New Options Shaking Up The Glaucoma Treatment Paradigm

The Grand Canyon Regional Ophthalmology Meeting

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Disclosures

- New World Medical, C
- Aerie Pharmaceuticals, S

Glaucoma Treatment

- IOP-lowering is the only proven method to prevent development and/or progression of glaucoma
- Neurovascular protection, gene therapy on the horizon

What's the Evidence?

- EMGT[1]
  - 1 mm Hg IOP-lowering → 10% reduced risk of visual field progression

- Significant increase in glaucoma risk with every 3 mm Hg increase in IOP[2]

[1]Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression. Results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268-1279.

[2]Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open-angle among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol. 1991;109:1090-1095.

Setting a Treatment Target

- Range of IOPs at which further glaucomatous damage unlikely
- Based on stage of disease as well as IOP level at which damage has occurred
- Remains an *estimate* for low risk of disease progression

Target Based on Disease Stage

Glaucoma Stage	Initial Target Reduction	Relevant Clinical Trial
Ocular Hypertension	20%	OHTS
Early/Mild Glaucoma	>30%	EMGT, CIGTS
Moderate/Severe Glaucoma	40-50%	AGIS
Normal Tension Glaucoma	30%	CNTGS

Choosing an Initial Agent

- Considerations:
  - Efficacy
  - Side Effects
  - Cost
  - Dosing Schedule
  - Preservative Load

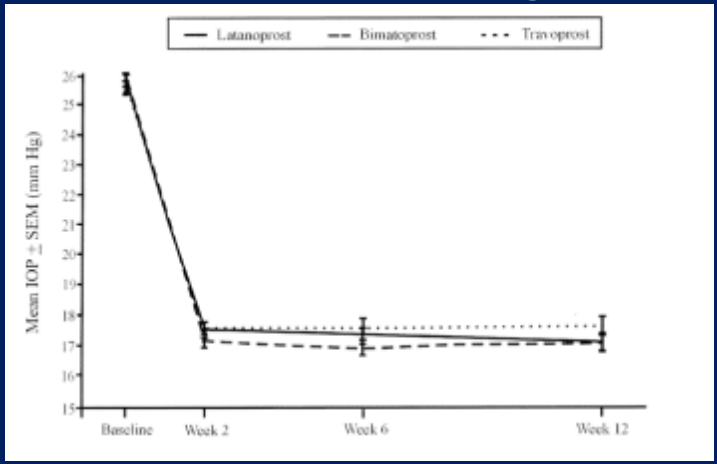
First-Line Therapy

- Prostaglandin Analogues
  - Good efficacy (25-30%) with single agent
  - Minimal risk of systemic side effects
  - Once daily dosing regimen

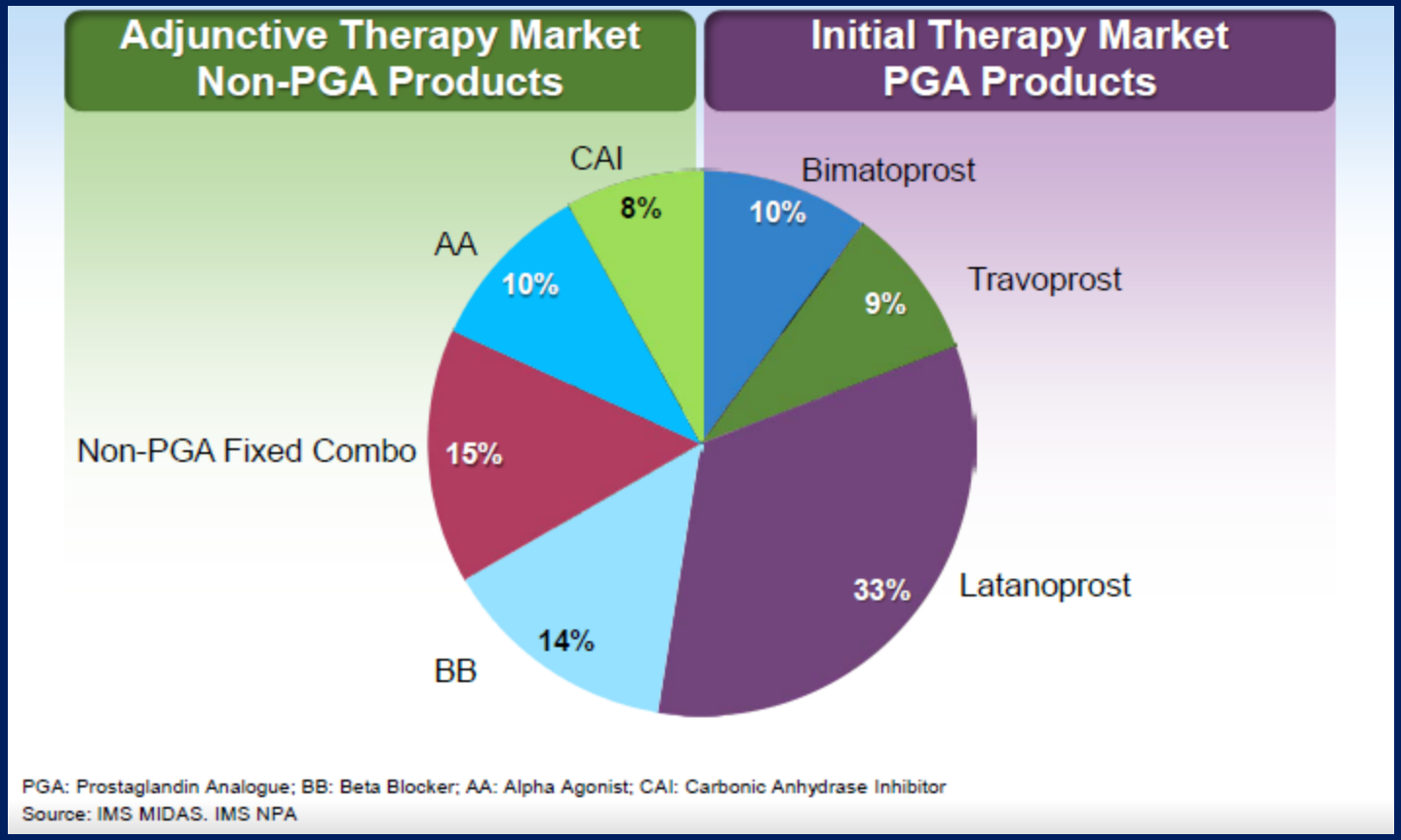
A Comparison of Latanoprost, Bimatoprost, and Travoprost in Patients With Elevated Intraocular Pressure: A 12-week, Randomized, Masked-evaluator Multicenter Study

RICHARD K. PARRISH, MD, PAUL PALMBERG, MD, PHD, AND WANG-PUI SHEU, MA, FOR THE XLT STUDY GROUP

- 410 randomized patients
- Primary outcome = mean IOP change at week 12
- Similar IOP reduction in all 3 groups (P<0.001)



What Next?

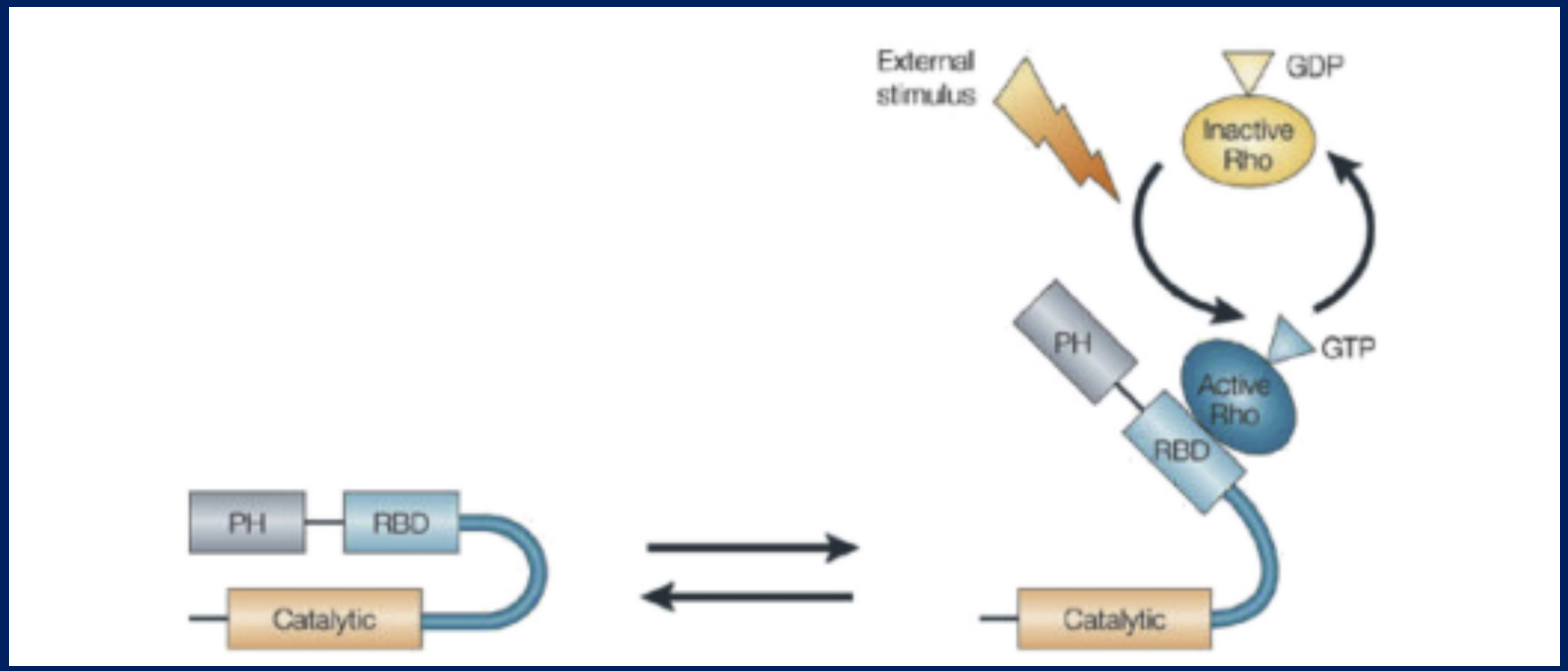

Adjunctive Therapy Market
Non-PGA Products
Initial Therapy Market
PGA Products
CAI
8%
AA
10%
Non-PGA Fixed Combo
15%
BB
14%
Bimatoprost
10%
Travoprost
9%
Latanoprost
33%
PGA: Prostaglandin Analogue; BB: Beta Blocker; AA: Alpha Agonist; CAI: Carbonic Anhydrase Inhibitor
Source: IMS MIDAS. IMS NPA

New Options!

- Netarsudil 0.02%
- Netarsudil 0.02%/Latanoprost 0.005%
- Latanoprostene Bunod 0.024%

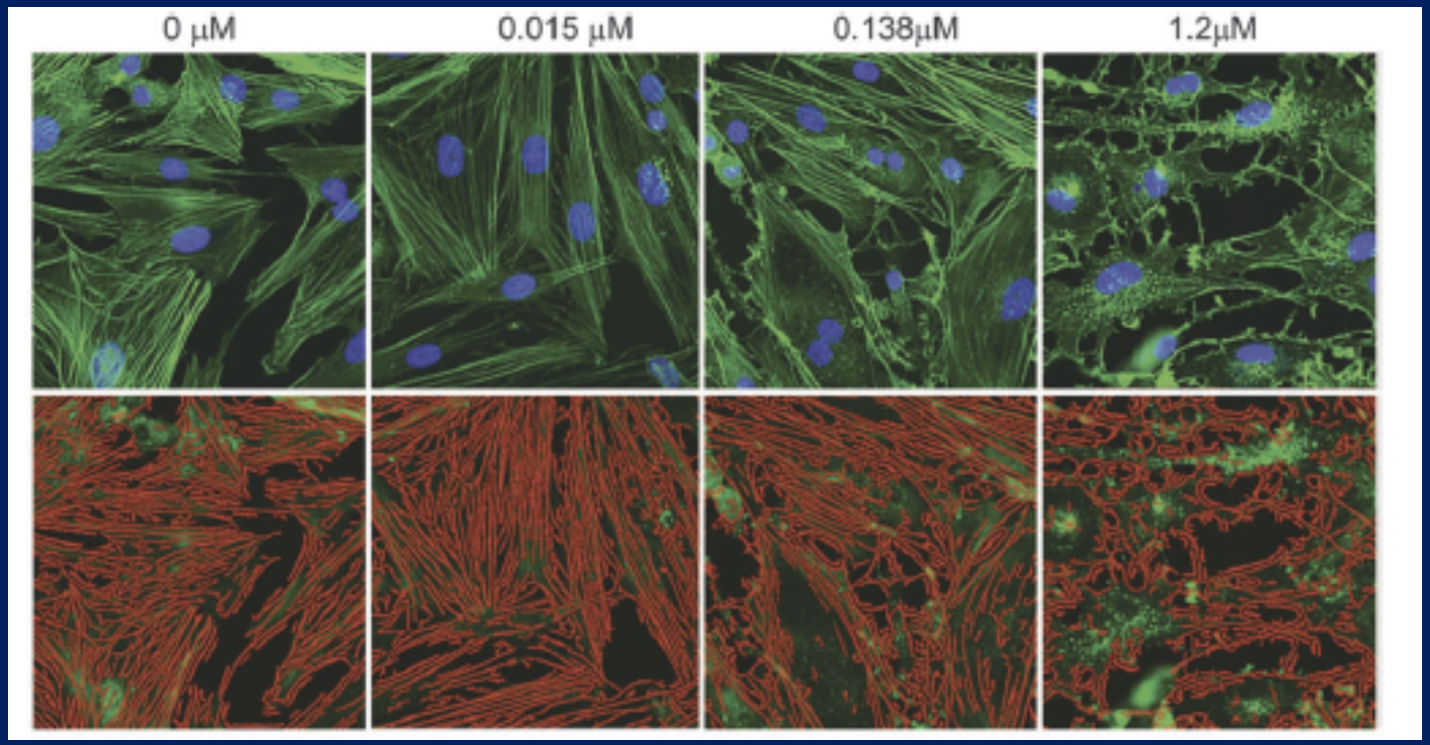
Netarsudil 0.02%

Rho-Kinase



Nat Rev Drug Discovery 2005;4:387-398.

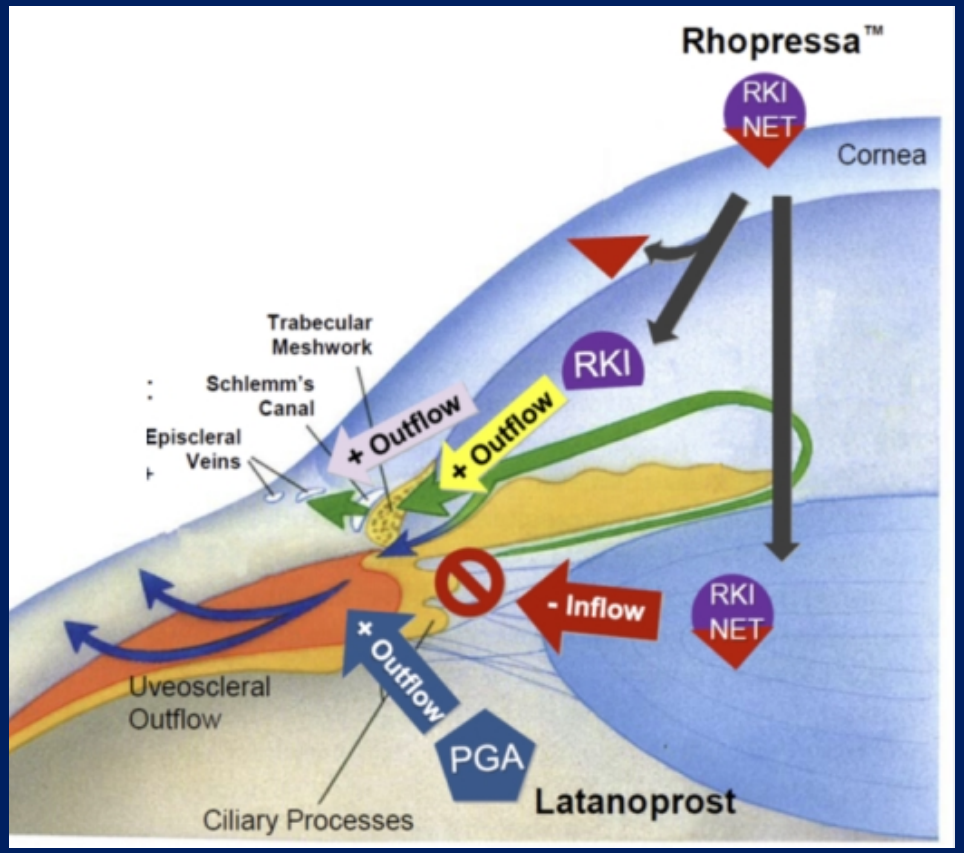
Disruption of Actin Stress Fibers



J Ocul Pharmacol Ther. 2018;34:40-51.

Triple-Mechanism

1) Decrease outflow resistance
2) Decrease aqueous production
3) Decrease episcleral venous pressure

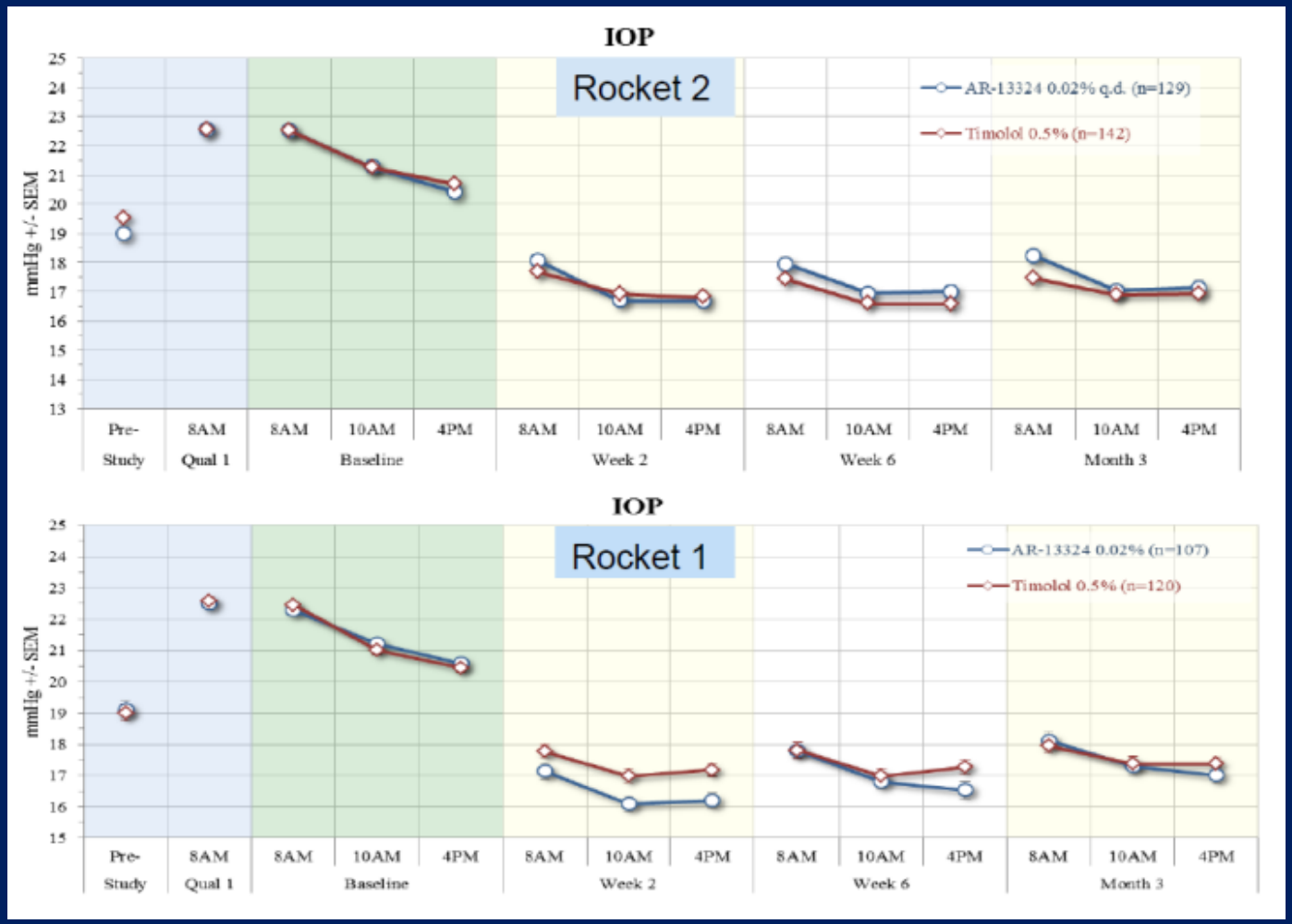


Clinical Efficacy

- ROCKET-1 & ROCKET-2 Studies
  - Double-masked, randomized, multicenter, phase 3 trials
  - Netarsudil 0.02% qdaily vs. timolol 0.5% bid in patients with IOP > 20 mm Hg and < 25 mm Hg (post-hoc endpoint for ROCKET-1)
  - Primary efficacy at 8AM, 10AM, 4PM time points at week 2, week 6, month 3

Serle JB, et al. Am J Ophthalmol. 2018;186:116-127

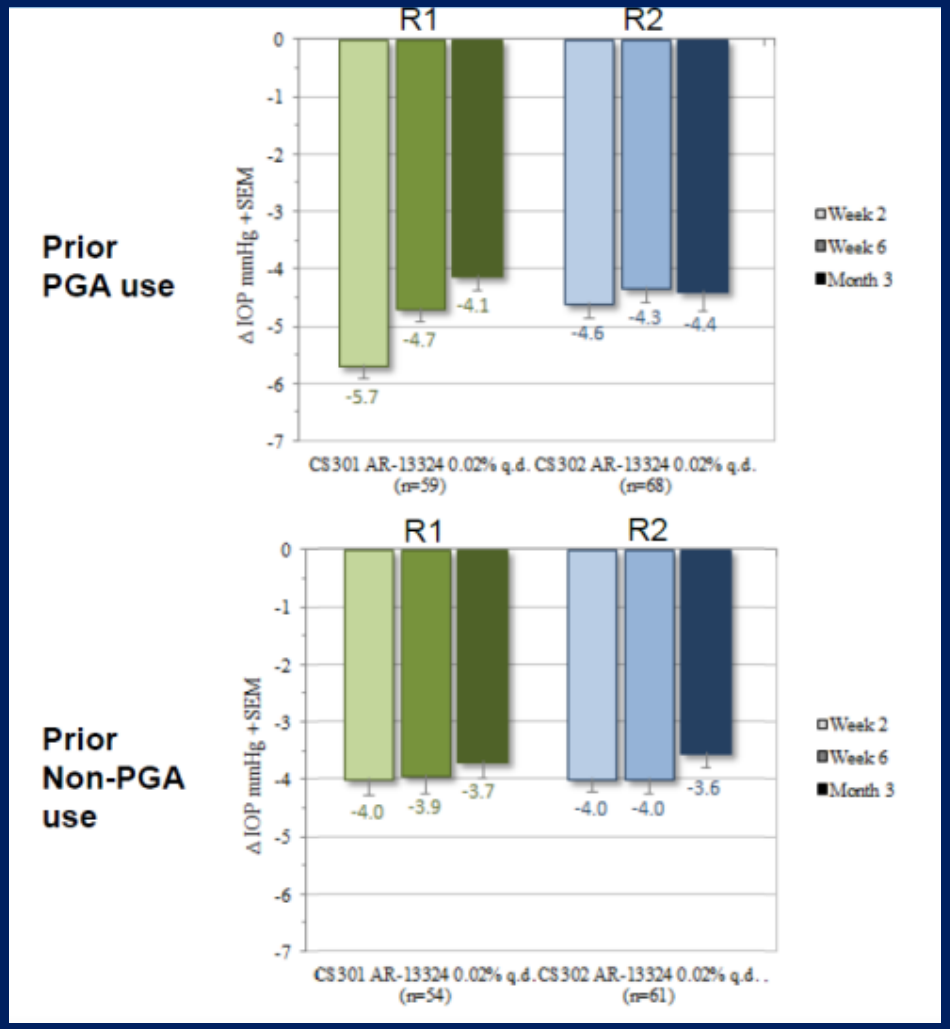
Netarsudil Efficacy Summary



Netarsudil Efficacy Summary

- ROCKET-1
  - Netarsudil: 20.6-22.4mmHg → 16.2-18.2mmHg (15-22% reduction)
  - Timolol: 20.5-22.5mmHg → 17.0-17.9mmHg (17-22% reduction)
- ROCKET-2
  - Netarsudil: 20.4-22.5mmHg → 16.7-18.2mmHg (16-21% reduction)
  - Timolol: 20.7-22.5mmHg → 15.7-17.6mmHg (18-23% reduction)

Prior PGA Use → Greater Response



Adverse Effects

- Conjunctival hyperemia (50-53%)
- Conjunctival hemorrhage (13.3-15%)
- Cornea verticillata (5.4-9%)

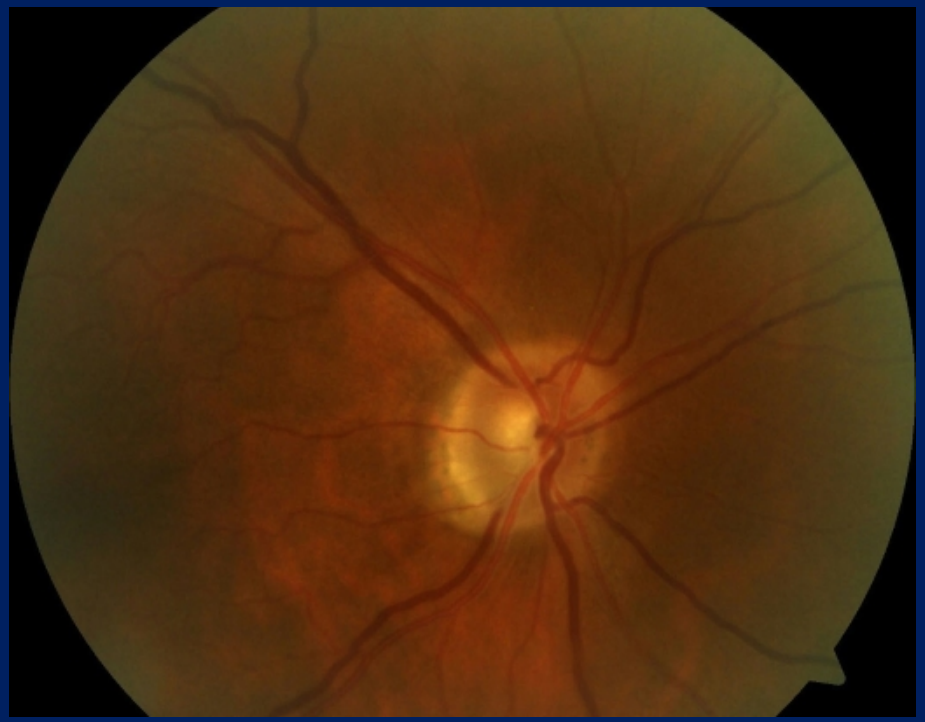
Case

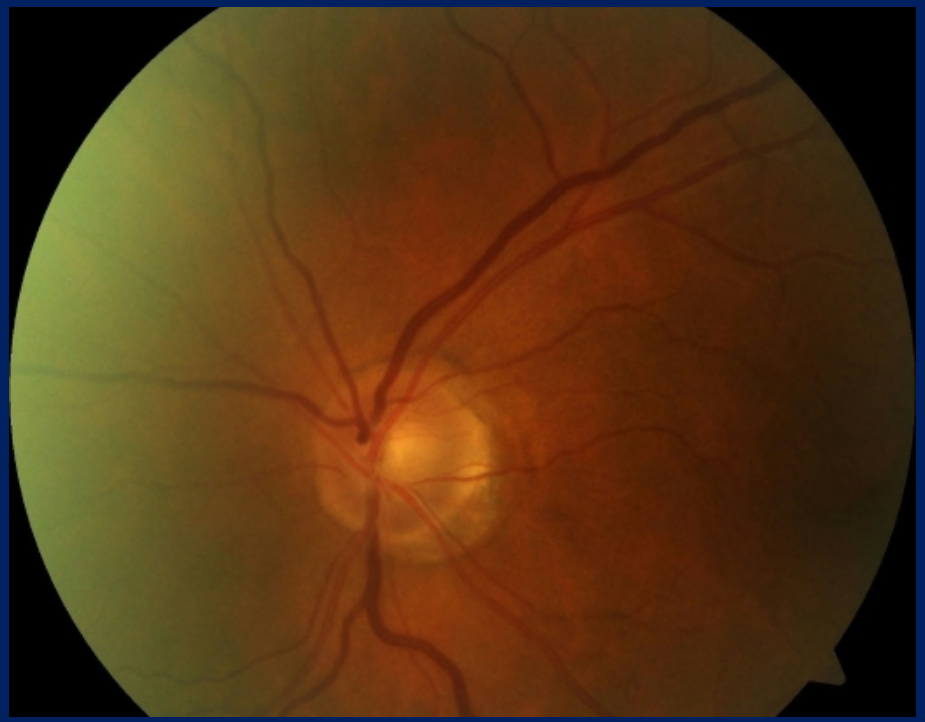
- 67 yo WF self-referred to transition glaucoma care
- Hx POAG OU tx'd with PGA and dorzolamide
- Timolol intolerance (hair loss)
- Tmax = mid-20s OU
- Mild Glare OU at night

Case

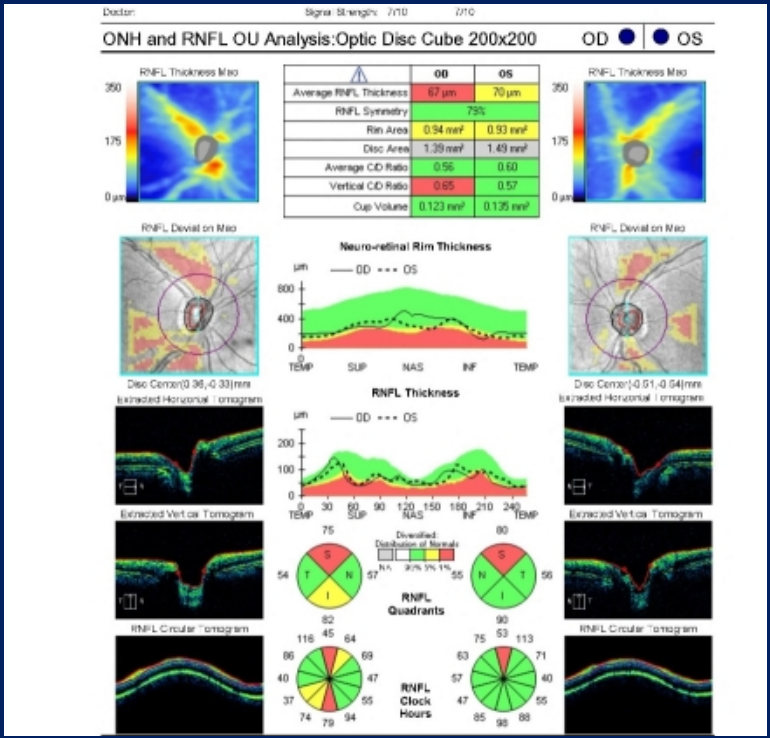
- VA
  - OD: 20/20: -0.74+0.25x075
  - OS: 20/25: plano
- IOPs
  - OD: 19 mm Hg
  - OS 17 mm Hg
- CCTs
  - 543 um OD, 559 um OS
- SLE: 1-2+ NS cats OU
- Gonio: Schaeffer II-III x 360

Optic Discs

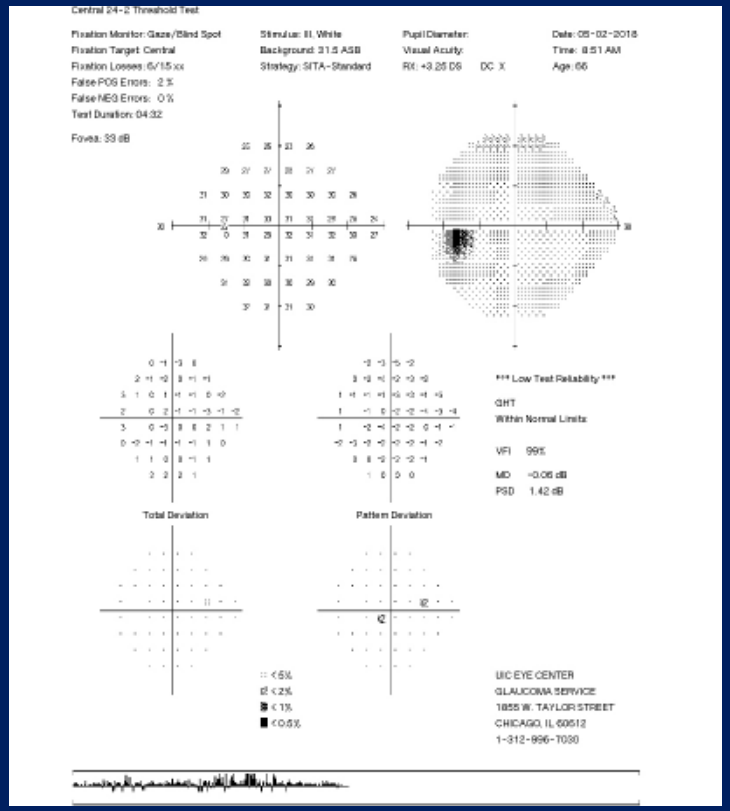


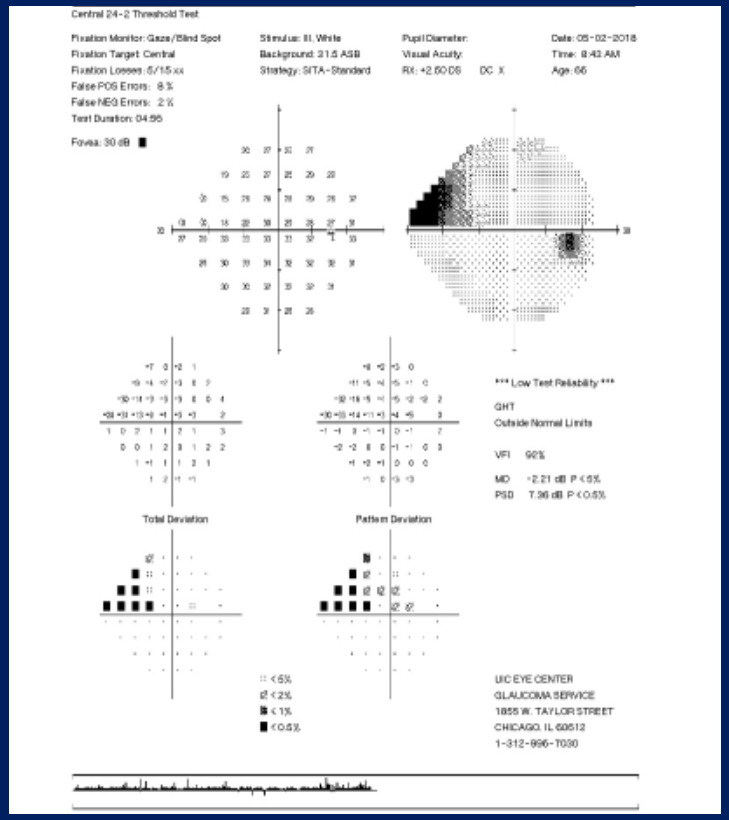


OCT RNFL


ONH and RNFL OU Analysis:Optic Disc Cube 200x200
OD
OS
OD
OS
Average RNFL Thickness
67 µm
70 µm
RNFL Symmetry
73%
Rim Area
0.94 mm²
0.93 mm²
Disc Area
1.39 mm²
1.49 mm²
Average C/D Ratio
0.56
0.60
Vertical C/D Ratio
0.65
0.57
Cup Volume
0.123 mm³
0.135 mm³
Neuro-retinal Rim Thickness
RNFL Thickness
RNFL Quadrants
RNFL Clock Hours

Visual Fields

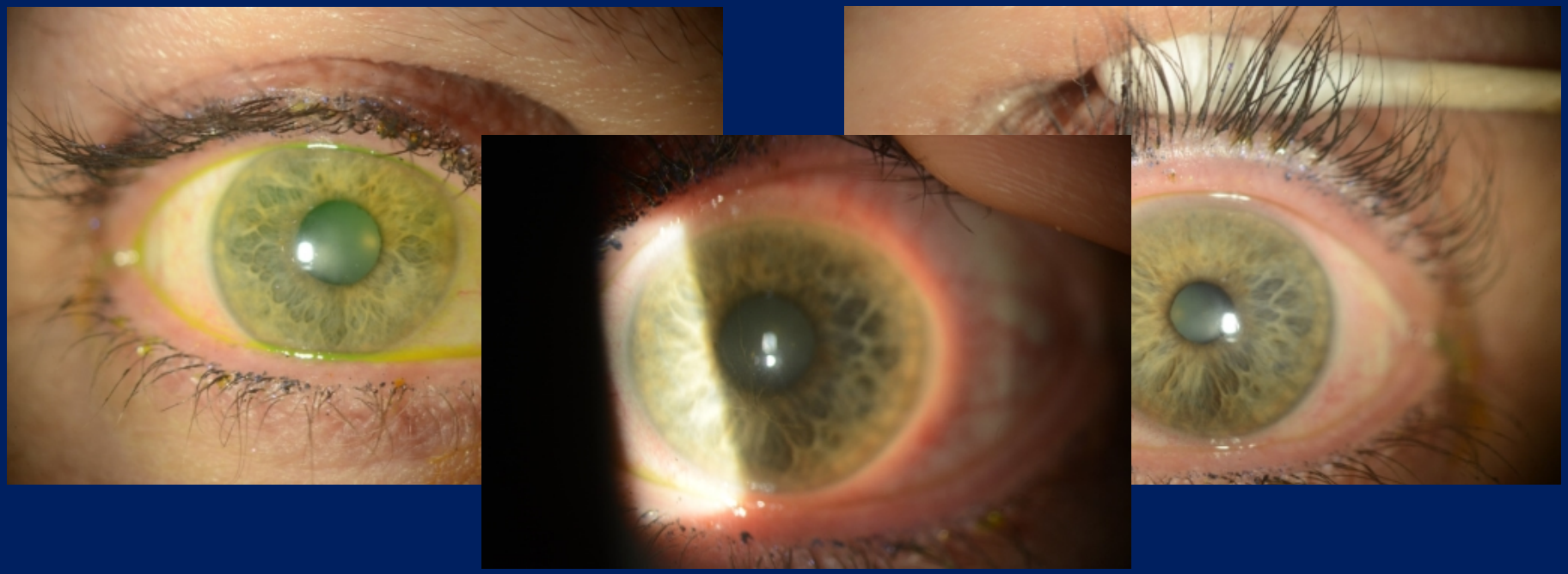




Case

- Assessment
  - POAG – moderate stage OD, mild stage OS
  - 24% reduction from baseline OD, 32% reduction from baseline OS
- PLAN
  - Suggest phaco/MIGS → patient defers
  - Start Netarsudil OU QHS with goal additional 10-15% lowering

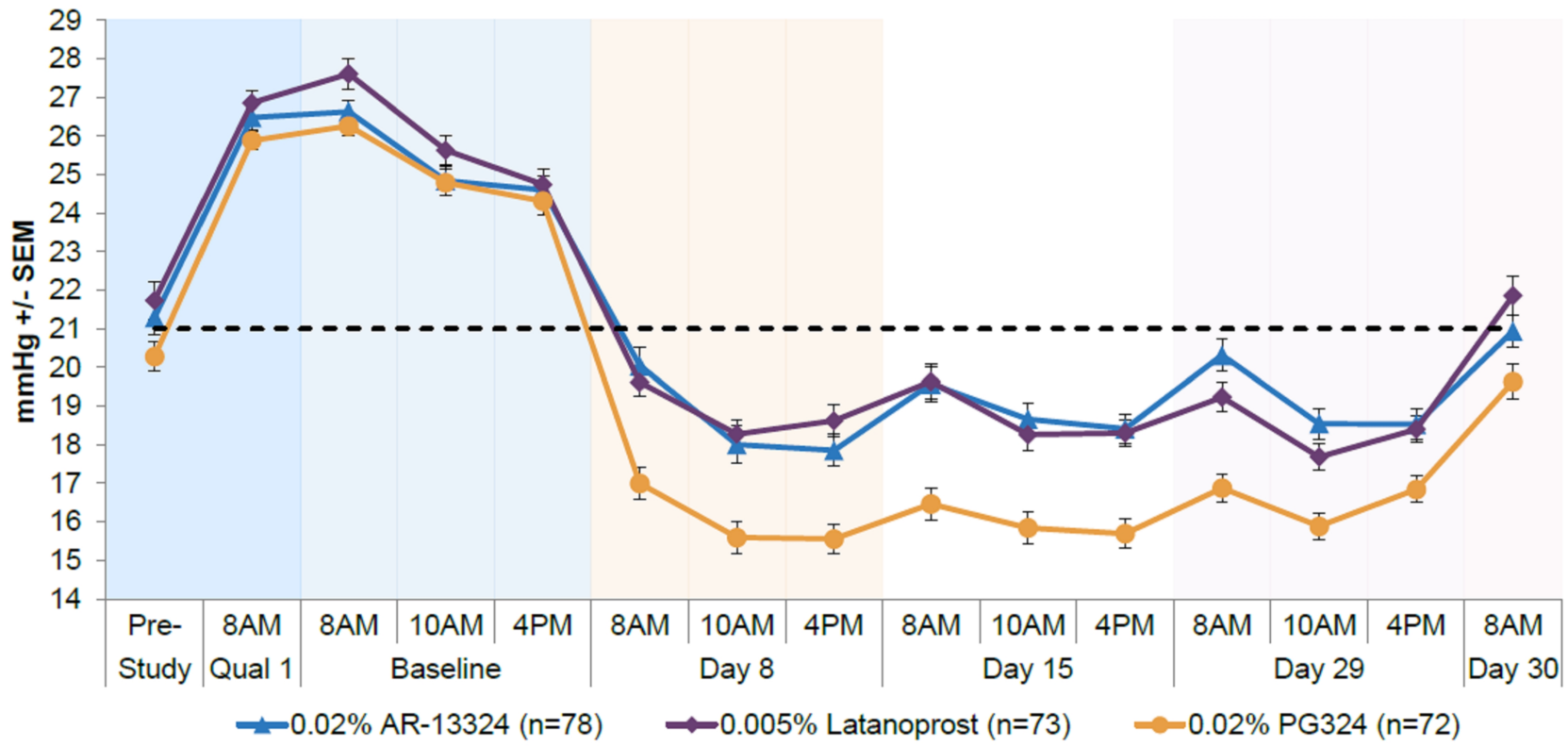
Case – Follow-up

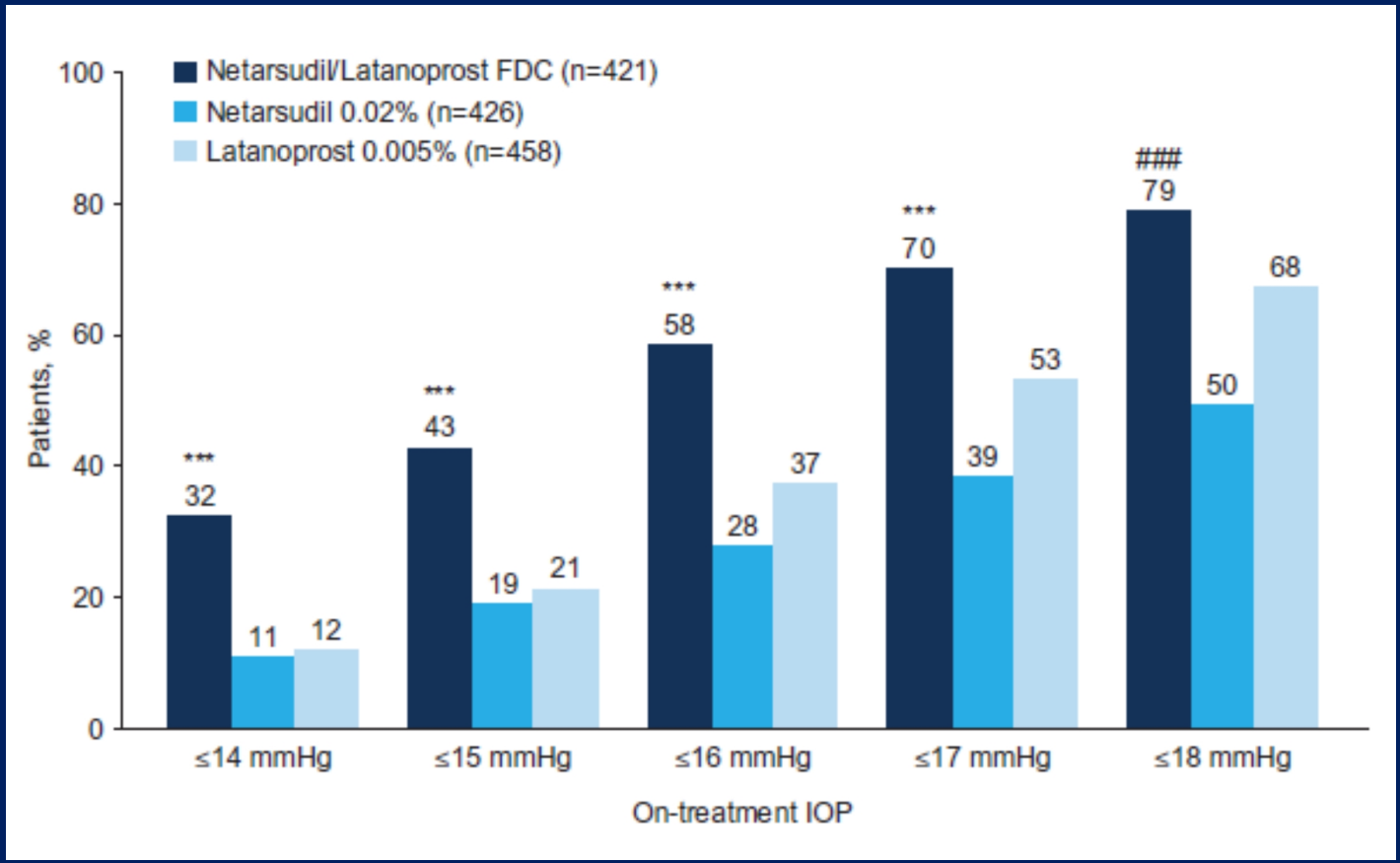


- Follow-up IOPs
  - OD: 14, 12 mm Hg (48% reduction)
  - OS: 14, 14 mm Hg (44% reduction)

Netarsudil/Latanoprost

Efficacy


mmHg +/- SEM
29
28
27
26
25
24
23
22
21
20
19
18
17
16
15
14
Pre-Study
8AM Qual 1
8AM
10AM
4PM
Baseline
8AM
10AM
4PM
Day 8
8AM
10AM
4PM
Day 15
8AM
10AM
4PM
Day 29
8AM Day 30
0.02% AR-13324 (n=78)
0.005% Latanoprost (n=73)
0.02% PG324 (n=72)


Netarsudil/Latanoprost FDC (n=421)
Netarsudil 0.02% (n=426)
Latanoprost 0.005% (n=458)
Patients, %
100
80
60
40
20
0
***
32
11
12
***
43
19
21
***
58
28
37
***
70
39
53
###
79
50
68
≤14 mmHg
≤15 mmHg
≤16 mmHg
≤17 mmHg
≤18 mmHg
On-treatment IOP

Adverse Effects

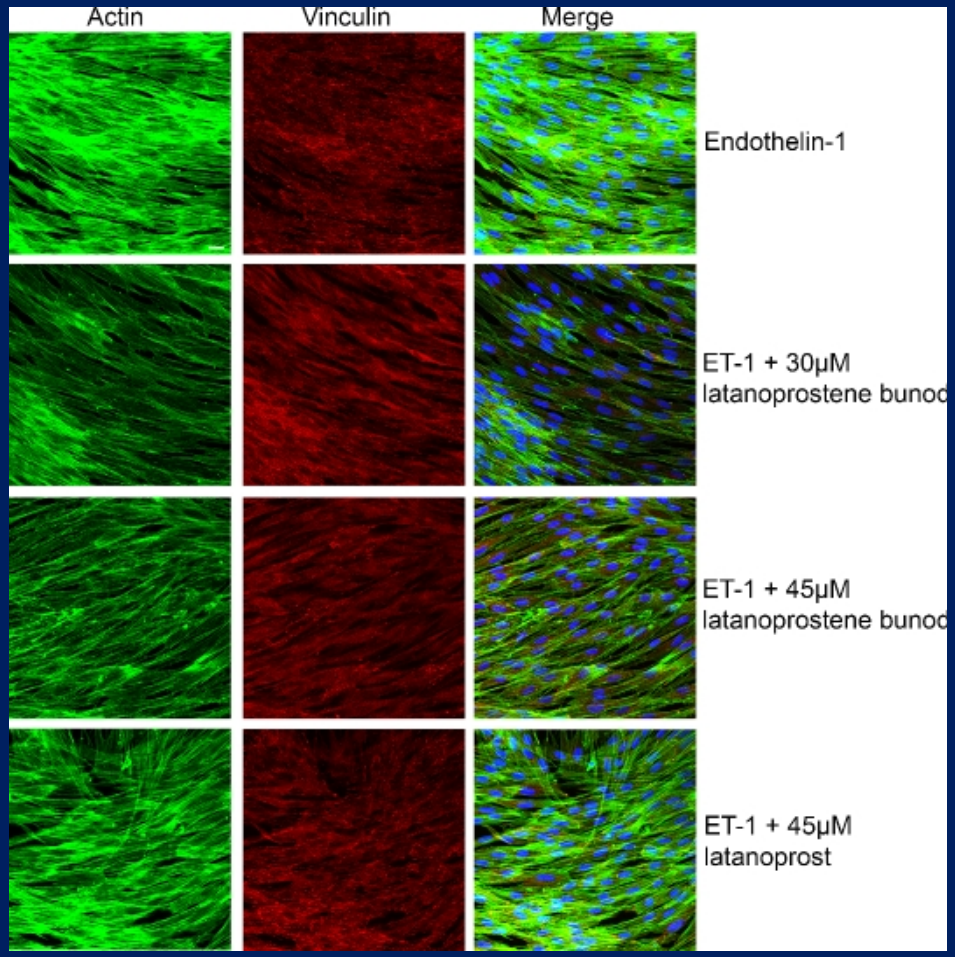
- Conjunctival hyperemia (587%)
- Cornea verticillata (15.4%)
- Conjunctival hemorrhage (10.8%)

Latanoprostene Bunod

Mechanism of Action

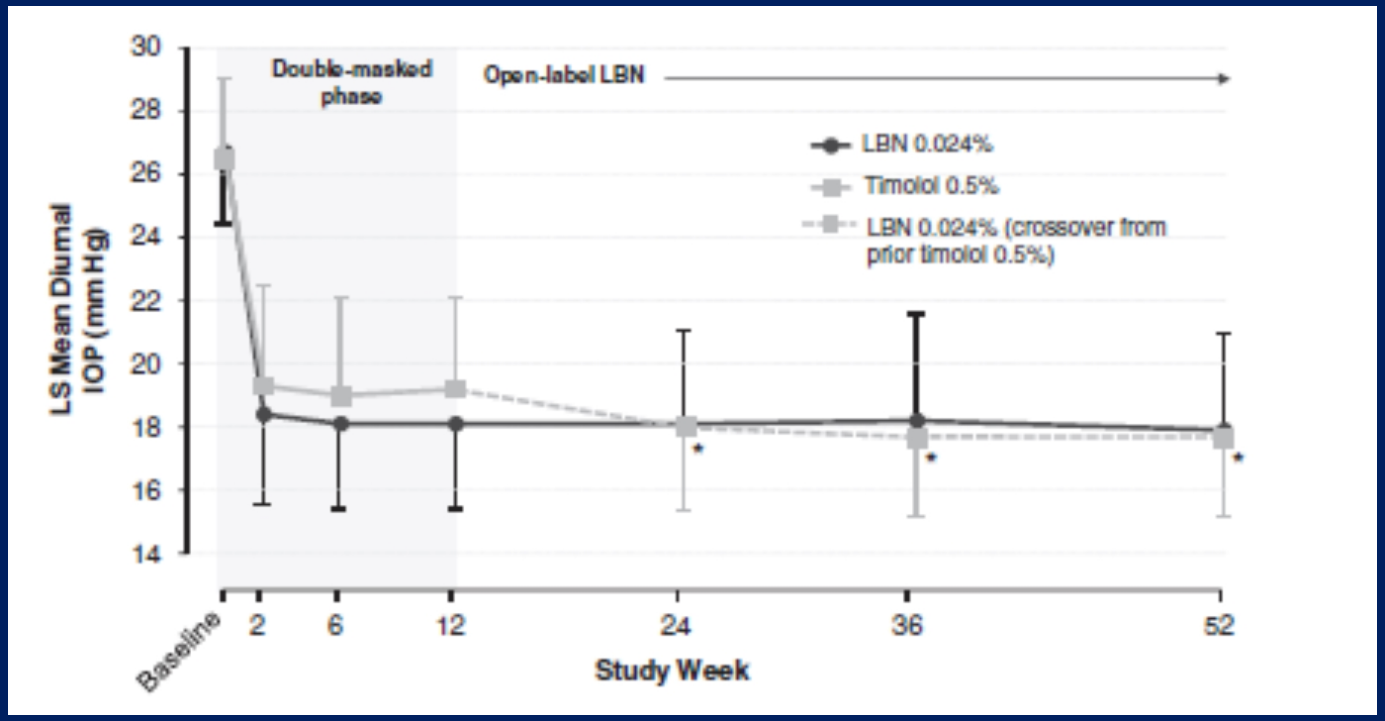
- Prodrug metabolized by corneal esterase into
  1) latanoprost acid
  2) butaendiol mononitrate → Nitric Oxide
- Nitric Oxide relaxes trabecular meshwork cells to decrease outflow resistance
- Enhanced uveoscleral outflow via latanoprost

In Vitro Effects



Cavet, ME, et al. Invest Ophthalmol Vis Sci 2015;56:4108-4116.

Pooled Results vs. Timolol



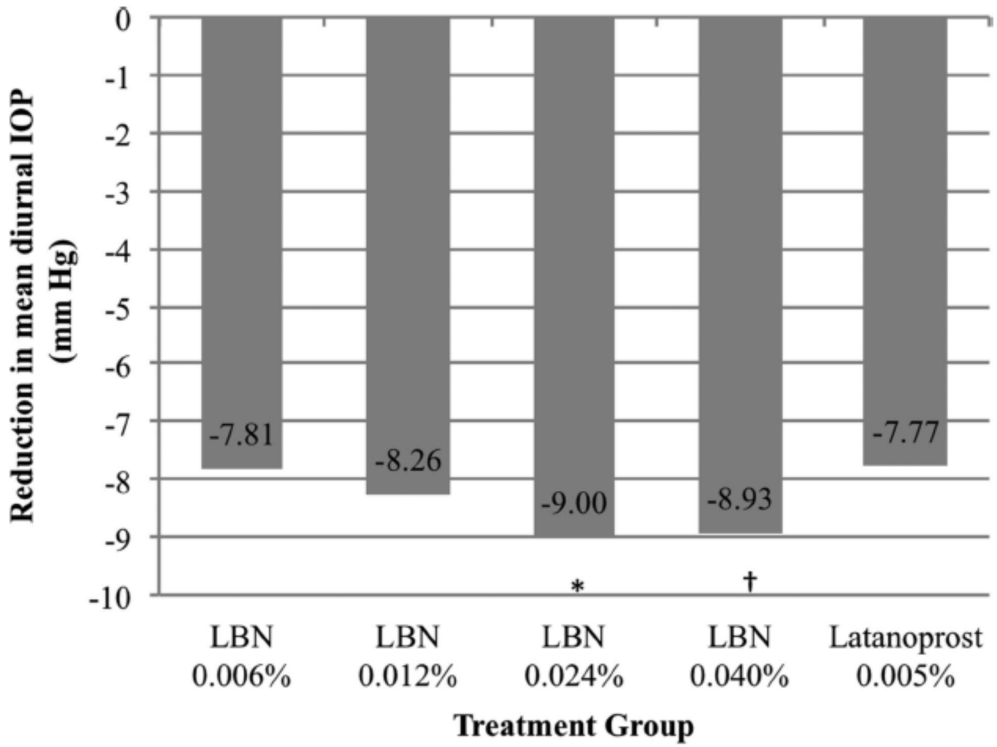
Latanoprostene: 26.7mmHg → 17.8mmHg at 3 mos

Timolol: 26.5mmHg → 19.1mmHg at 3 mos

P<0.001

Weinreb RN, et al. J Glaucoma. 2018;27:7-15.

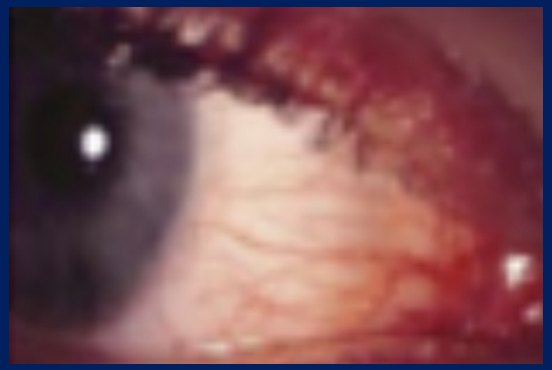
Latanoprostene vs. Latanoprost



*P=0.005 vs. latanoprost
†P=0.009 vs. latanoprost

Adverse Effects

- Conjunctival hyperemia
  - Increase from 32.6% at baseline to 45.5% at 3 mos
  - No significant increase in timolol comparator group



AGS 2019 – Real World Data

- Retrospective data from 5 tertiary care centers
- Netarsudil or Latanoprostene added as adjunctive therapy to 1-4 meds in 140 patients
- Unpaired t-test and ANOVA statistical analysis to compare outcomes

AGS 2019 – Real World Data

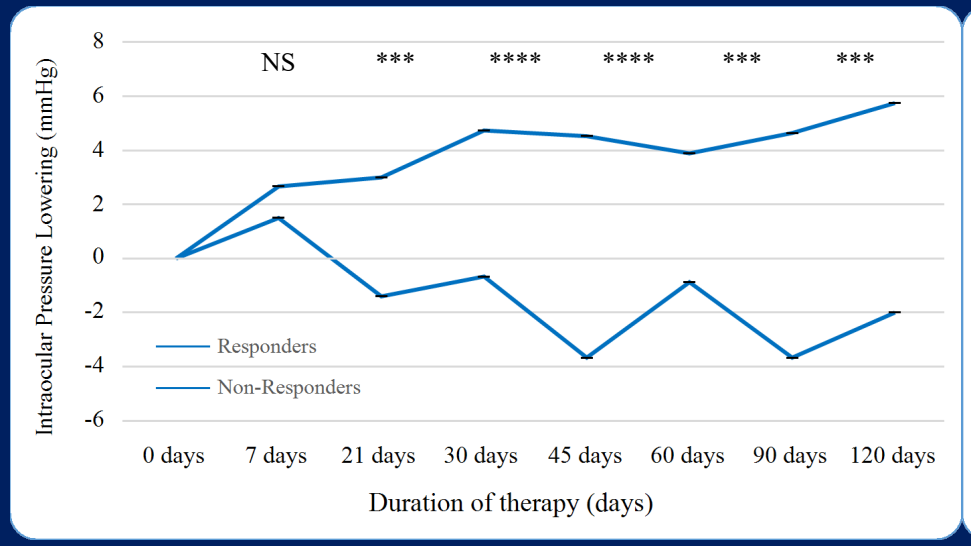
	Netarsudil	Latanoprostene
Number of eyes (patients)	134 (98)	62 (42)
Age in year (mean ± STDEV)	63 ± 9 years	67 ±12 years

	Netarsudil	Latanoprostene
Change in IOP	3.53 (p <0.0001)	3.27 (p<0.001)
% Reduction in IOP	15.69	15.06

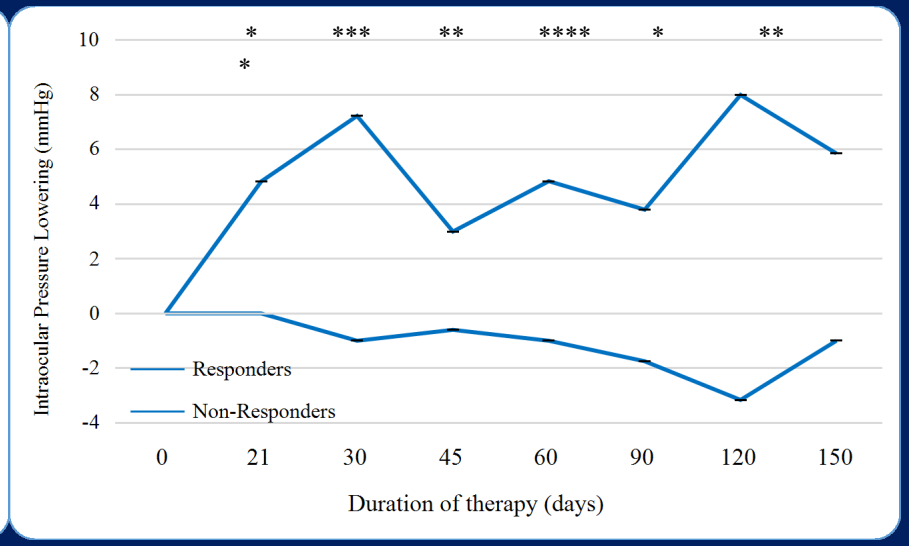
	5% Other	5% Other
Change in IOP	3.53 (p <0.0001)	3.27 (p<0.001)
% Reduction in IOP	15.69	15.06
Change log MAR BCVA	0.04 (p <0.59)	0.014 (p<0.92)
# Patients stopped	Dec-98	Jul-42
Follow up duration in days (range)	54.3 (7-120)	82.9 (7-210)

AGS 2019 – Real World Data

Netarsudil



Latanoprostene Bunod



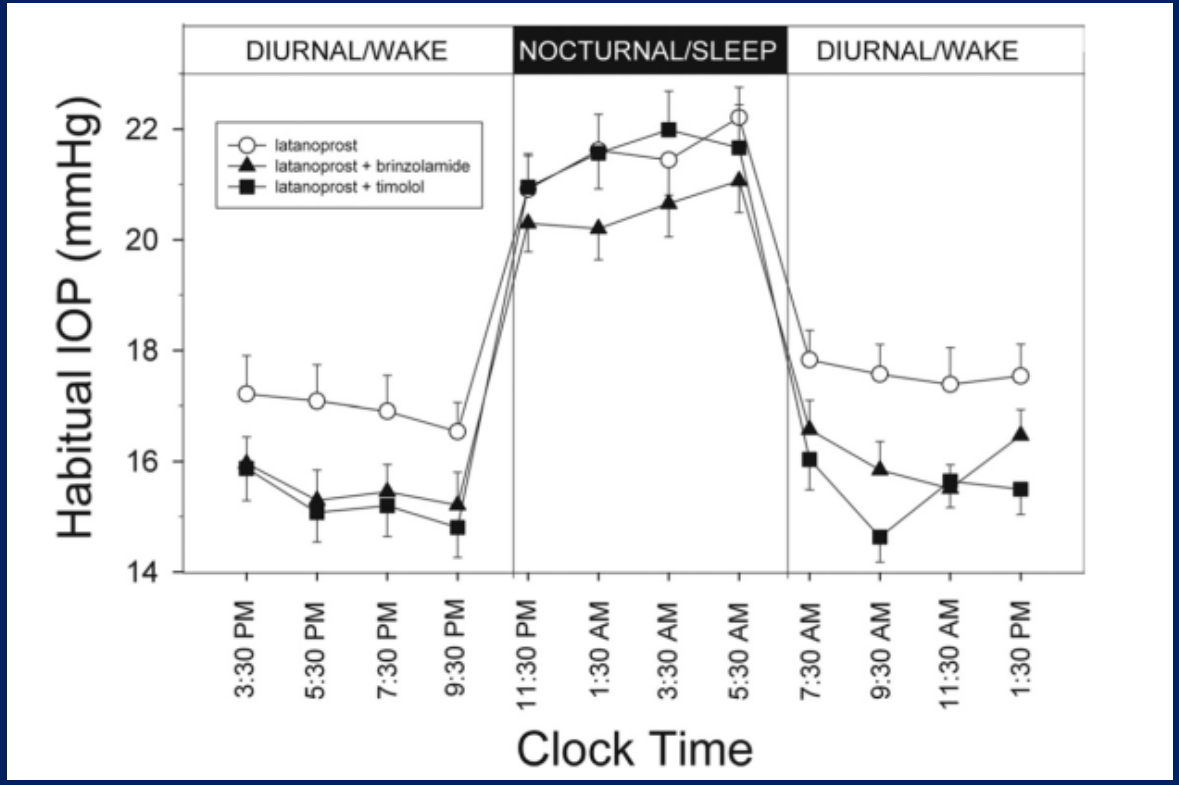
24-hour IOP Lowering

- Peak IOP at night in most individuals

- Agents shown to lower IOP at night:
  - Latanoprost
  - Brinzolamide
  - Fixed combination brinzolamide/brimonidine
  - Netarsudil (pilot study, n=12)

Comparing Diurnal and Nocturnal Effects of Brinzolamide and Timolol on Intraocular Pressure in Patients Receiving Latanoprost Monotherapy

John H. K. Liu, PhD, Felipe A. Medeiros, MD, PhD, J. Rigby Slight, MD, Robert N. Weinreb, MD

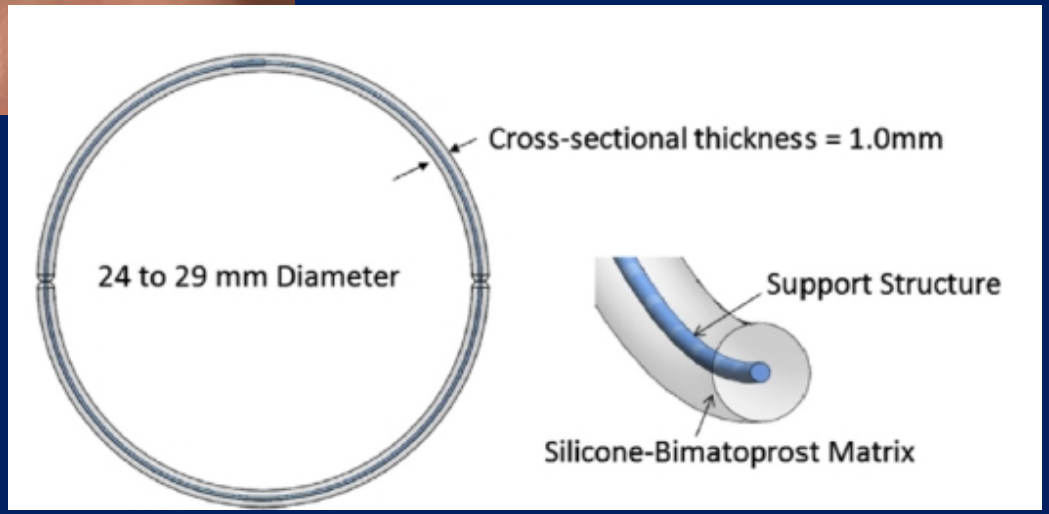


Don’t Forget the Ocular Surface

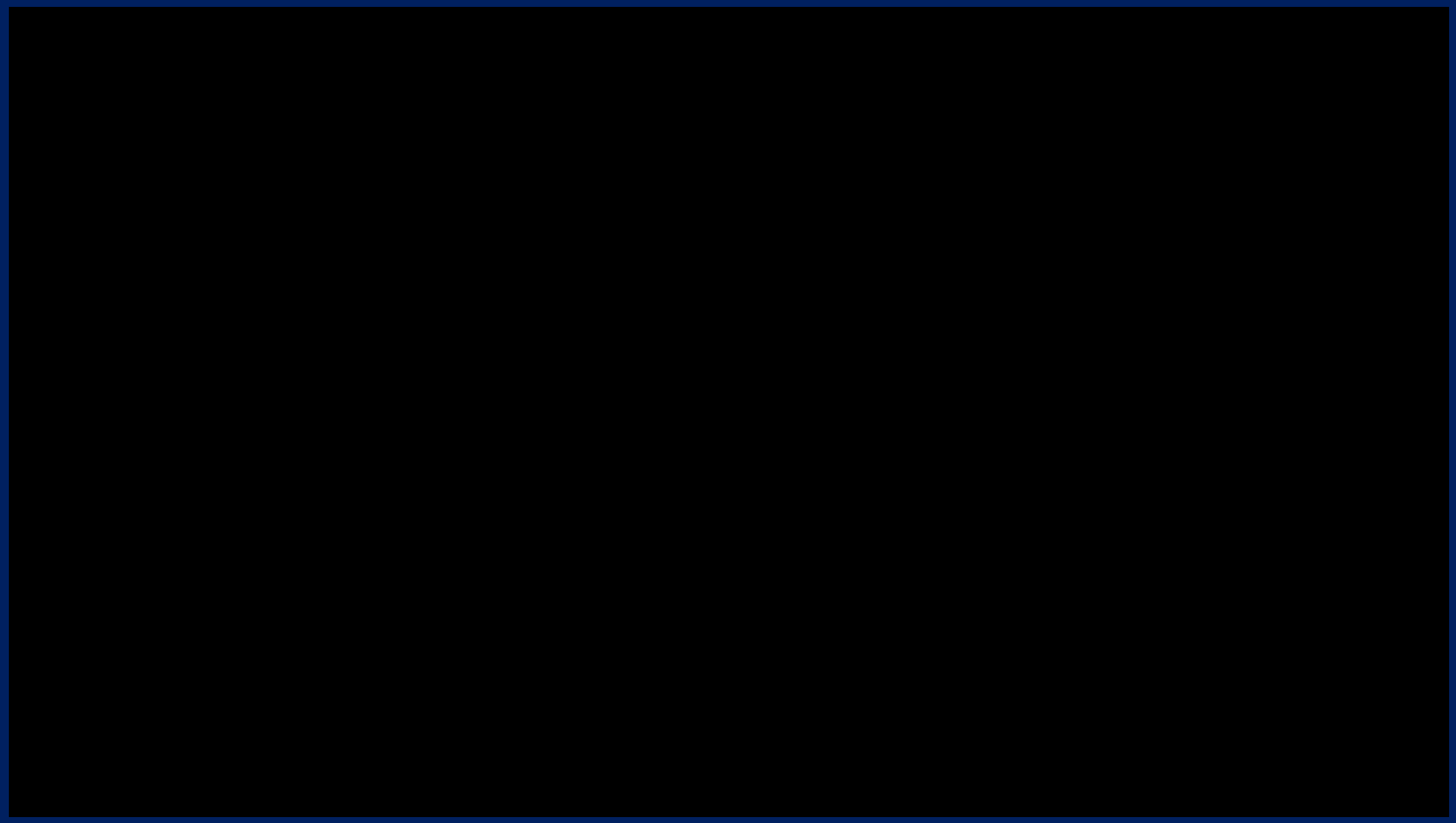
- Preservative-free therapies
- Combination agents
- Oral agents
- Non-medical therapy

Sustained Drug Delivery

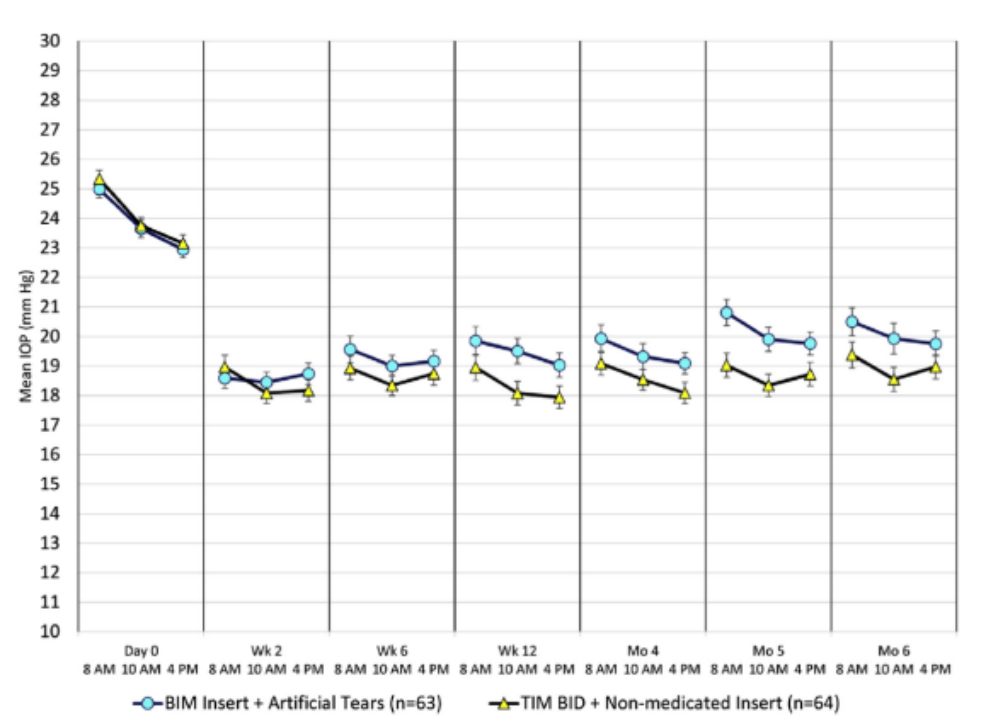
Bimatoprost Ring



Bimatoprost Ring



Bimatoprost Ring Efficacy



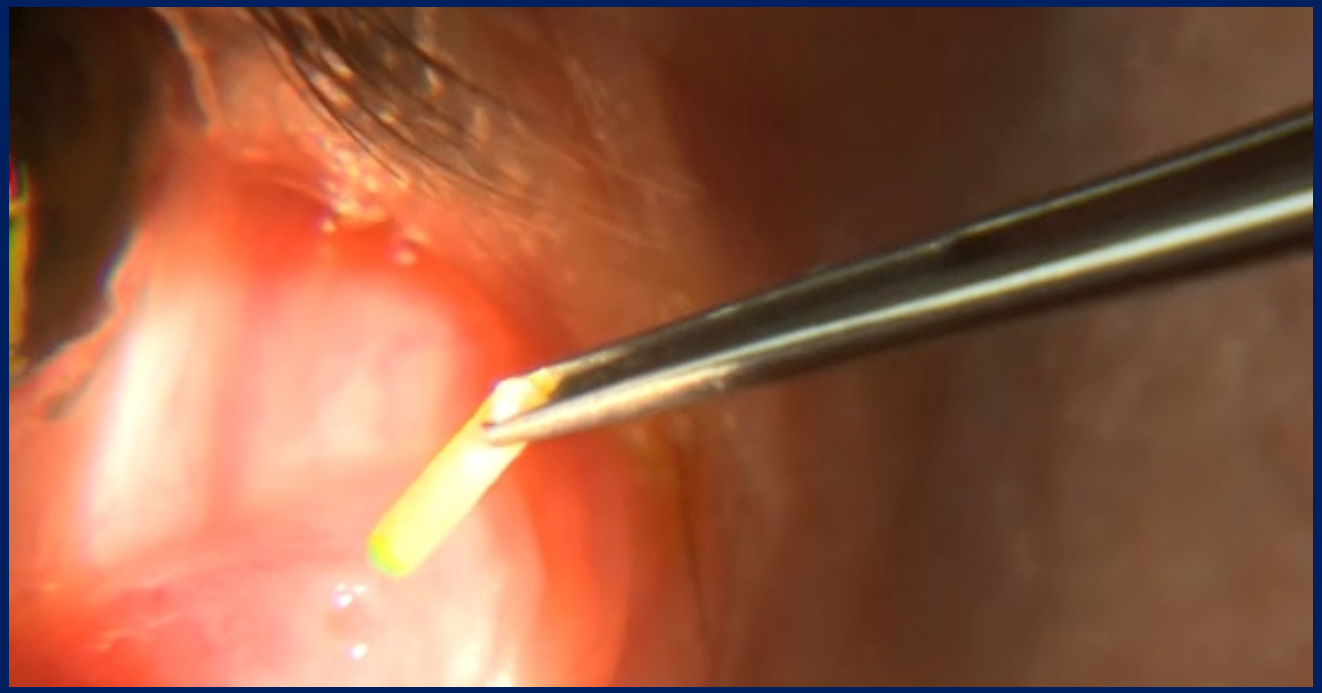
- Mean IOP Lowering
  - ➢Bimatoprost Ring: 3.2 to 6.4mmHg (≥ 20% reduction)
  - ➢Timolol BID: 4.2 to 6.4mmHg

Brandt JD, et al. Ophthalmology 2016;123:1685-1694.

Bimatoprost Ring Adverse Effects

- Mucus Discharge (21.3% at 12 mos)
- Device Dislodgment (20.8% men, 5.2% women)
- Otherwise similar to PGAs

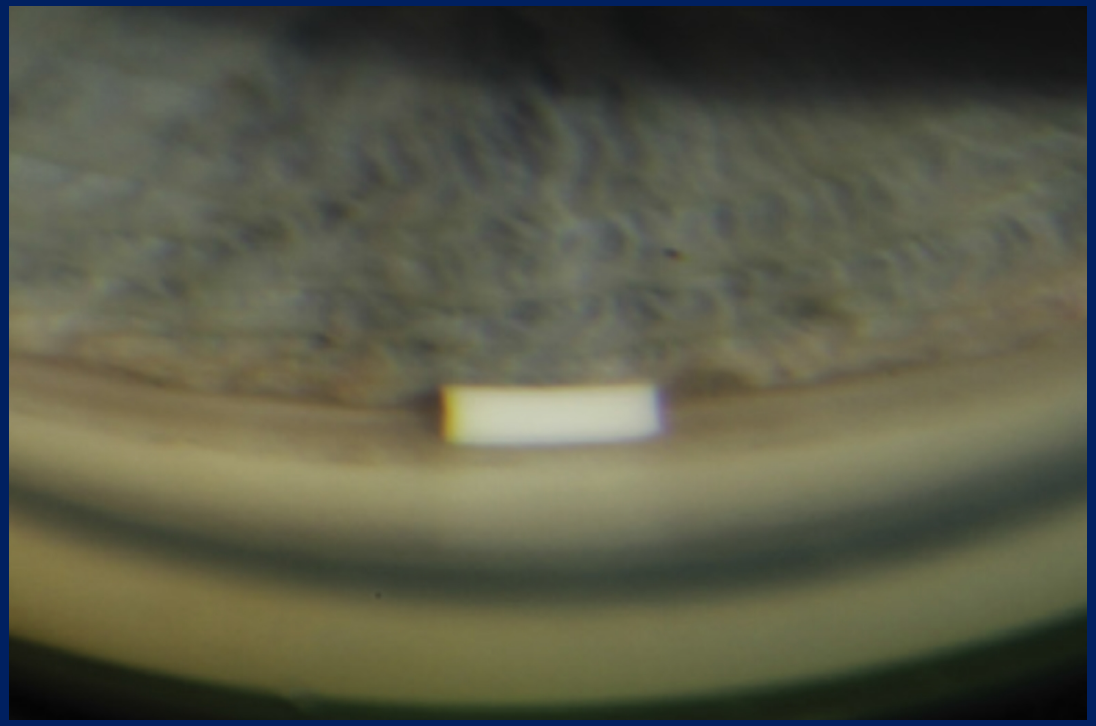
Sustained Release Punctum Plugs



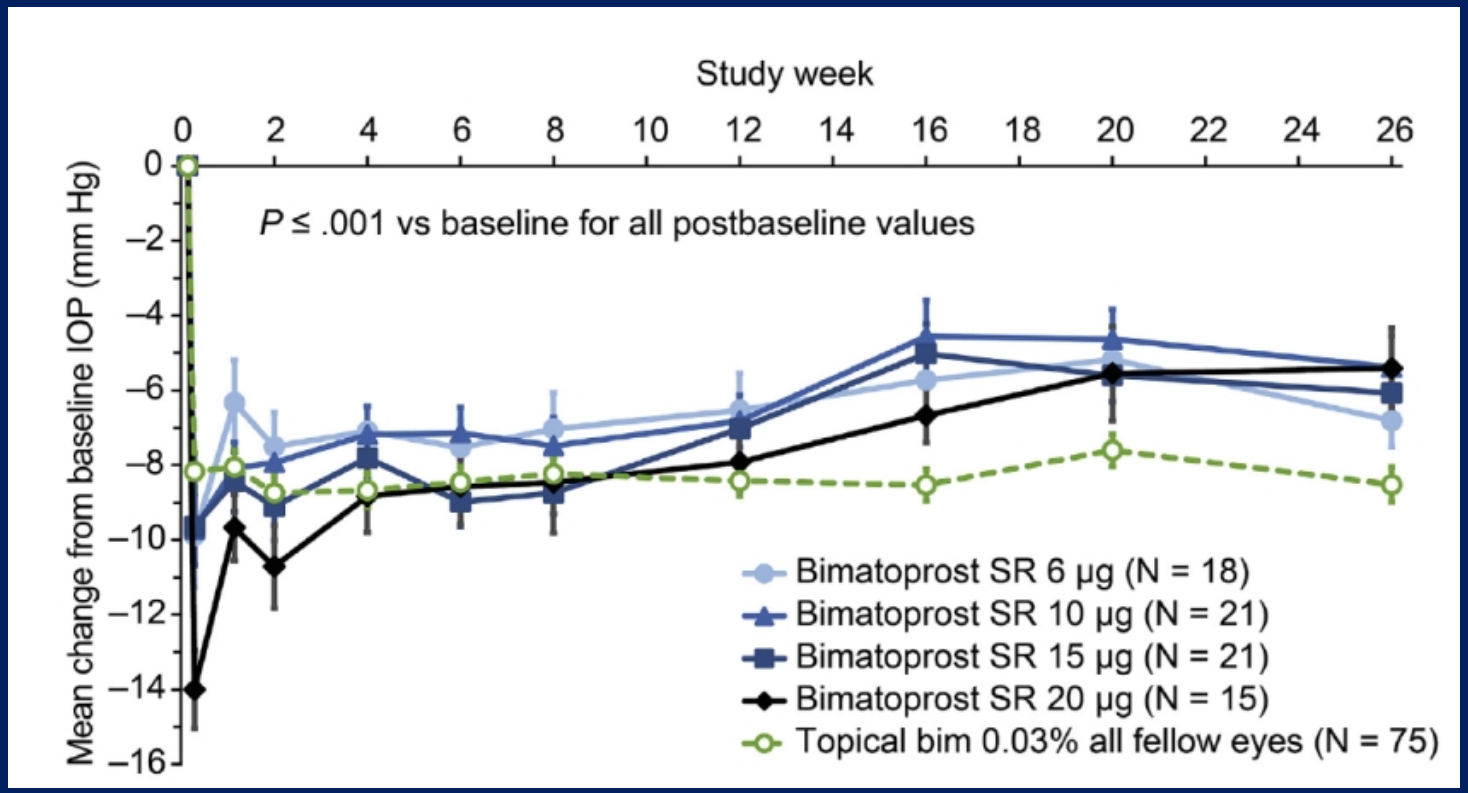
Punctum Plugs

- Travoprost Punctum Plug (OTX-TP, Ocular Therapeutix, Bedford, MA)
  - Encapsulated travoprost within resorbable hydrogel rod
  - Hydrolysis over 90-day period
  - Fluorescein incorporated within rod for visualization
  - Phase 2b: 4.5-5.7 mm Hg reduction at 90 days
    - 88% retention at 75 days
- Latanoprost Punctal Plug Delivery System (Evolute, Mati Therapeutics, Austin, TX)
  - Latanoprost matrix surrounded by silicone
  - 20% IOP reduction and 92-96% retention at 90 days

Bimatoprost Intraocular Implant



Bimatoprost Intraocular Implant

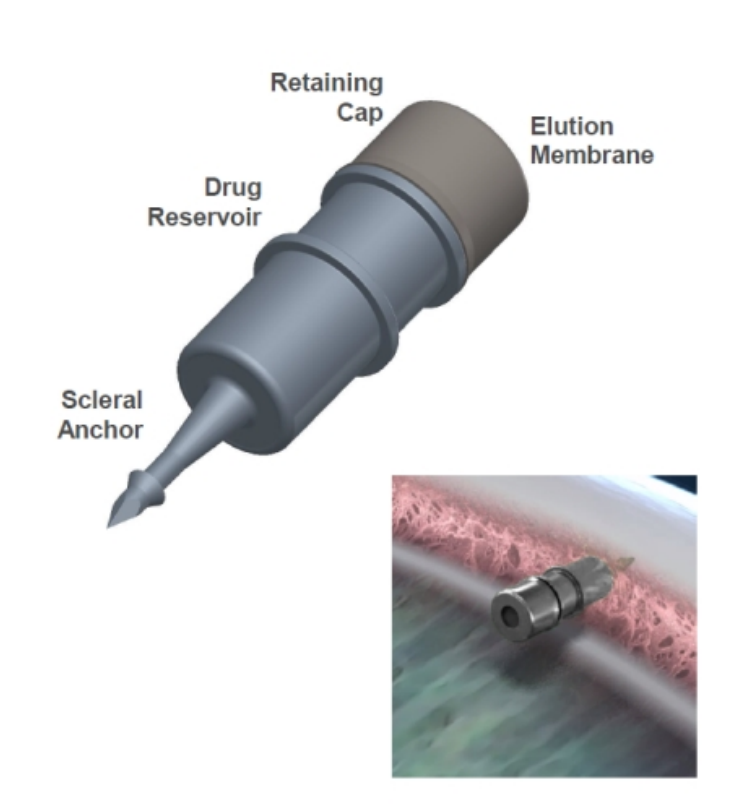


- Bimatoprost SR: 7.2-9.5 mm Hg lowering at week 16
- Topical Bimatoprost 0.03%: 8.4 mm Hg lowering at 16 weeks

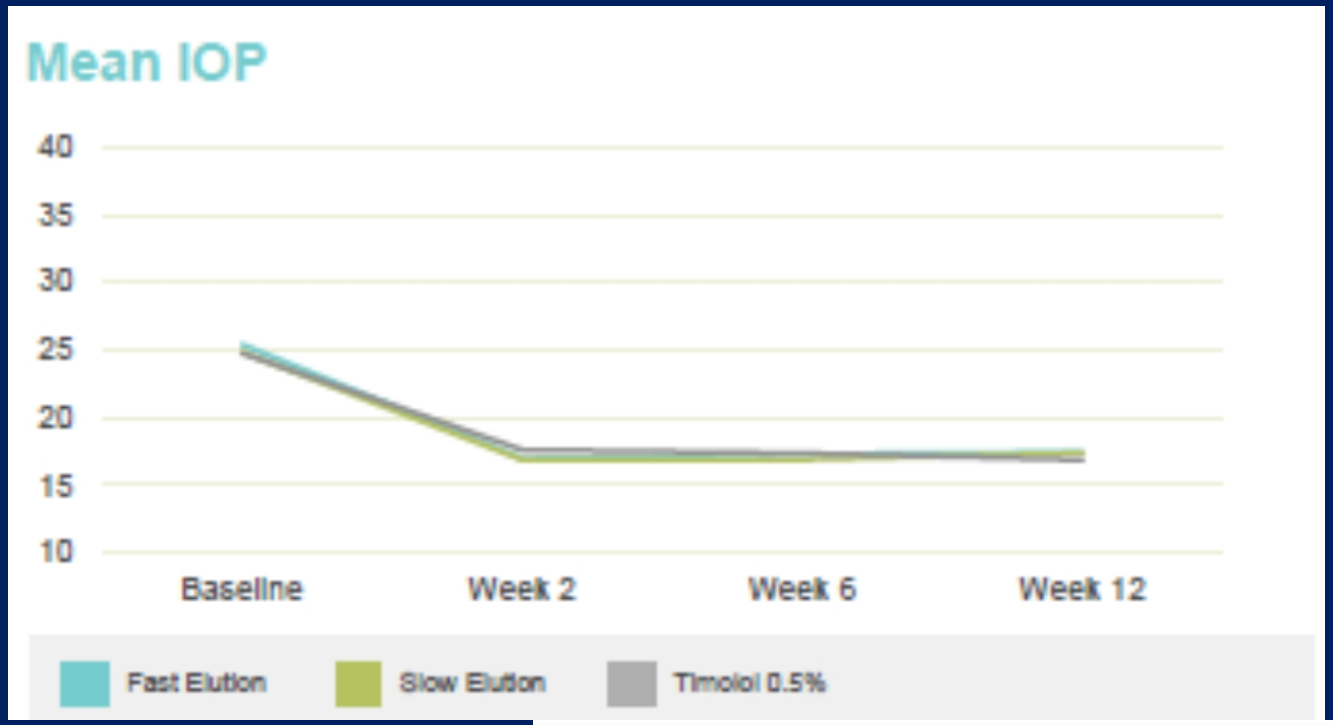
Lewis RA, et al. Am J Ophthaolmol 2017;175:137-147.

iDose Implant

- Titatnium implant
- Filled with travoprost formulation
- Designed to elute drug over 1 year
- Replaceable drug reservoir



iDose Implant – Phase 2 Results



Implant	Week 12 Mean IOP	IOP Reduction At Week 12
Fast-Elution (n=51)	17.4 mm Hg	31%
Slow-Elution (n=54)	17.3 mm Hg	30%

Patient Perspectives, AGS 2018

- Questionnaire administered to 178 glaucoma patients
- Questions regarding barriers to medical care, receptivity to placement of sustained release device
- Collection of ocular history and demographics

72 Patient Perspectives on Sustained Release Therapies for Glaucoma

NIRMAL GOSALIA[1], Dingcai Cao, Ahmad Aref
[1] University of Illinois at Chicago

Purpose/Relevance

To survey patient opinions on implanting a sustained release device (SRD) for lowering intraocular pressure (IOP), aiming to elucidate best practices for ophthalmologists looking to recommend these devices as a viable treatment option.

Methods

An interviewer delivered a self-designed questionnaire to 178 glaucoma patients (age: 65.6 ± 12.8, range 20-93 yrs) who presented to a tertiary care outpatient glaucoma service. Patients were asked to rate various possible barriers to adherence on a Likert scale of 1-5. Patients were also asked if they would be receptive to placement of an SRD if this device completely or partially eliminated the need to use of any topical IOP lowering agents. The degree of receptivity (scale of 1-10) for five different SRDs was assessed. The current number of IOP lowering eye drops, baseline diagnosis, severity of disease, as well as basic demographic data were collected through the electronic medical records. Logistic regression or ANOVA statistical testing was performed to assess the association between receptivity rating of a given SRD and

Results

Among 178 patients, 65% were receptive to an SRD with complete replacement of topical IOP lowering agents and 52% were receptive to an SRD with partial replacement topical IOP lowering agents. Receptivity for complete and partial replacement was significantly associated with the current number of IOP lowering agents ($p = 0.04$, $p = 0.007$ respectively) and age ($p = 0.005$, $p = 0.11$ respectively). No significant association was detected between any barriers to adherence and receptivity of complete or partial replacement of topical therapy ($p > 0.05$). Patients rated their degree of receptivity towards punctum plug devices higher than any other SRD (mean = 5.17 ± 3.65, $p \leq 0.004$). Mean receptivity for less invasive SRDs (ocular insert and punctum plug) was greater than more invasive SRDs (injections) (4.48 ± 3.04 vs 3.87 ± 3.20, $p = 0.009$) and significantly associated with age ($p = 0.042$).

Discussion

Adherence to topical eye medications is a barrier to lowering IOP and preventing visual field deficits caused by glaucoma.[1] Understanding factors that influence patient opinions would better position the ophthalmologist to recommend SRDs with maximum efficacy. Our study found that younger patients and patients who use a greater number of IOP lowering topical agents are most receptive to trying an SRD. Additionally, younger patients are more receptive to placement of invasive SRDs than older patients. Patients are most receptive to placement of punctum plugs compared to any other SRD surveyed.

Conclusion

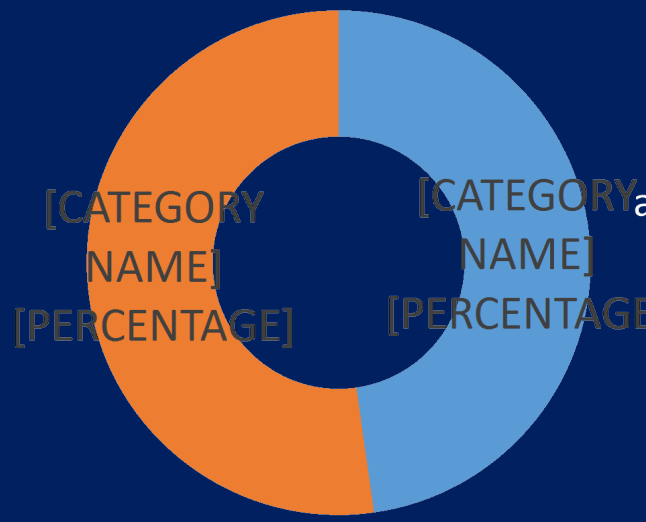
Patient age and number of topical IOP lowering agents have the most significant influence on patient receptivity of SRD implants

PROGRAM AND ABSTRACTS
AGS 2018 Annual Meeting
NYC
March 1–4 • New York Marriott Marquis

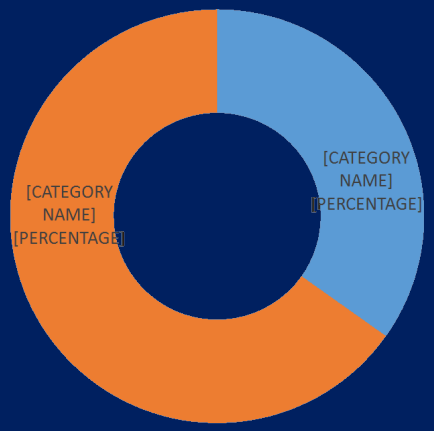
AMERICAN GLAUCOMA SOCIETY

Patient Perspectives, AGS 2018

Would you be receptive to placement of a sustained release device by a physician if this allowed for partial replacement of your eye drops?



Would you be receptive to placement of a sustained release device by a physician if this allowed for complete replacement of all your eye drops?



Patient Perspectives, AGS 2019

		Receptivity			
		Complete Replacement of Eye Drops		Partial Replacement of Eye Drops	
		X2 or Odds Ratio	p-value	X2 or Odds Ratio	p-value
Barriers to Adherence	Cost of Medication	1.20(.15)	0.139	1.08(.12)	0.504
	Physical Instillation	1.24(.23)	0.236	1.17(1.8)	0.321
	Insufficient Medication	1.13(.14)	0.324	1.02(.11)	0.838
	Remembering to Place Drops	1.22(.22)	0.277	1.13(.18)	0.446
	Side Effects	.91(.14)	0.551	.84(.13)	0.258
Demographics	Age	.67(.11)	0.016	.98(.01)	0.109
	Ethnicity	X2(3)=0.805	0.848	X2(3)=0.792	0.852
	Number of Glaucoma Eye Drops	1.44(.258)	0.04	1.60(.28)	0.007
	Severity of Disease	1.05(.24)	0.82	1.18(.26)	0.425

Glaucoma Treatment Paradigm

Glaucoma Treatment Paradigm

Thank you

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