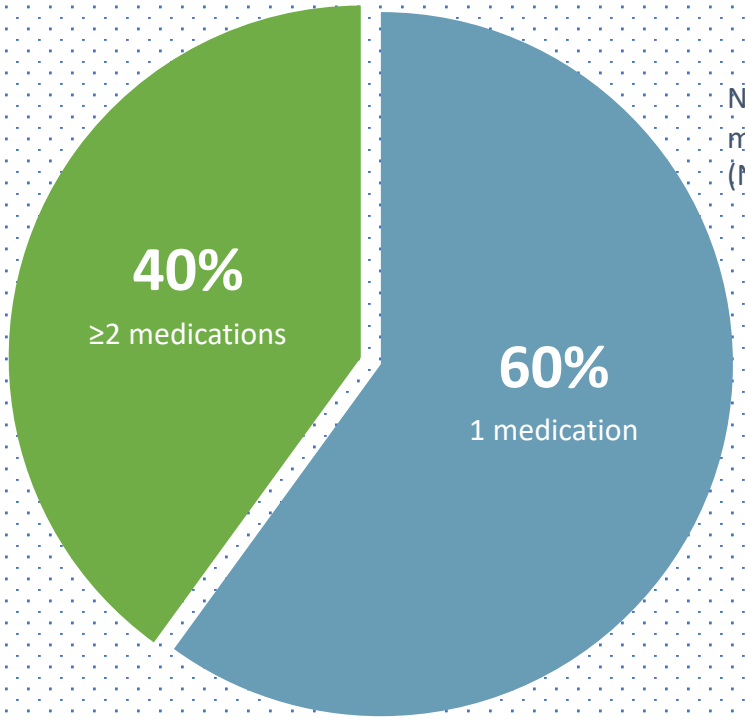
- What are you trying to achieve?
- Risk/ benefit profile
- How many risk factors does patient have?
- How fast is the patient progressing?
- Be aware of the compliance problem
- How Low Do You Need To Go?

- *HOW DO I KNOW WHAT TO DO?????*

Individualizing the target IOP

Target IOP should be individualized and updated early and aggressively as needed

- Periodically reassess the IOP target by comparing optic nerve status (optic disc appearance, quantitative assessments of disc and nerve fiber layer) and VF with previous examinations[1]
- Consider switching or adding medications if target is not yet achieved with initial therapy[1]
- Many patients require 2 or more medications to achieve target IOP[2]



Number of IOP-lowering medications used (NDTI Audit)[2]

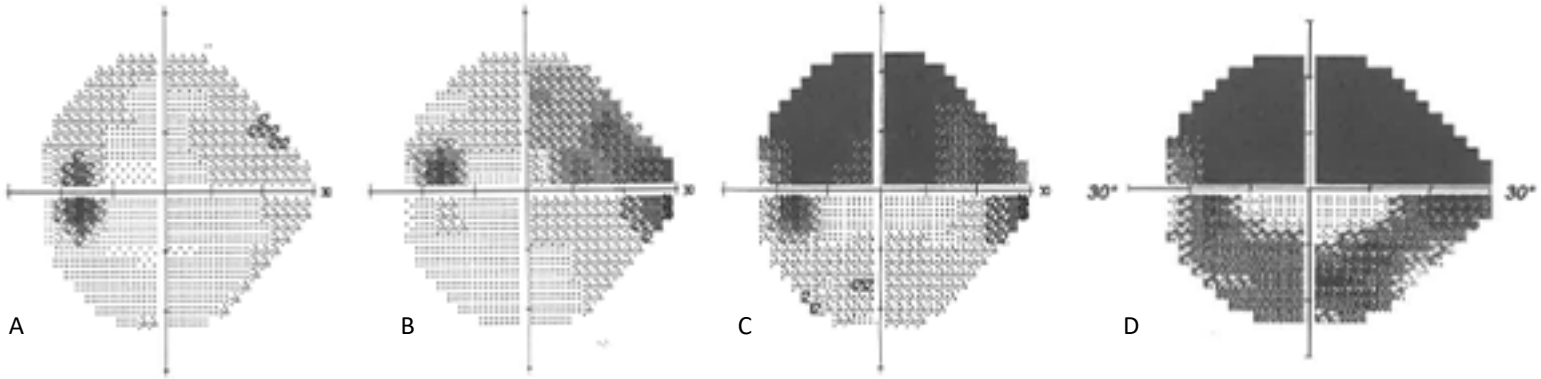
IOP=intraocular pressure; NDTI=National Disease and Therapeutic Index™; VF=visual field.

1. Prum BE Jr et al. *Ophthalmology*. 2016;123(1):P41-P111. 2. Glaucoma & ATU Message Recall Study Report. Strategic Research Insights, 2018.

What Is Maximum Medical Therapy In The Year 2021?

Why adherence is so important!

In a 2011 study that examined VF progression and adherence rates in patients with glaucoma using an electronic dosing aid device:



Patients with **stable VFs** had a median **adherence rate of 85%**

Patients who **progressed** had a median **adherence rate of 21%**

VF=visual field.

Rossi CM et al. *Eur J Ophthalmol*. 2011;21(4):410-414.