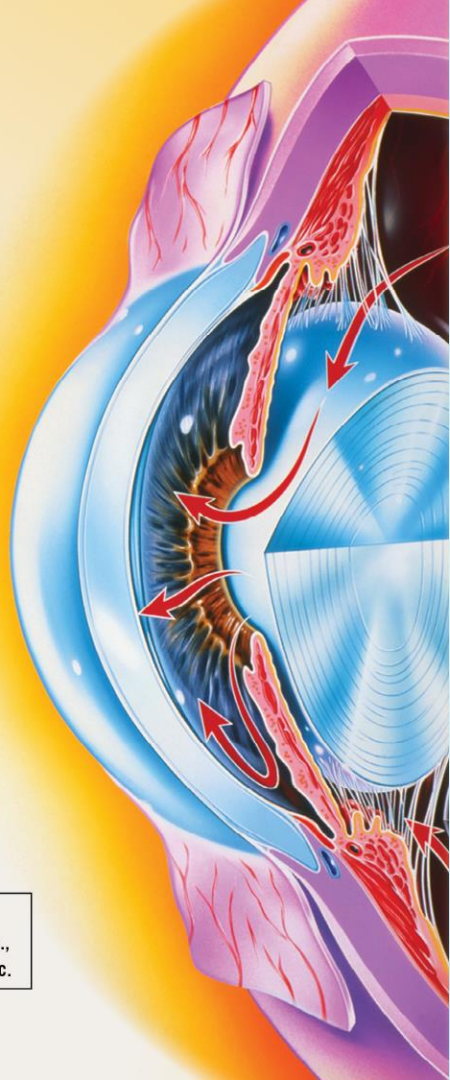
MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

PHARMACOLOGIC & SURGICAL ADVANCES FOR REFRACTORY POAG OR NON-ADHERENCE



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This activity is jointly provided by Postgraduate Institute for Medicine and HealthmattersCME.

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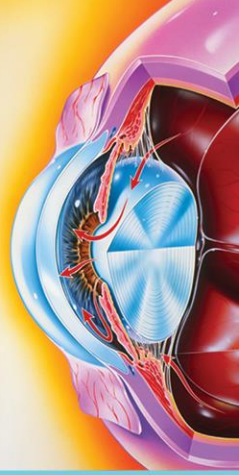


Demographics and POAG: Time to Consider Alternative Care Models

David S. Friedman, MD, MPH, PhD

Director, Dana Center for Preventive Ophthalmology
Wilmer Eye Institute, Alfred Sommer Professor of Ophthalmology
Johns Hopkins University School of Medicine
Professor, Department of International Health
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD

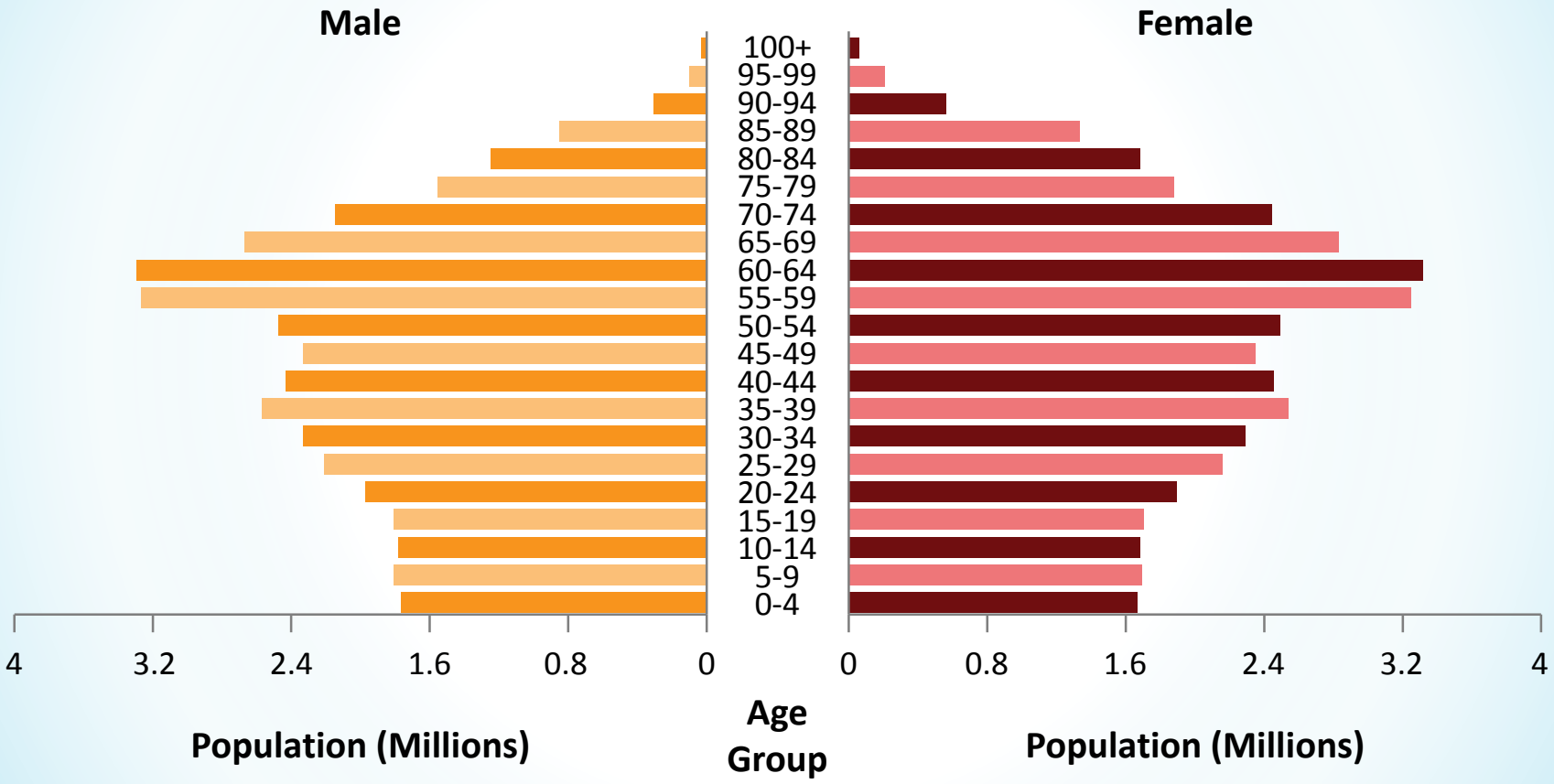
The Times They Are a Changin’

- Populations are aging
- Number of ophthalmologists is not adequate
- Cost of care is high and much of what we do during the care process is ineffective
- Technology is improving

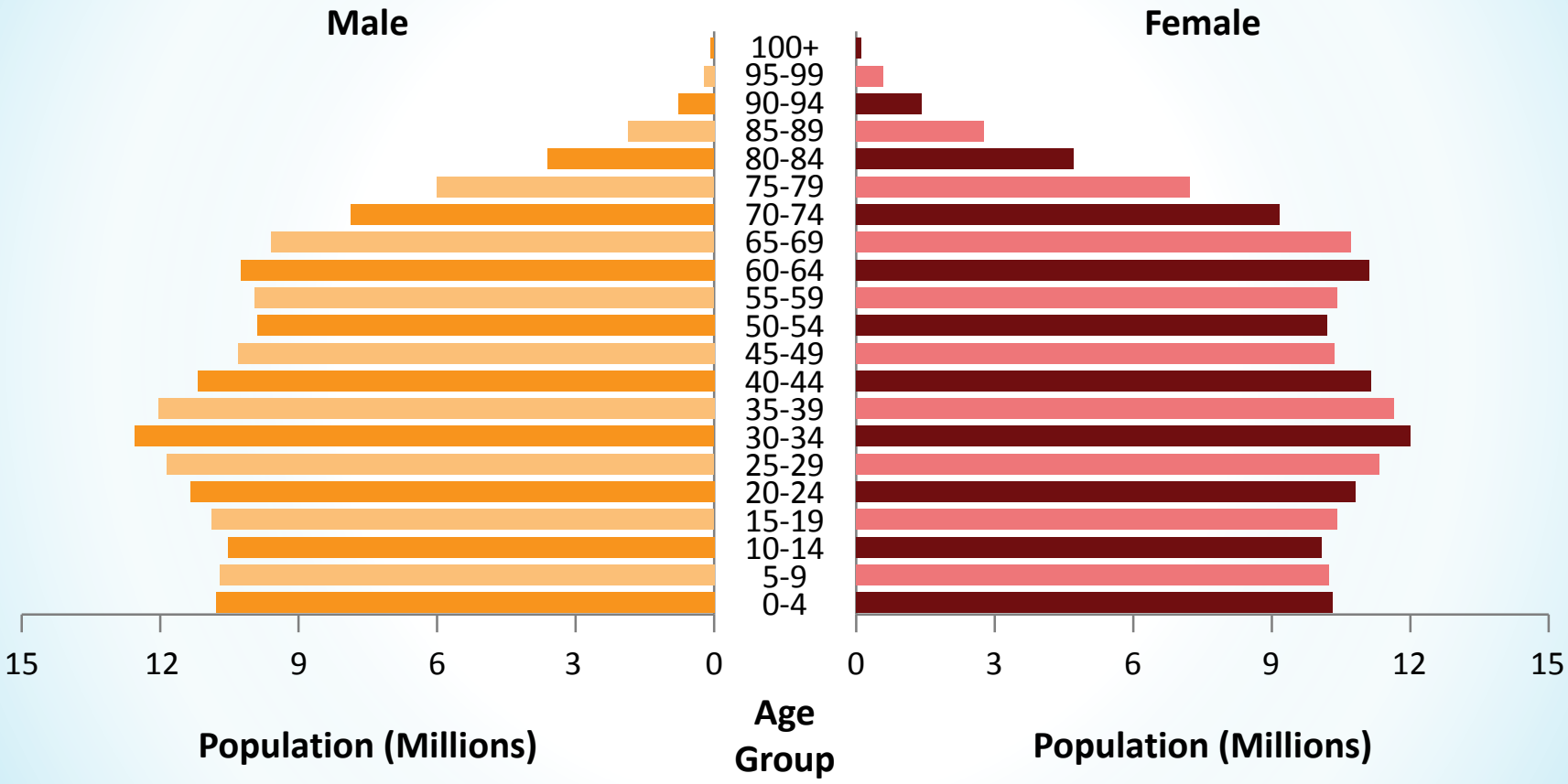
Developed countries are aging and there will be fewer working age individuals.

Who will see all of the glaucoma patients?

German Population by Age – 2025



United States Population by Age – 2025



No New Ophthalmologists!!!

The number of ophthalmologists in the United States will increase by about 2% and full time equivalents (FTE) will decrease over the next decade

About 10% of Whites and **over 15%** of African-derived populations over 75 years of age

Nearly **100 million** globally with glaucoma in 2020

Many More Need Monitoring

Patients

Large numbers with angle closure without glaucoma

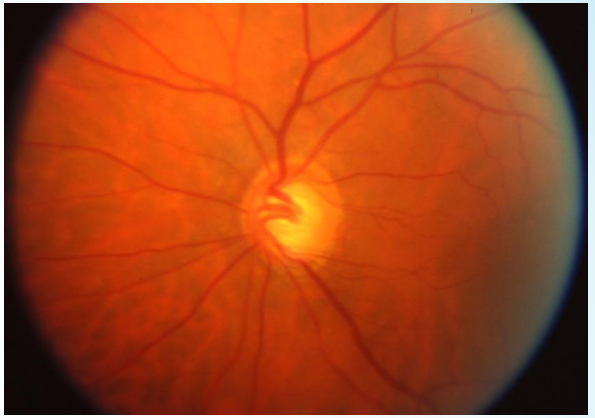
Half of glaucoma care costs
are for glaucoma visits

Quigley HA, et al. *Ophthalmol*. 2013;120(11):2249-2257.

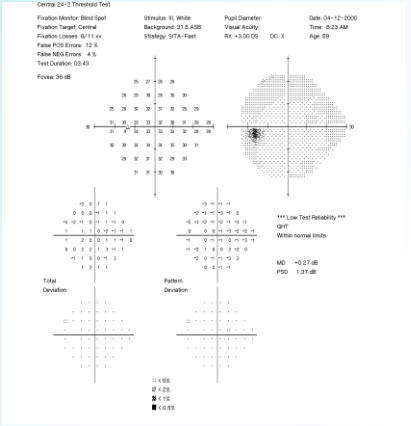
Current management is
inefficient
and often
ineffective

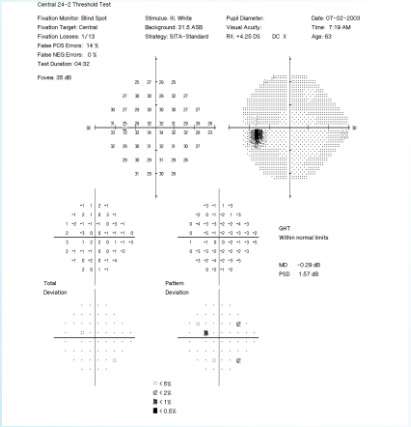
Is This Ideal?

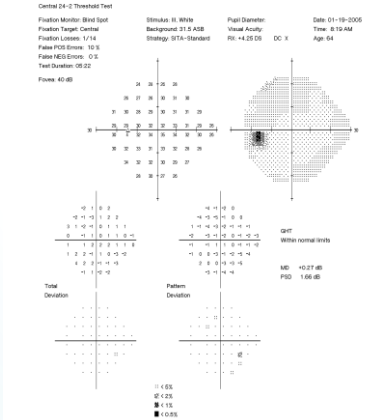
2001

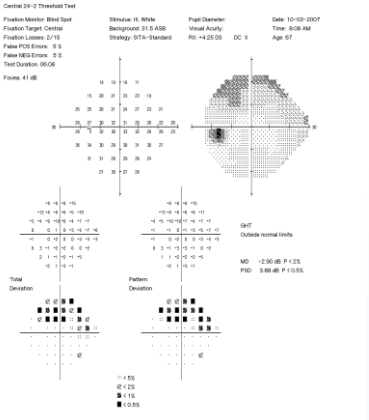


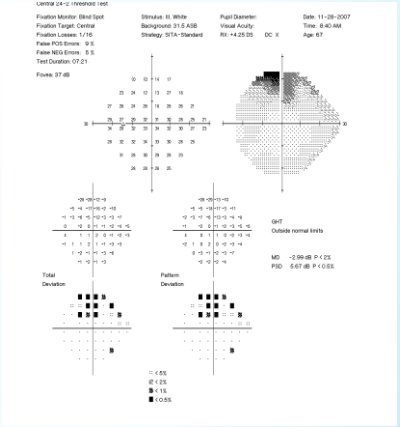
2007









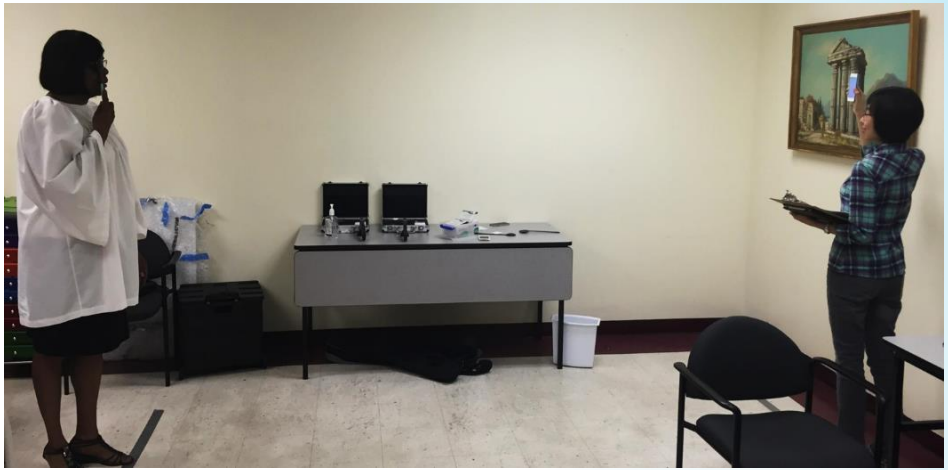


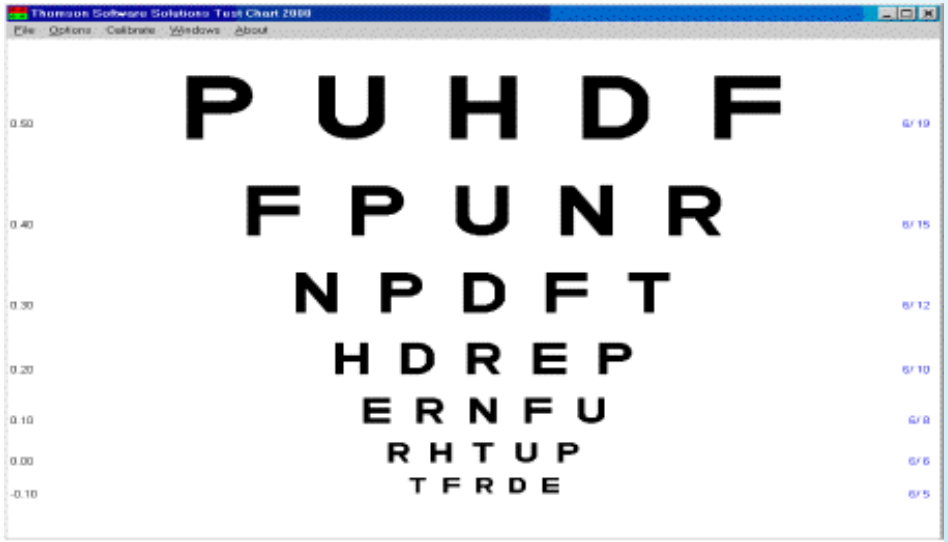
Lots of Wasted Time and Effort

- Patient seen every 4 to 6 months
- IOP stable, field stable, nerve imaging stable
- 5 years later confirmed field loss

How much of the time spent with the patient was time well spent???

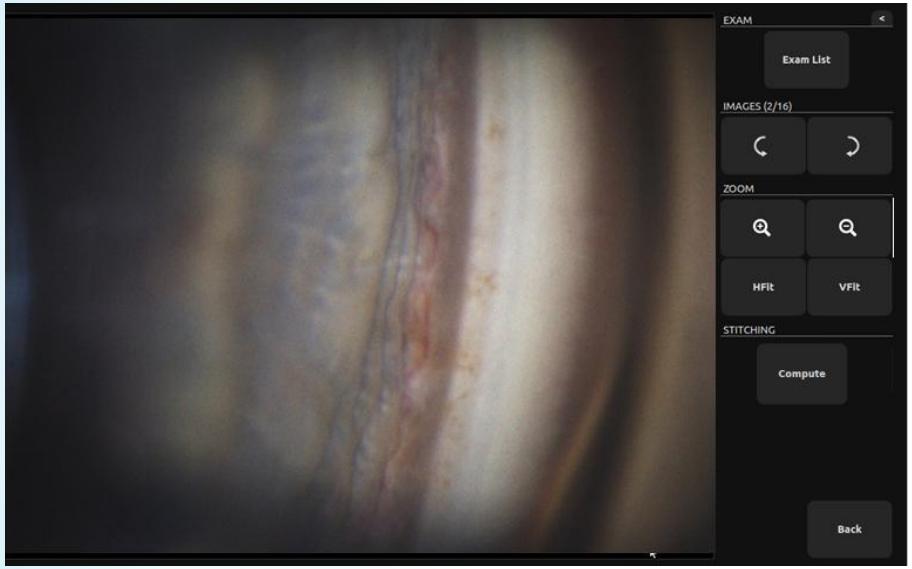
Visual Acuity





Intraocular Pressure

Anterior Chamber Angle



Anterior Chamber Angle

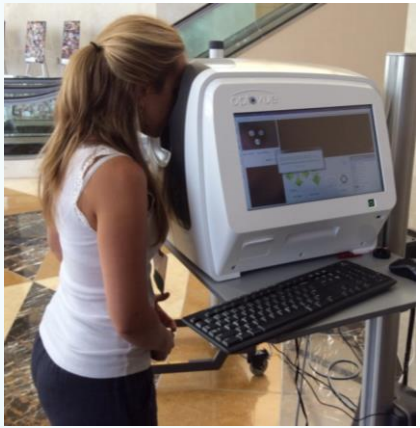
Fundus Photography

Fundus Photography

NFL Imaging

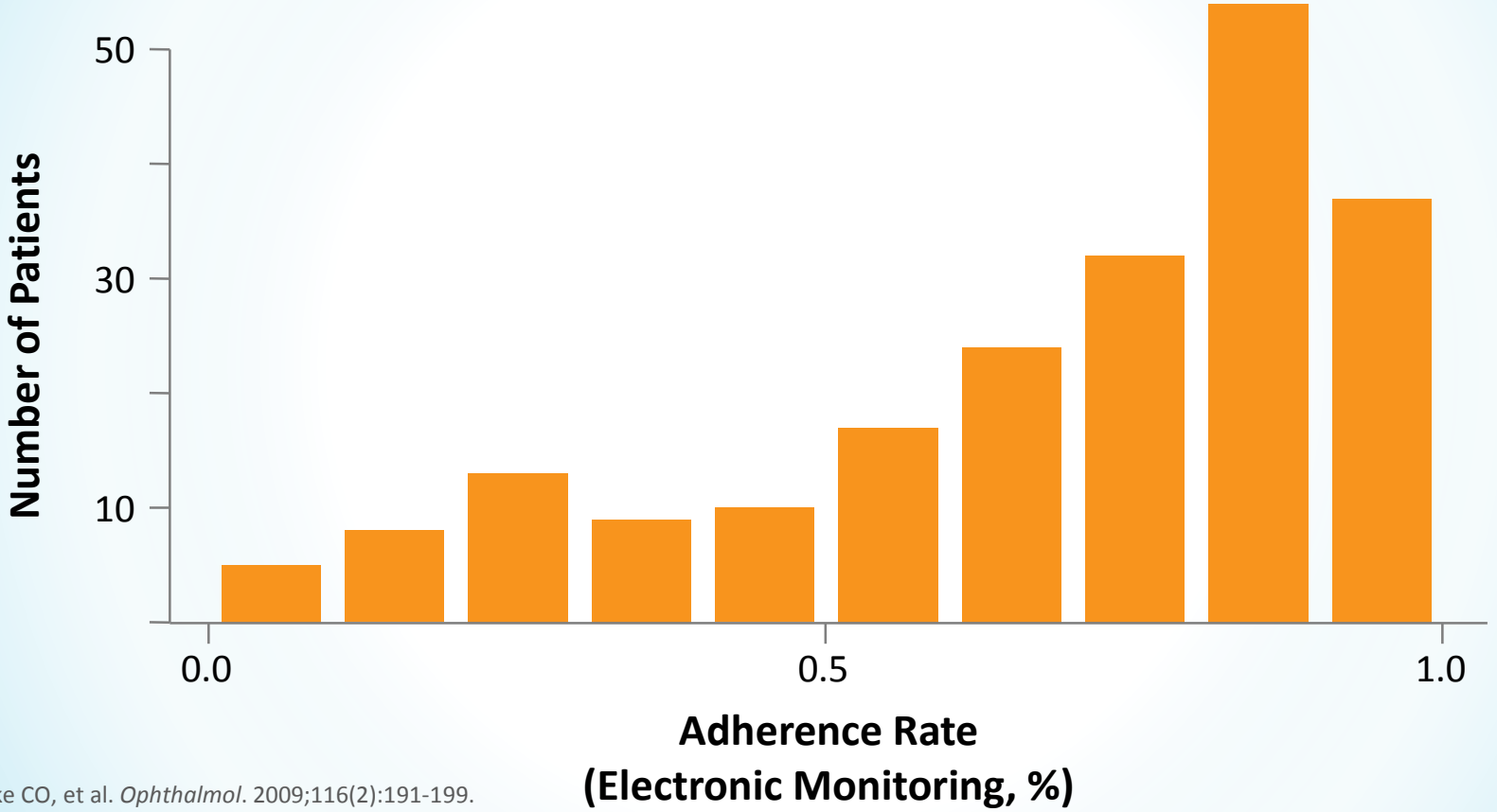
Visual Field Testing

Visual Field Testing



What about counseling?

Adherence in Clinic Patients



Okeke CO, et al. *Ophthalmol*. 2009;116(2):191-199.

13 of 50 patients admitted to non-adherence in research interview

Physicians detected only 3 of them

Friedman DS, et al. *Ophthalmol*. 2009;116(12):2277-2285.

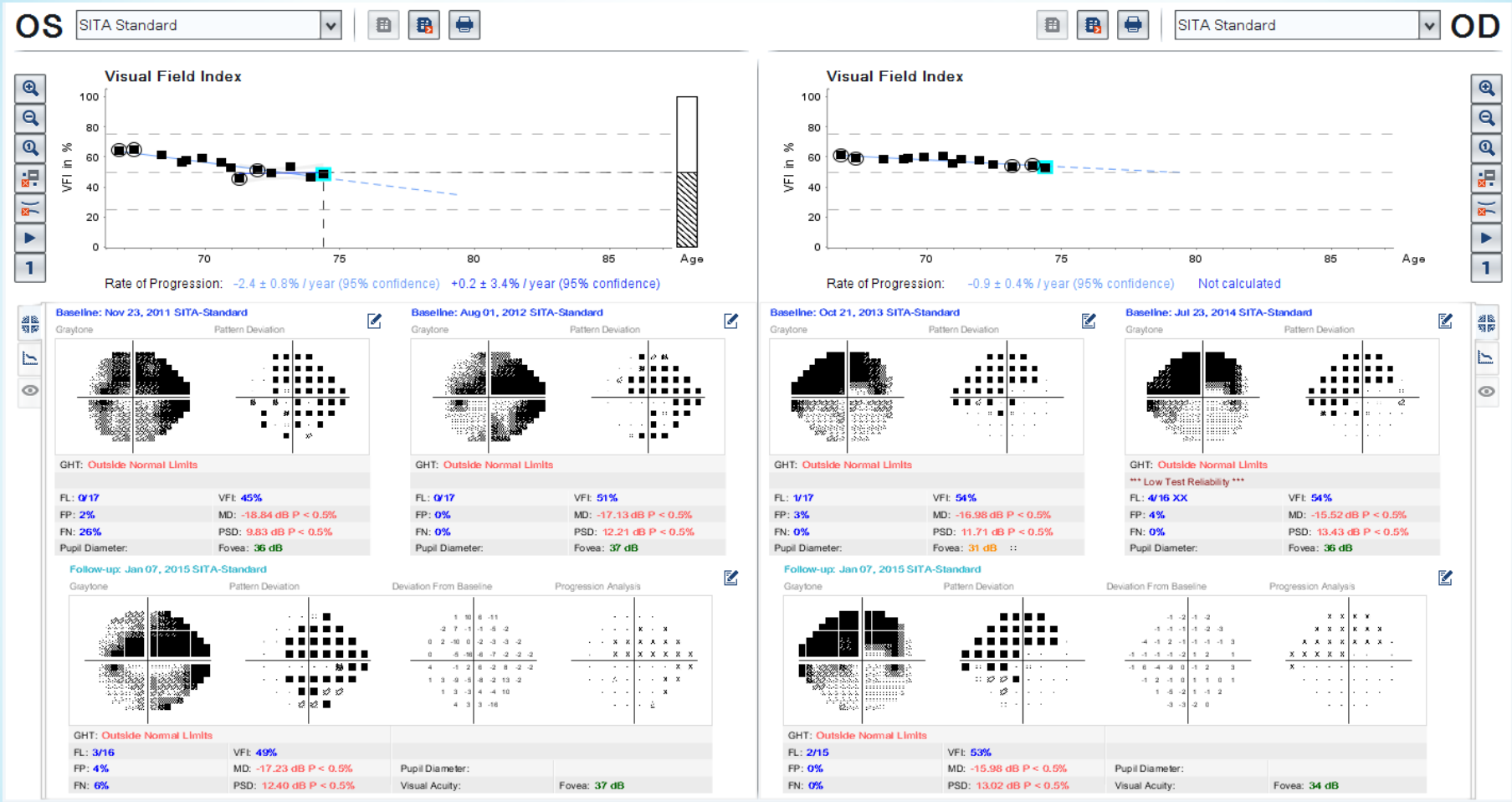
Determining Worsening???

	Clinician B			
Clinician A	**Definitely Stable**	**Probably Stable**	**Probably Progressing**	**Definitely Progressing**
Definitely Stable	5	4	1	0
Probably Stable	4	1	2	1
Probably Progressing	0	3	1	3
Definitely Progressing	0	1	0	1

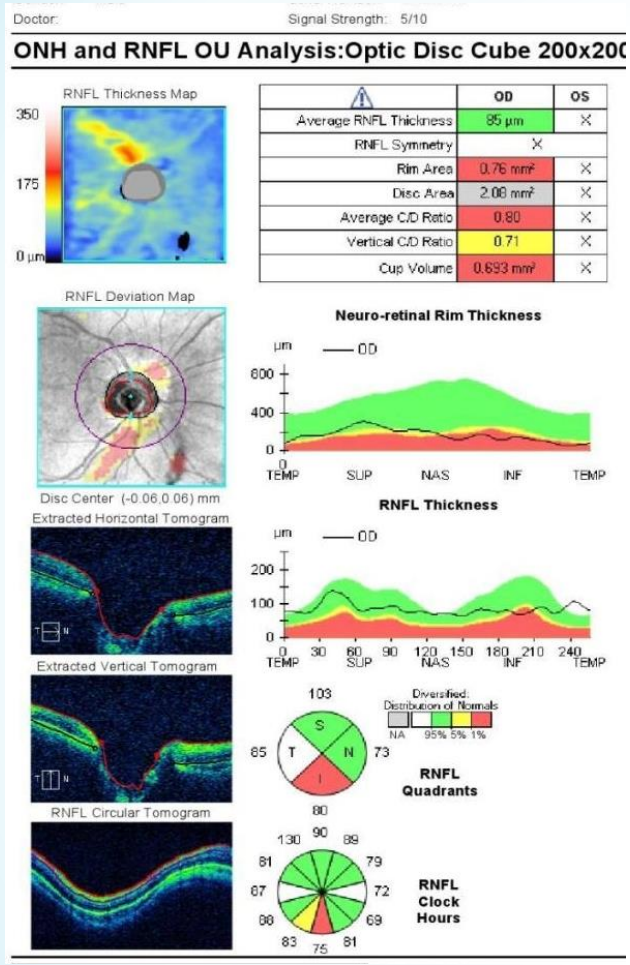
Median weighted kappa for 5 clinicians = 0.32

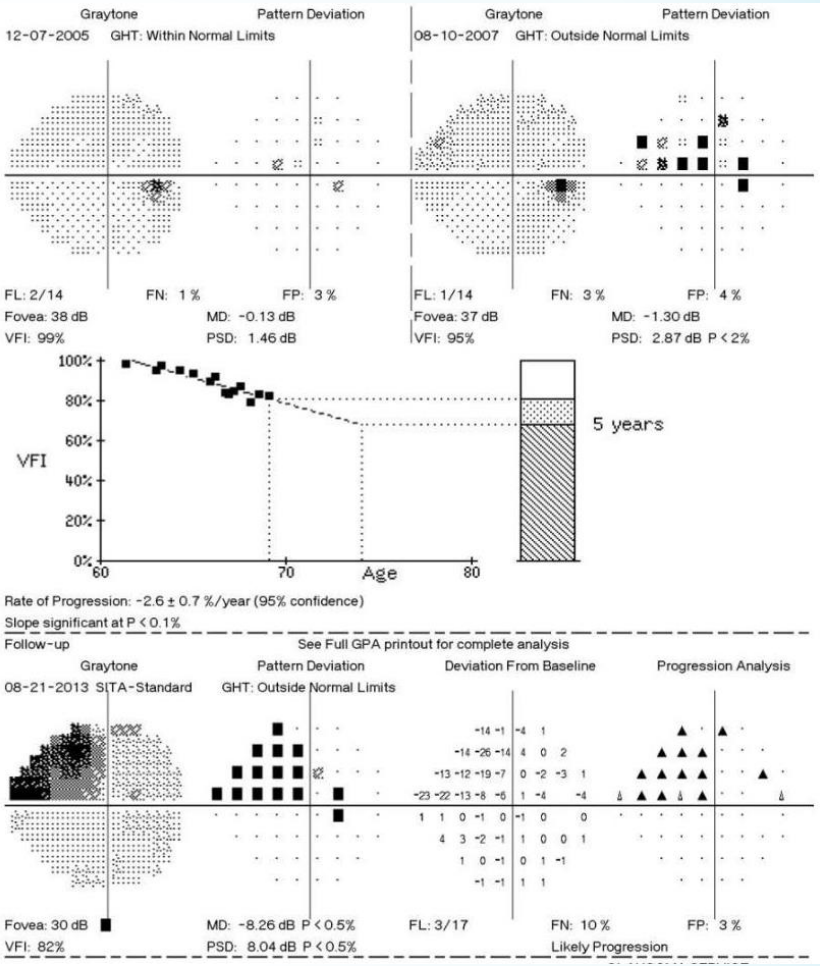
Viswanathan AC, et al. *Br J Ophthalmol*. 2003;87:726-730.

Technology can improve performance



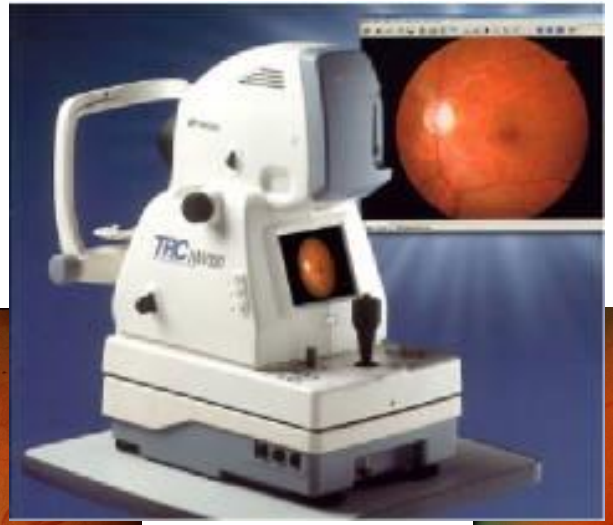
MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

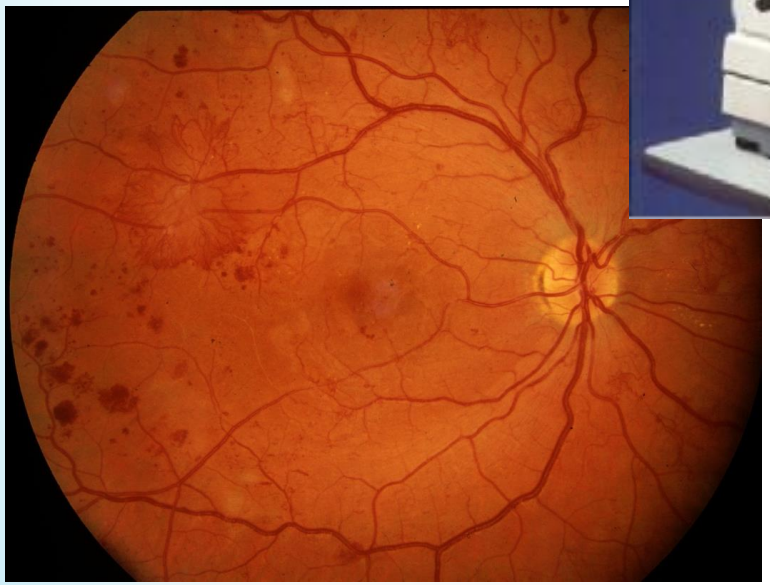


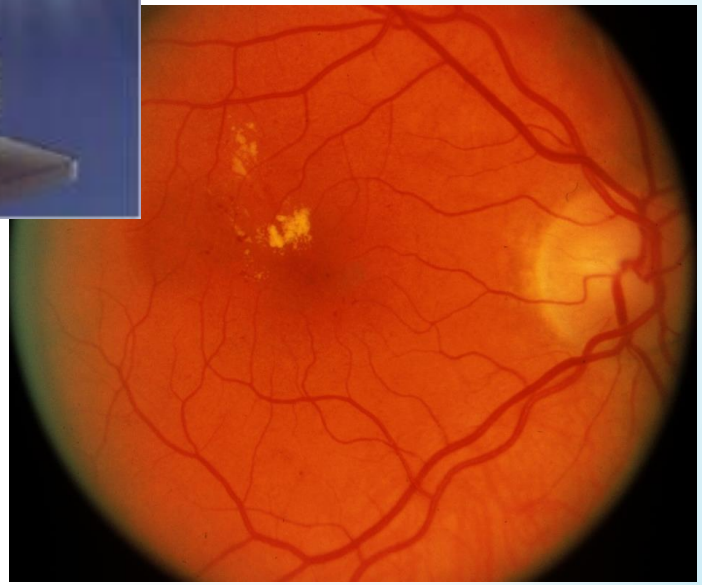


MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

Photoscreening for DR







Local Testing at Remote Locations

- Better integration of data
- More resources allocated to interpretation
- Physician with better data and more time to interact with those who need time
- Rapid upgrade to better technology over time

A New Model of Care

- Testing using ancillary personnel for most visits
- Longer physician appointments when major clinical change is recommended

Health delivery systems can be improved in order to provide high quality care more efficiently and effectively

The Office of Tomorrow

- Data collected remotely
- Physician with multiple screens reviews
- Ancillary staff interact with the patient
- Longer visits with the doctor for change of care or change of status

The Future Is Here

- Populations are aging and growing
- Resources are finite
- Physician supply is not growing, technology is improving
- All that remains is to figure out the logistics

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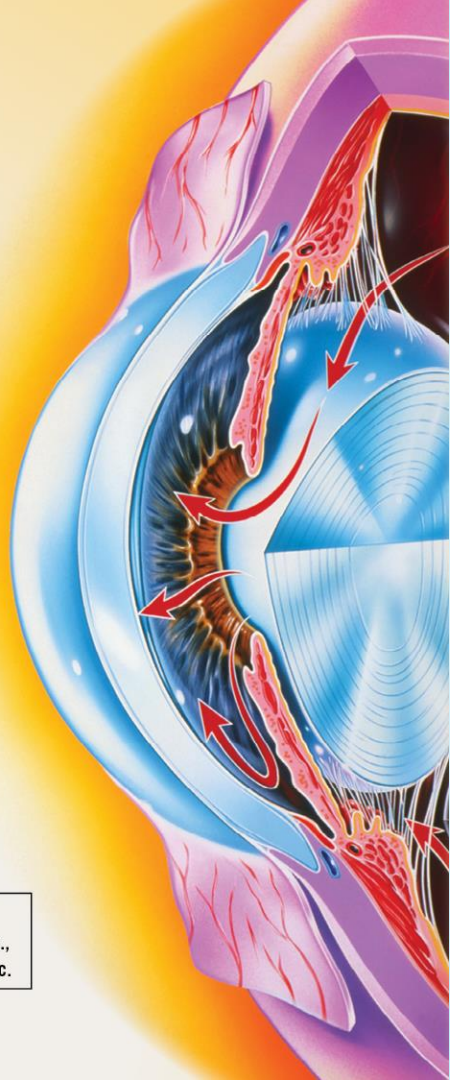

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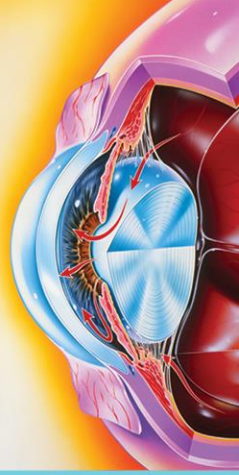


Recent Discoveries in the Pathophysiology of Glaucoma: Novel Treatments

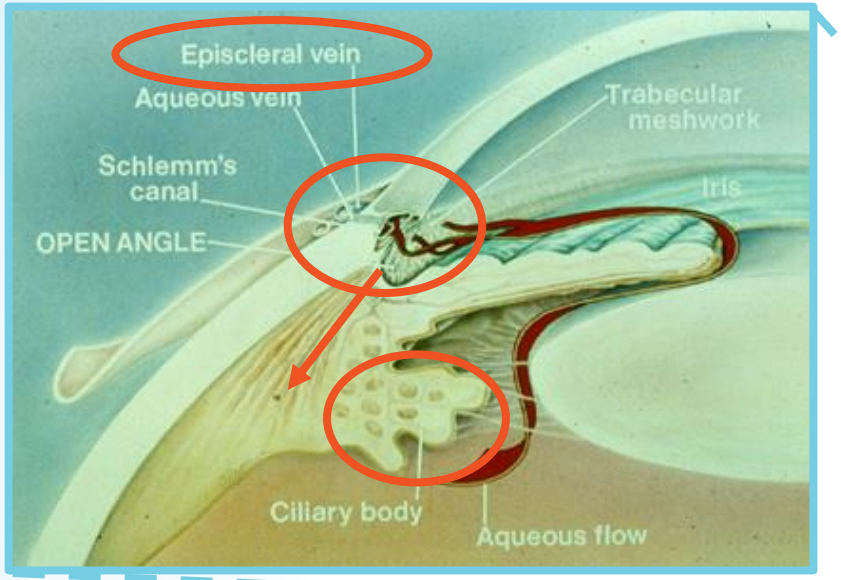
W. Daniel Stamer, PhD

Joseph A. C. Wadsworth Professor of Ophthalmology
Professor of Biomedical Engineering
Duke University
Durham, NC

Which Currently Available Glaucoma Medications Secondarily Target the Conventional Outflow Pathway?

- **Prostaglandins** (direct, but secondary to changes in uveoscleral outflow pathway)
- **Pilocarpine** (indirect, via ciliary muscle contraction)

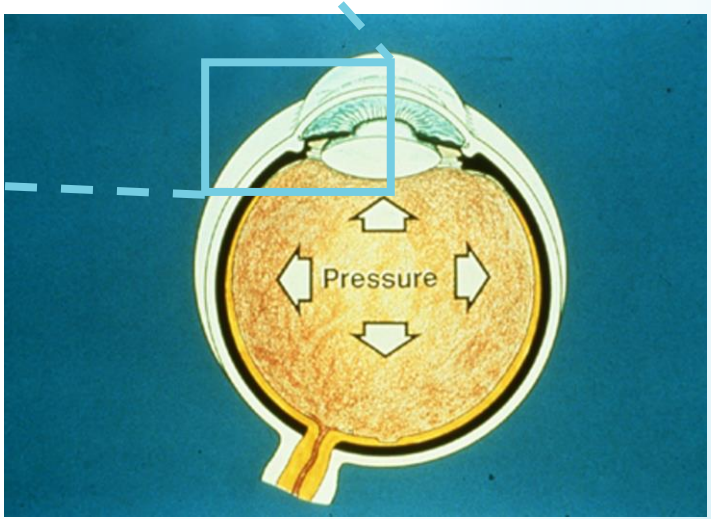
Aqueous Humor Dynamics: IOP Regulation



$$IOP = (F - U)/C + EVP$$

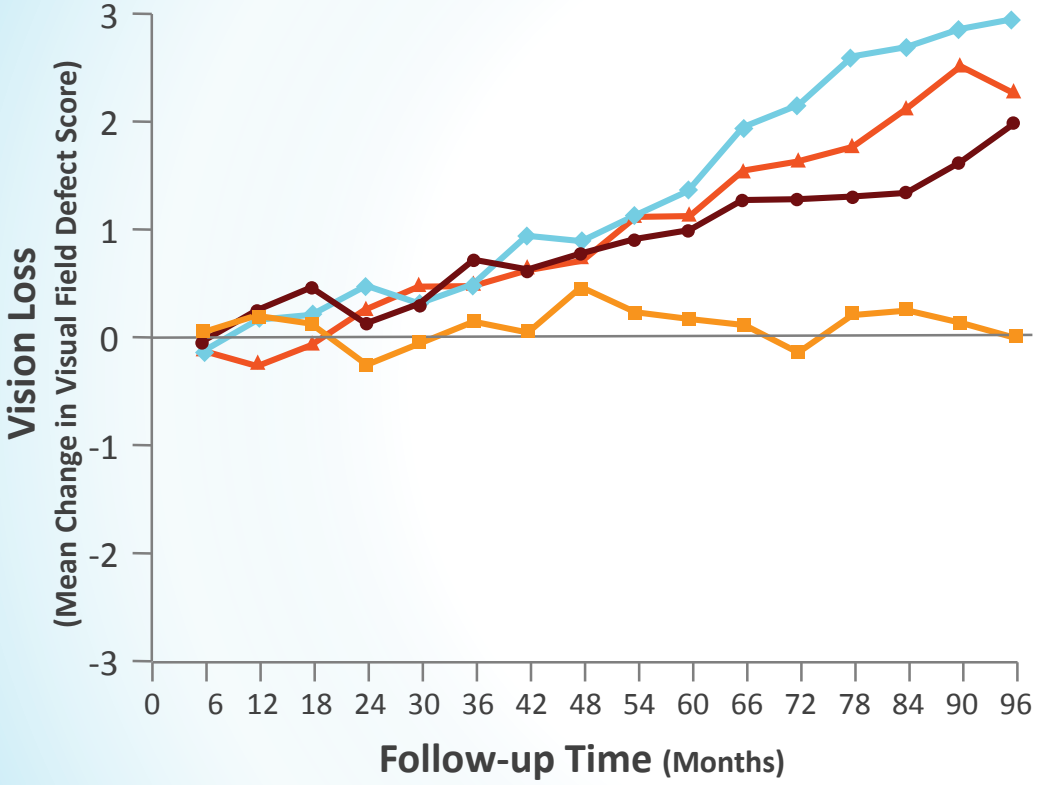
Simplified Goldman Equation

$$C = 1/R$$



IOP, intraocular pressure;
F, rate of aqueous formation;
U, uveoscleral outflow;
C, facility of aqueous outflow;
EVP, episcleral venous pressure

Lowering Eye Pressure Is Neuroprotective



The lower the pressure…

The better the outcome

The AGIS Investigators. Am J *Ophthalmol*. 2000,Oct;130(4):429-440.

How Do We Medically Lower Eye Pressure?

$$IOP = (F - U)/C + EVP$$

Simplified Goldman Equation

Decrease inflow

ß-adrenergic blockers
Carbonic anhydrase inhibitors
a_2-adrenergic receptor agonists

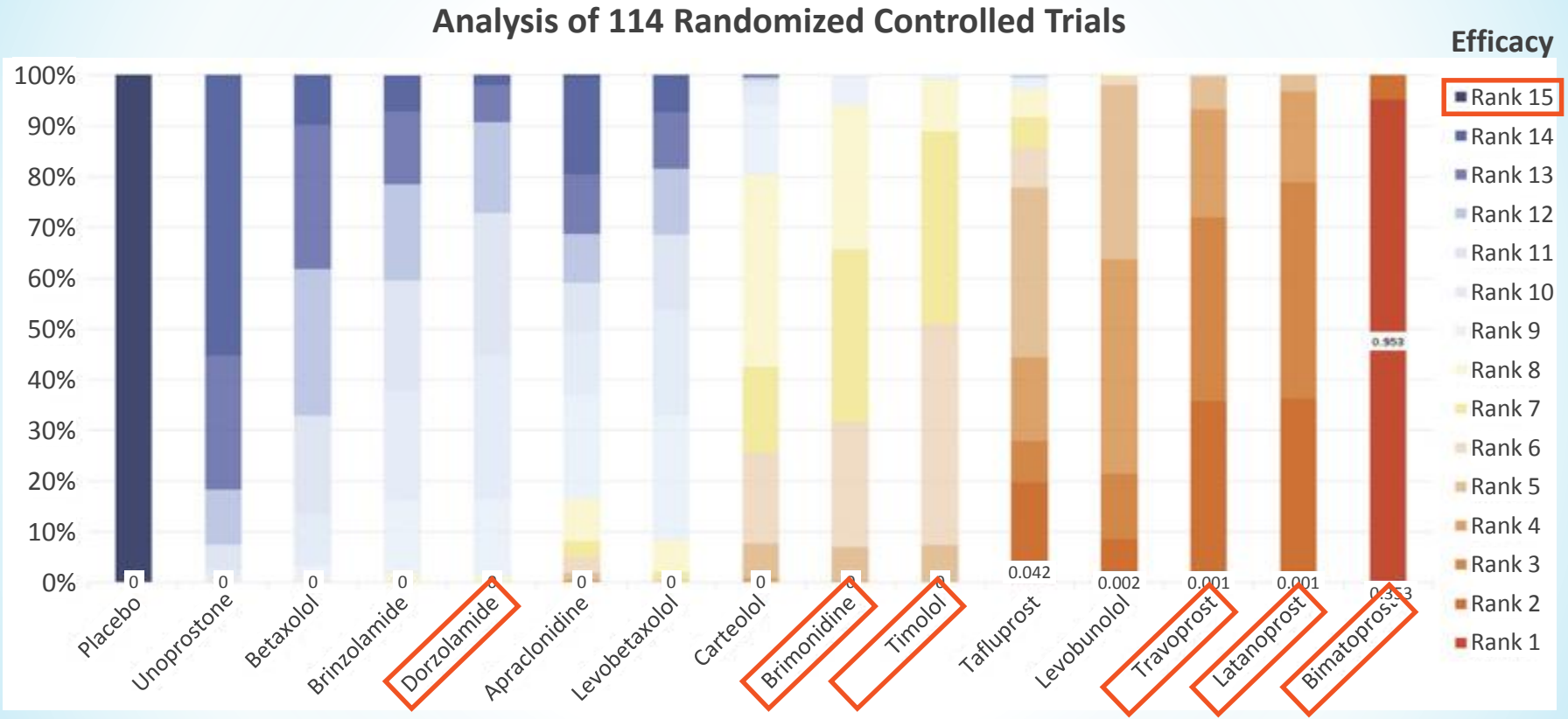
Increase uveoscleral outflow

Prostaglandin F_{2a} receptor agonists

Increase conventional outflow

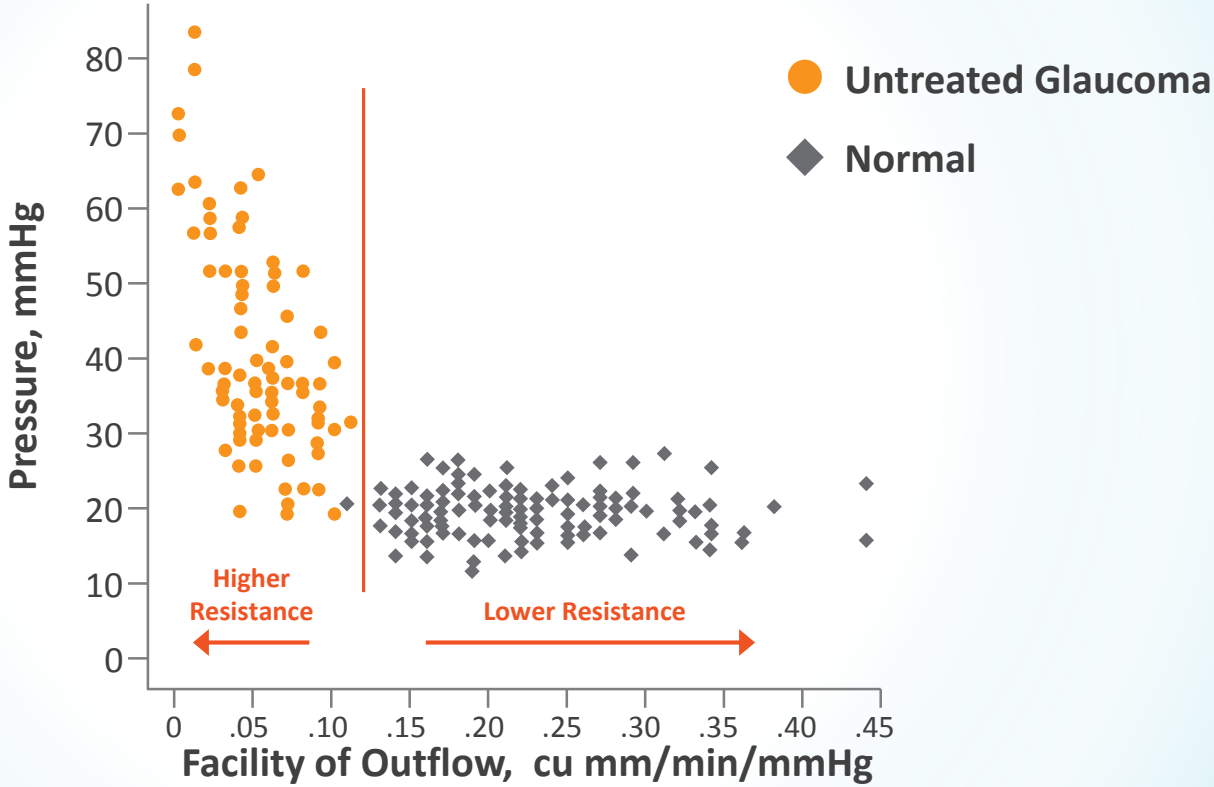
None currently available in US

Comparative Effectiveness of First-Line Medications for Primary Open-Angle Glaucoma: A Systematic Review and Network Meta-analysis



Li T, et al. *Ophthalmol*. 2016;123(1):129-140.

Higher Resistance to Conventional Outflow Causes Ocular Hypertension in Glaucoma



Grant WM. *Trans Am Acad Ophthalmol Otolaryngol*. 1951;55:774-781.

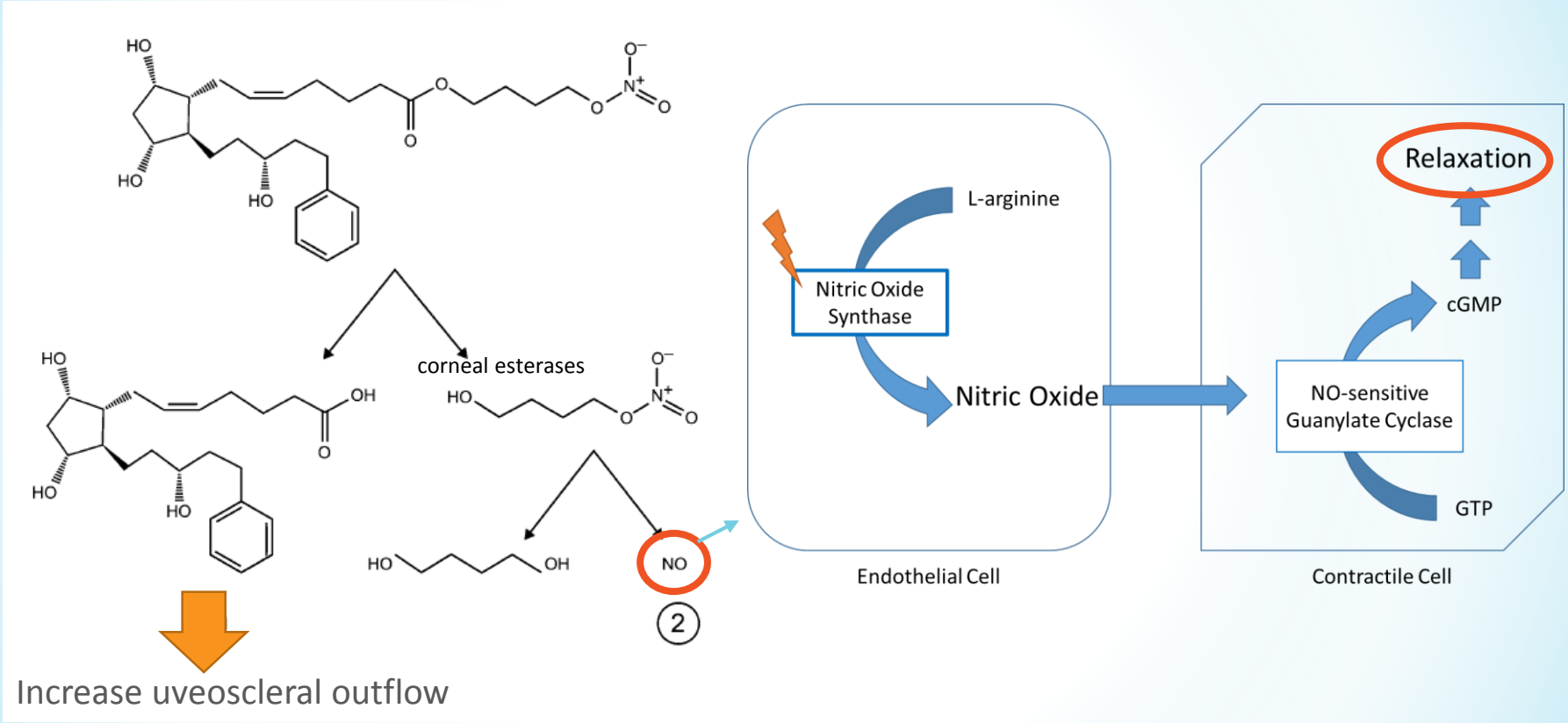
Why Do We Need a Conventional Outflow Drug?

- Majority of outflow (70%-90%) via conventional route, offering greater eye-pressure-lowering ability than PGAs
- Avoid interventional treatments (e.g. surgery, laser)
- Additive with current eye-pressure-lowering drugs: Current medical treatments do not lower eye pressure enough in most
- Restore function to conventional pathway
  - Diseased tissue
  - Better perfusion of tissues/cells
  - Possible stimulation of cell division and repopulation/remodeling of tissue
  - Dampen eye pressure fluctuations

Conventional Outflow Drugs/Current Status

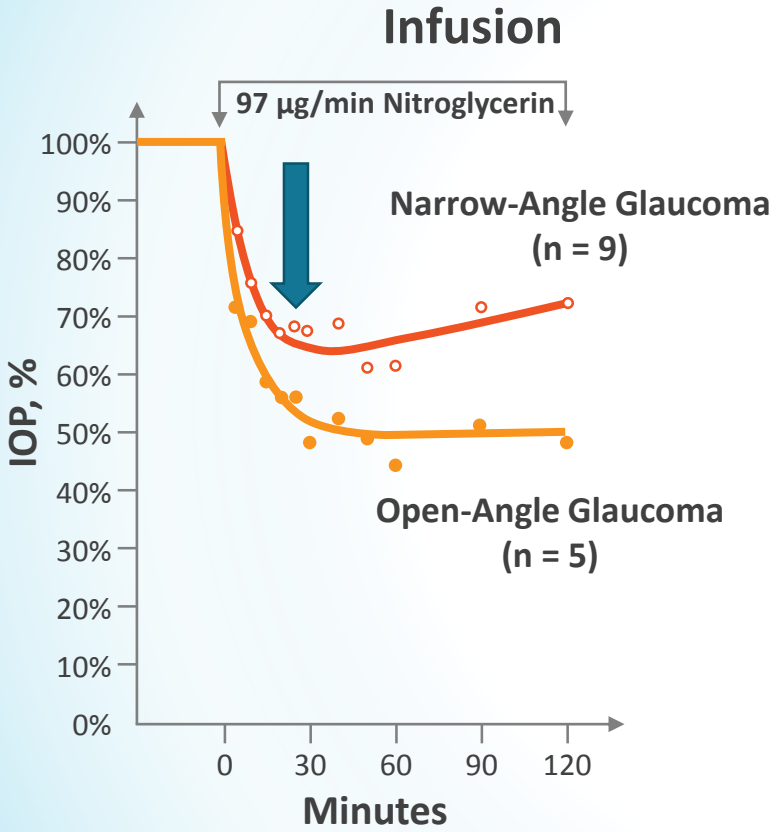
- Rho kinase inhibitors
  - Netarsudil (Awaiting FDA approval in US)
  - Netarsudil/latanoprost (Phase III)
  - Ripasudil (Approved in Japan)
- Nitric oxide donors
  - Latanoprostene bunod (Recently approved in US)
  - Nipradilol (Approved in Japan)

Latanoprostene Bunod: Mechanism of Action

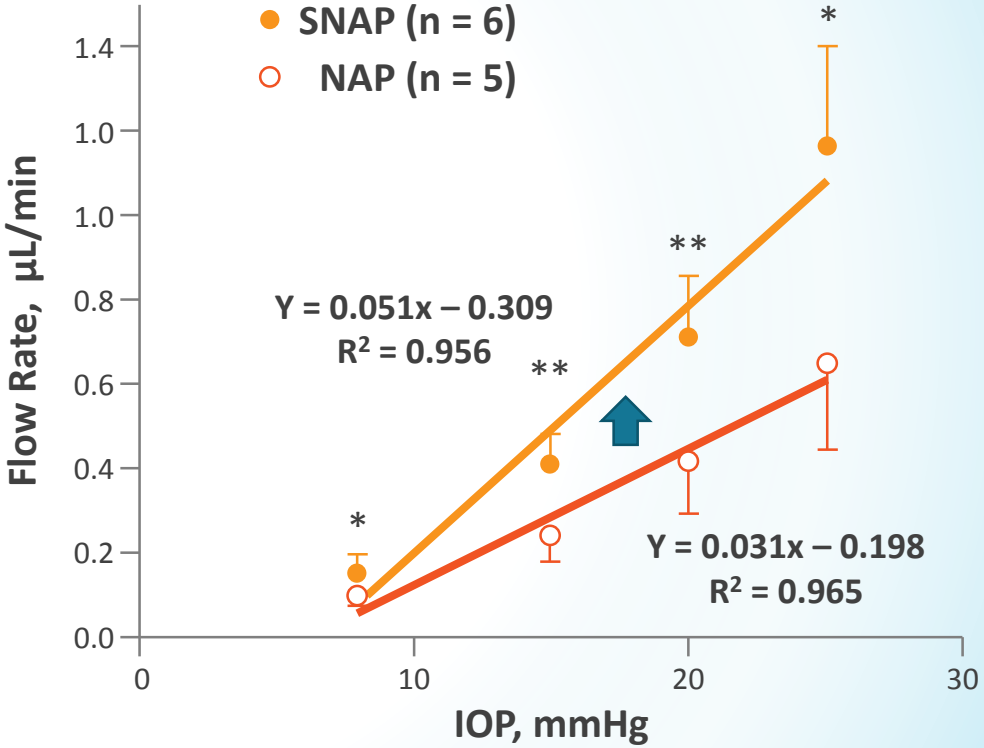


Kawase K, et al. *Adv Ther. 2016*;33(9):1612-1627.

Nitric Oxide Lowers IOP by Increasing Outflow Facility

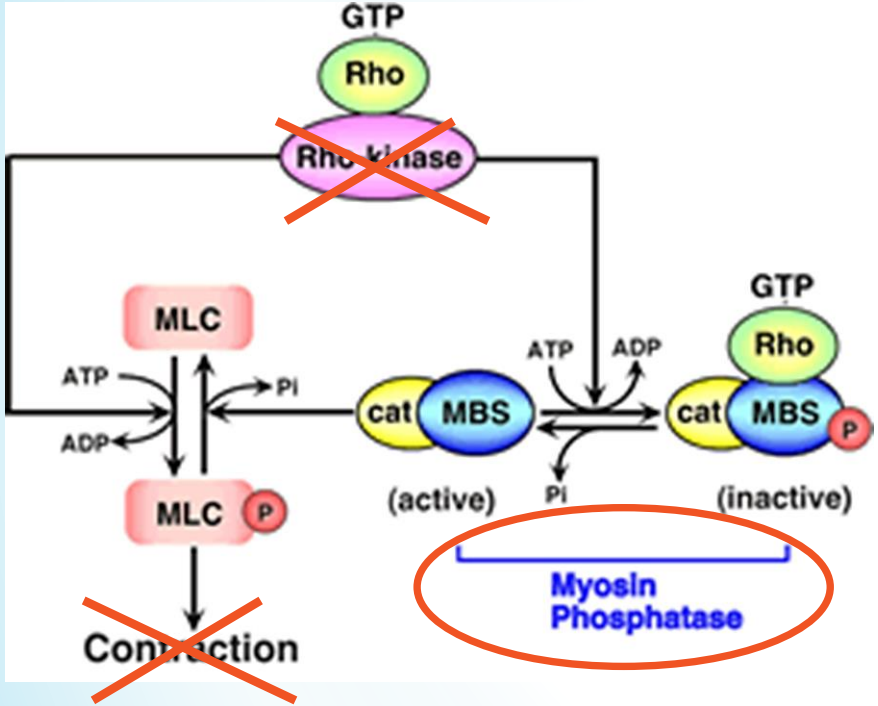


Wizemann AJ, et al. *Am J Ophthalmol*. 1980;90(1):106-109.

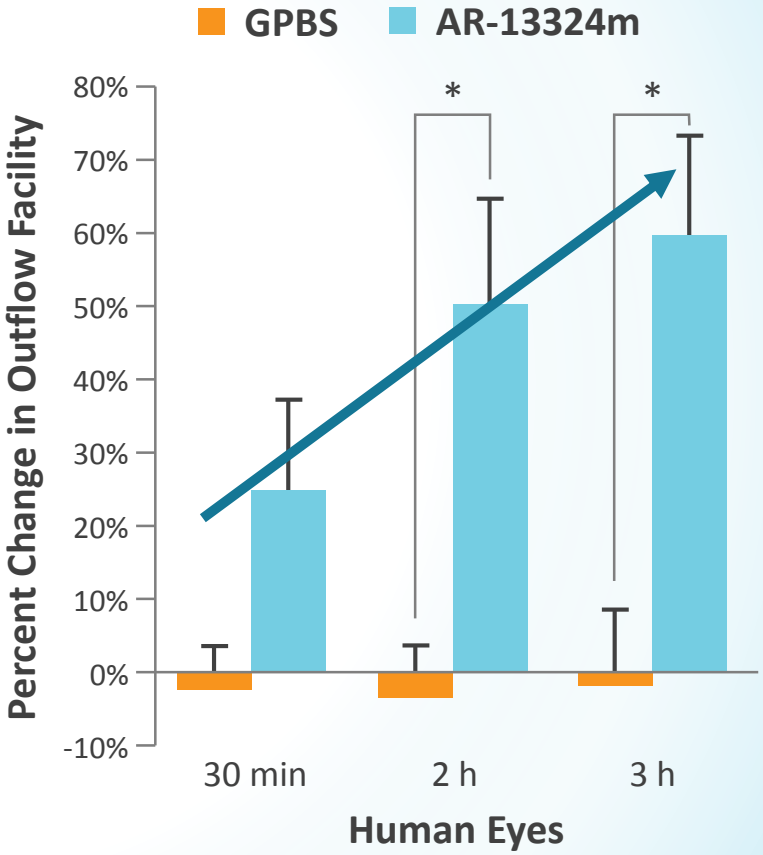


Chang JY, et al. *Am J Physiol Cell Physiol*. 2015;15:309(4)C205-C214.

Rho Kinase Inhibitors: Mechanism of Action



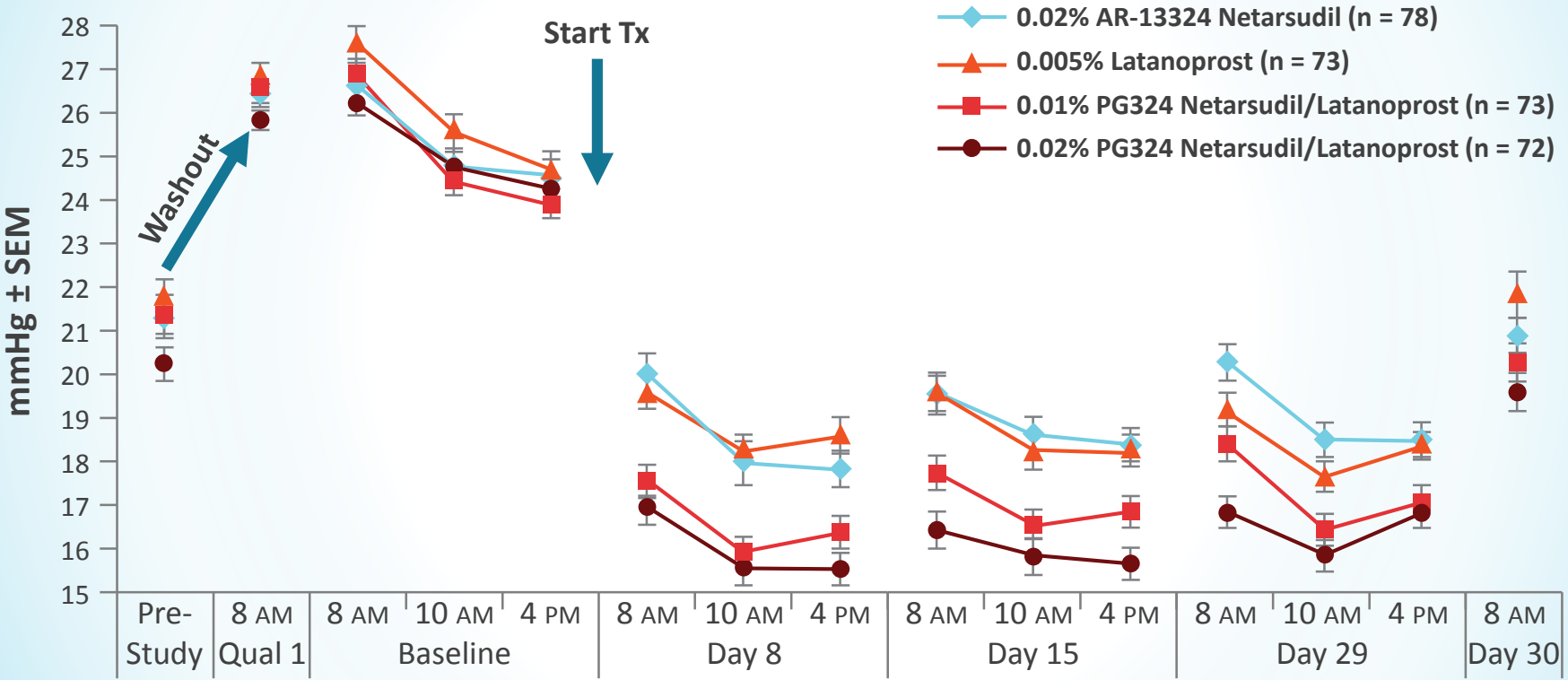
Relaxation



MLC, myosin light chain.

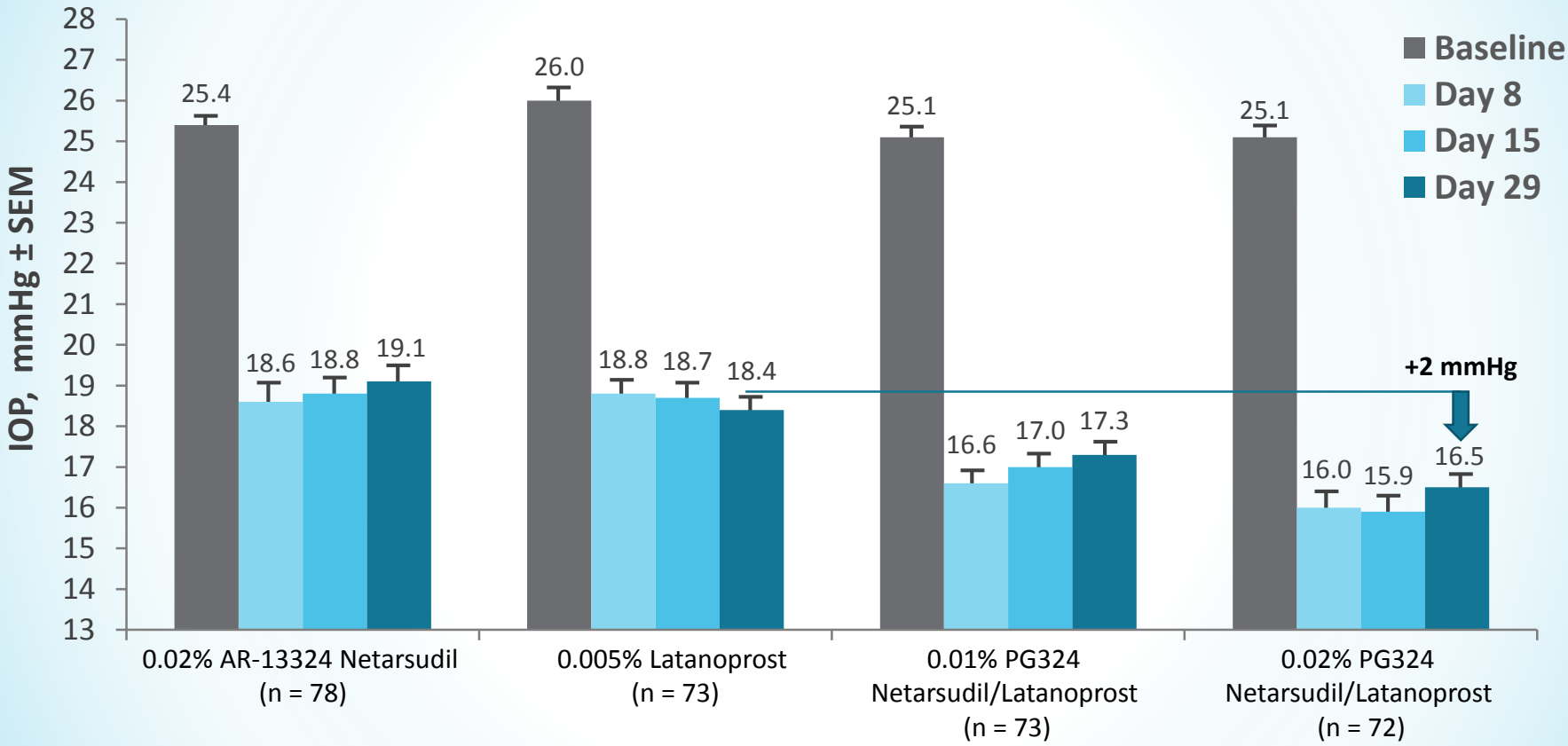
Ren, et al. *Invest Ophthalmol Vis Sci.* 2016;57(14):6197-6209.

Netarsudil vs Latanoprost vs Netarsudil/Latanoprost (N = 292)



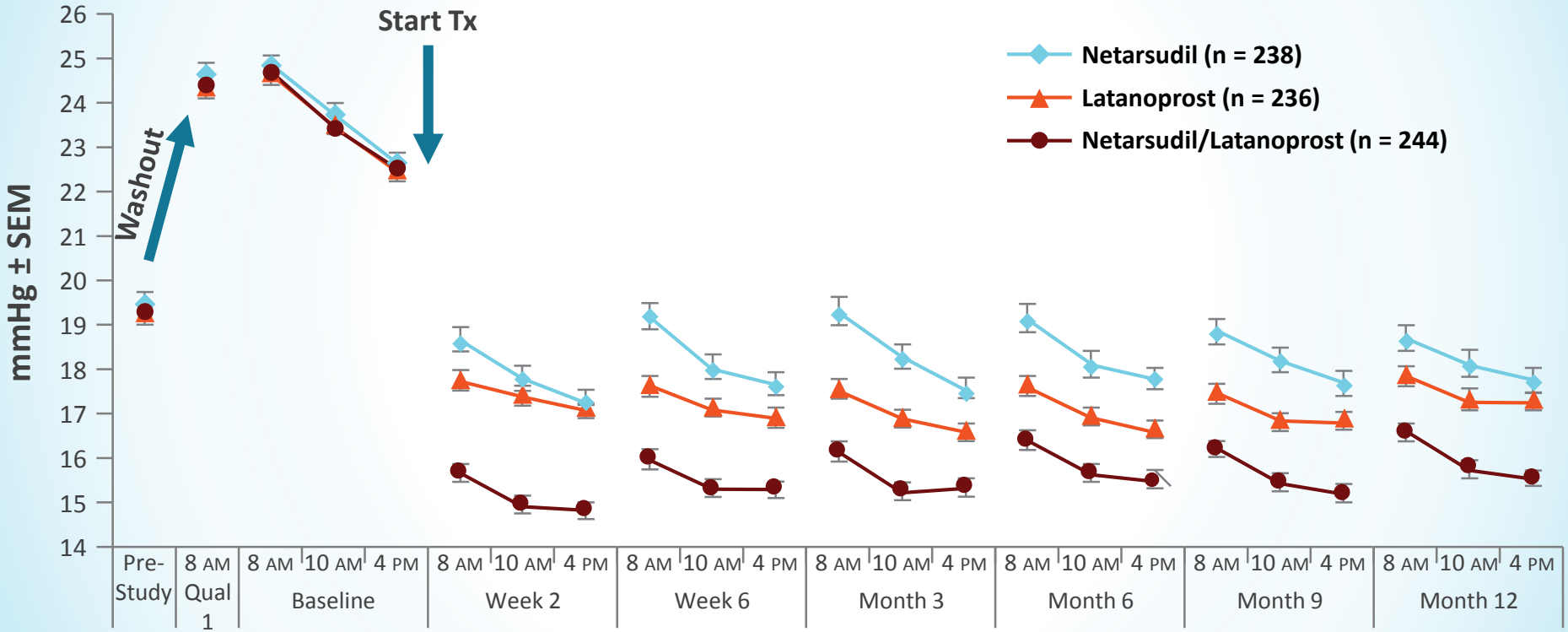
Lewis RA, et al. *Br J Ophthalmol*. 2016;100(3):339-344.

Mean Diurnal IOP Reduction



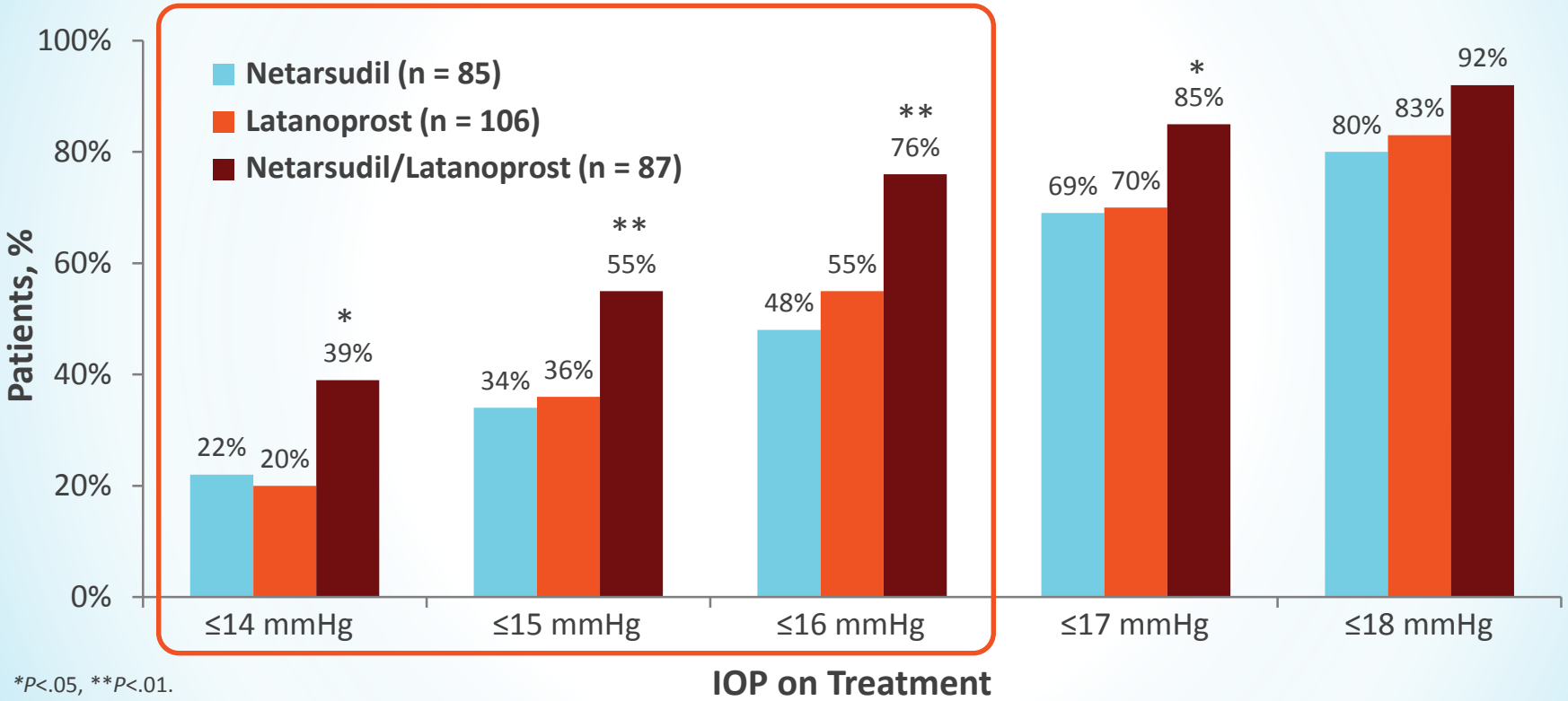
Lewis RA, et al. *Br J Ophthalmol*. 2016;100(3):339-344.

MERCURY 1, 12-Month Netarsudil/Latanoprost vs Individual Components (n = 718)



Source: http://investors.aeriepharma.com/events-and-presentations.

At Month 12: Percentage of Patients with IOP Reduced to 18 mmHg or Lower



*P<.05, **P<.01.

Source: http://investors.aeriepharma.com/events-and-presentations.

12 Month Phase III Safety Profile of Netarsudil vs Latanoprost vs Netarsudil/Latanoprost

Adverse Events (≥5.0% in any group)	Netarsudil/ Latanoprost N = 238	Netarsudil n = 243	Latanoprost N = 237
* **Eye Related**			
Conjunctival Hyperemia	150 (63.0%)	125 (51.4%)	52 (21.9%)
Conjunctival Hemorrhage	31 (13.0%)	44 (18.1%)	3 (1.3%)
Cornea Verticillata	42 (17.6%)	33 (13.6%)	0
Eye Pruritus	27 (11.3%)	22 (9.1%)	3 (1.3%)
Punctate Keratitis	12 (5.0%)	18 (7.4%)	10 (4.2%)
Lacrimation Increased	17 (7.1%)	20 (8.2%)	1 (0.4%)
Visual Acuity Reduced	13 (5.5%)	13 (5.3%)	6 (2.5%)
Vision Blurred	11 (4.6%)	15 (6.2%)	3 (1.3%)
Blepharitis	14 (5.9%)	8 (3.3%)	5 (2.1%)
Administration Site Conditions			
Instillation Site Pain	55 (23.1%)	60 (24.7%)	18 (7.6%)

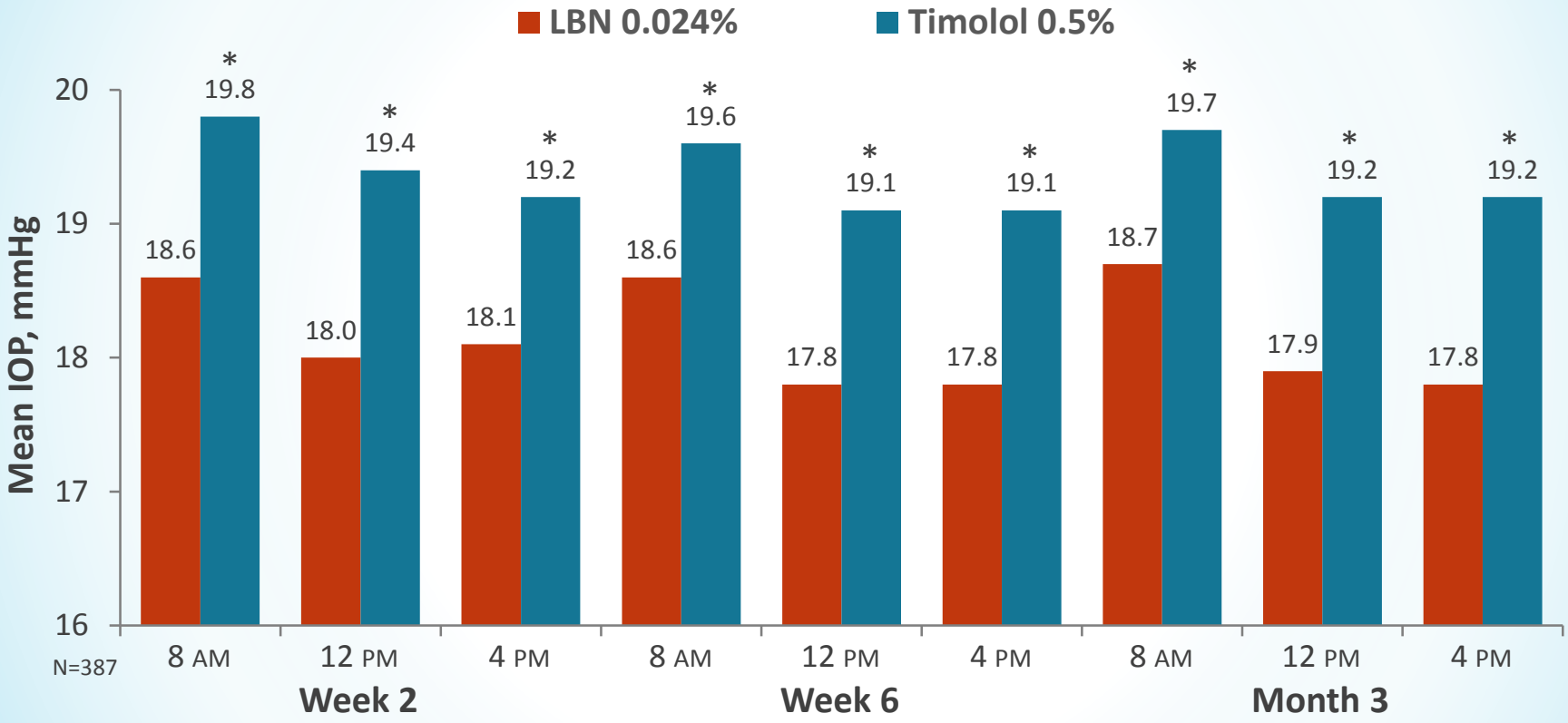
Grade	Image	Description
0		None/Normal
1		Mild
2		Moderate
3		Severe

*70% scored as mild by biomicroscopy

*Reported as adverse events.

Source: http://investors.aeriepharma.com/events-and-presentations.

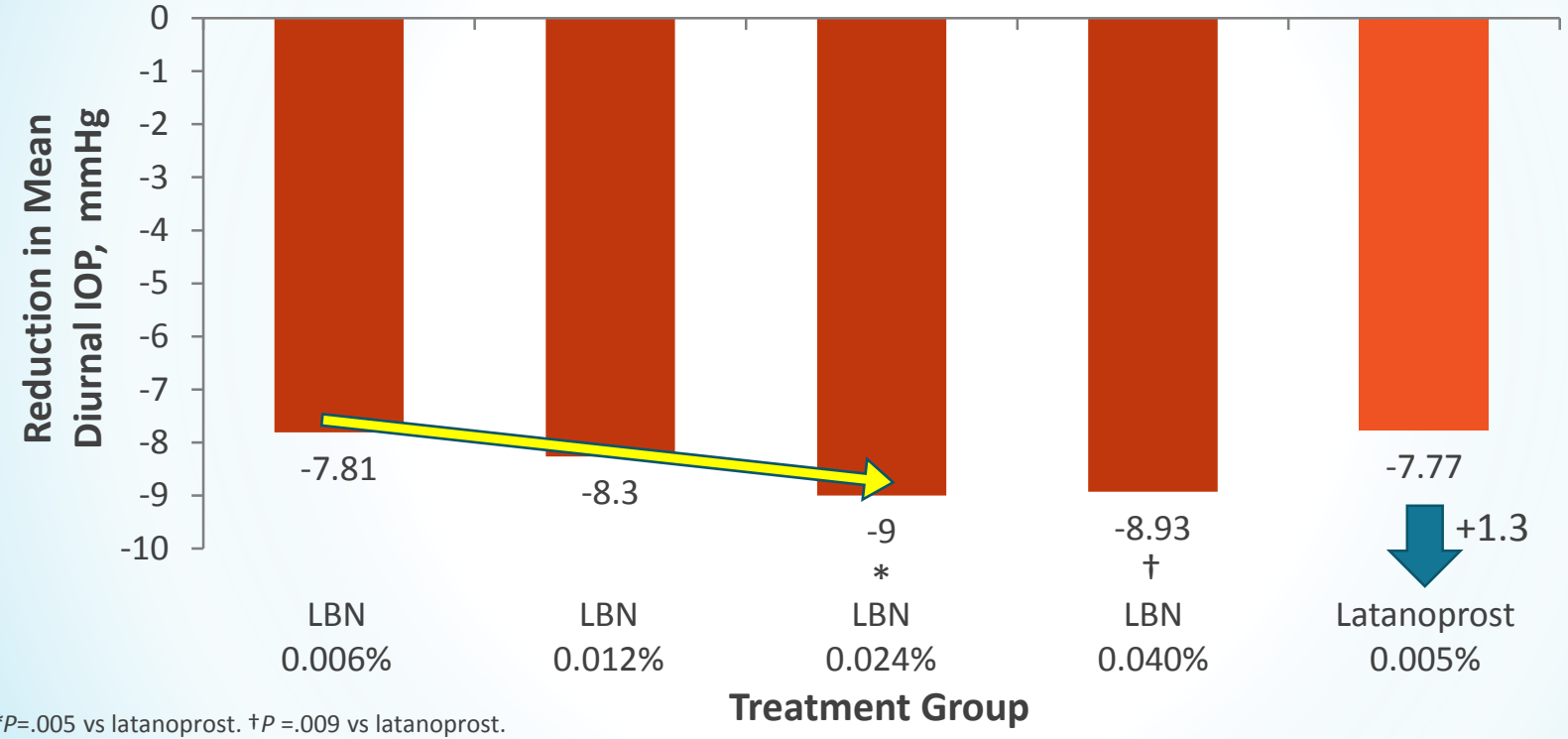
Latanoprostene Bunod (LBN), Phase III Apollo Study



Weinreb RN, et al. *Ophthalmol*. 2016;123(5):965-973.

*$P \leq 0.002$ versus timolol at the same assessment point.

3-Month Latanoprostene Bunod, Voyager Phase III Trial (N = 396)



**P*=.005 vs latanoprost. †*P* =.009 vs latanoprost.

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

Safety: 12-Month Latanoprostene Bunod Treatment in Japanese Subjects: The Jupiter Study

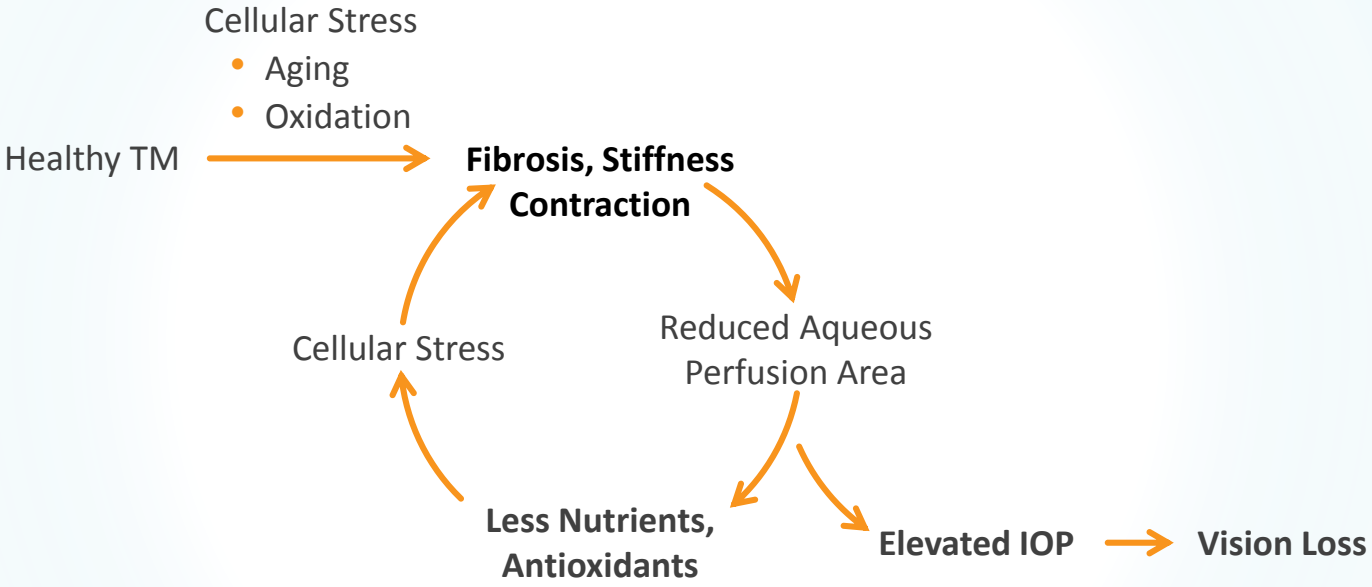
Incidence of Ocular Treatment-Emergent Adverse Events Occurring in at Least 1% of Subjects in the Study Eye or the Treated Fellow Eye (Safety Population)

Adverse Events	Study Eye (N = 130) n (%)	Treated Fellow Eye (N = 126) n (%)
≥1 Ocular AE	76 (58.5)	78 (61.9)
≥1 Treatment-Related Ocular AE	62 (47.7)	61 (48.4)
Eye Disorders		
Conjunctival Hyperemia*	23 (17.7)	21 (16.7)
Growth of Eyelashes	21 (16.2)	21 (16.7)
Eye Irritation	15 (11.5)	15 (11.9)
Eye Pain	13 (10.0)	13 (10.3)
Iris Hyperpigmentation	5 (3.8)	5 (4.0)
Blepharal Pigmentation	4 (3.1)	4 (3.2)
Blepharitis	3 (2.3)	3 (2.4)
Eye Pruritus	3 (2.3)	3 (2.4)
Asthenopia	3 (2.3)	2 (1.6)
Conjunctival Hemorrhage	2 (1.5)	3 (2.4)

*Reported as adverse events.

Kawase K, et al. *Adv Ther. 2016*;33(9):1612-1627.

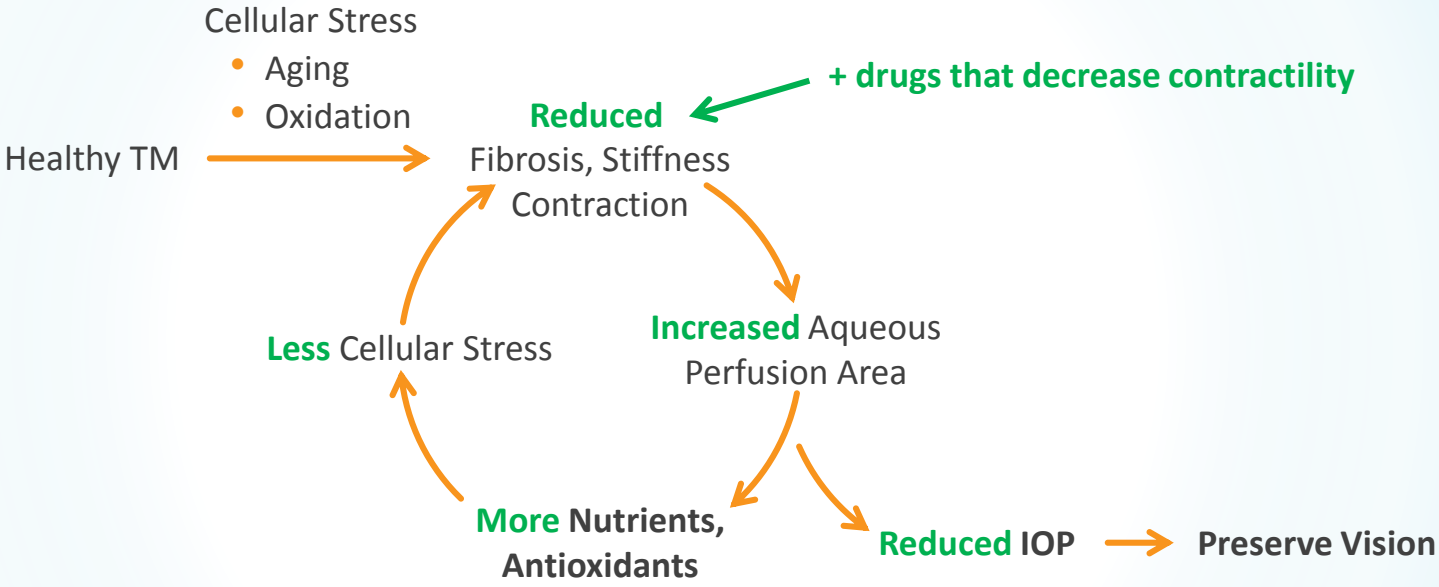
Disease Modification: Addressing the Major Contributors to Elevated IOP and Vision Loss



Progressive Degeneration of the Trabecular Meshwork Drives Elevated IOP and Vision Loss in Glaucoma

Wang SK, et al. *Clin Ophthalmol*. 2014;9;8:883-890. He Y, et al. *Clin Ophtalmol*. 2008;58(11):3366-3376. Li G, et al. *Eur J Pharmacol*. 2016; Sept 15;787:2031.

Outflow Drugs Have the Potential to Improve Health of TM in Patients With Glaucoma



Reducing Fibrosis, Increasing Trabecular Outflow Could Stop Degeneration of Outflow Tissues in POAG

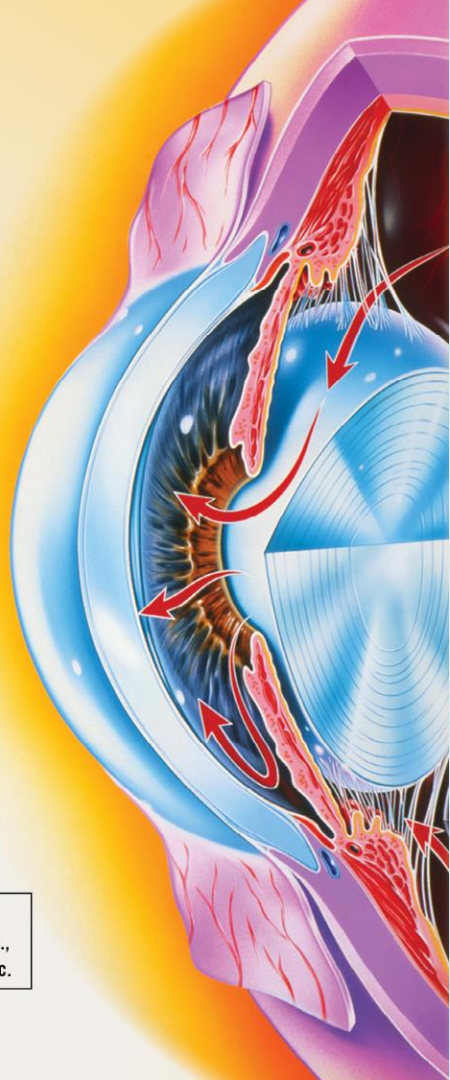
Wang SK, et al. *Clin Ophthalmol*. 2014;9;8:883-890. He Y, et al. *Clin Ophtalmol*. 2008;58(11):3366-3376. Li G, et al. *Eur J Pharmacol*. 2016; Sept 15;787:2031.

Summary: Take Home Messages

- Conventional outflow dysfunction causes ocular hypertension
- Effectively lowering IOP preserves vision
- No medication currently available primarily targets the conventional outflow pathway
- One drug that relaxes the trabecular meshwork and increases conventional outflow may soon be available, and another was recently approved for patients
  - Safe
  - Efficacious (additive with current medications)
  - Therapeutic potential
    - Increase functionality of trabecular meshwork (i.e. ability to dampen IOP fluctuations)
    - Increase blood flow to optic nerve head (evidence of vascular dysfunction in some forms of glaucoma)

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

PHARMACOLOGIC & SURGICAL ADVANCES FOR REFRACTORY POAG OR NON-ADHERENCE



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This activity is supported by independent educational grants from **Aerie Pharmaceuticals, Inc.**, **Alcon Pharmaceuticals Ltd.** and **Bausch & Lomb, Inc.**

MECHANISMS OF
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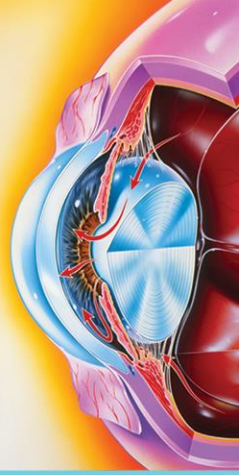
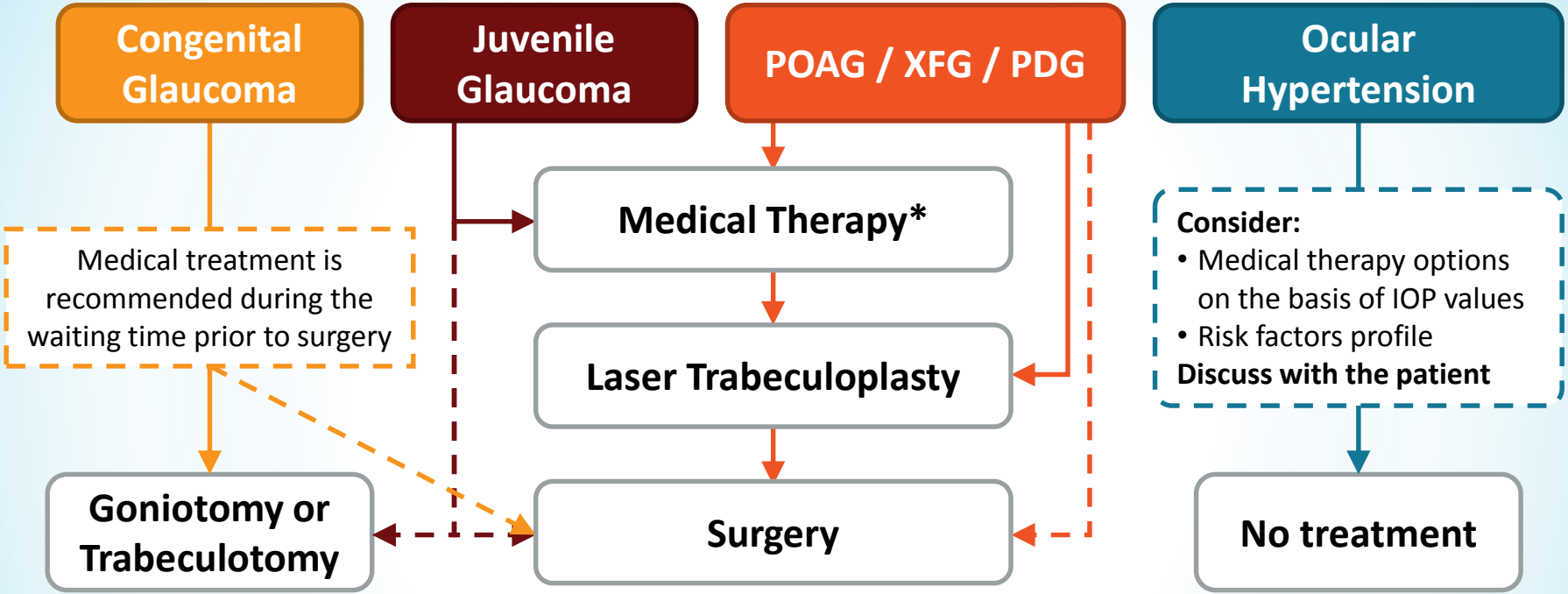


Mechanisms of Pressure Relief in Glaucoma: Pharmacologic & Surgical Advances for Refractory POAG or Non-Adherence

Steven J. Gedde, MD

John G. Clarkson Chair in Ophthalmology
Professor of Ophthalmology
Bascom Palmer Eye Institute
University of Miami Health System
Miami, FL

Treatment Algorithm



If the above procedures not successful or feasible, consider repeat filtration surgery with anti-metabolites or long-tube drainage implant/cyclodestructive procedure

*Up to 2-3 different drugs. Do not add a drug to a non-effective one; consider switching.

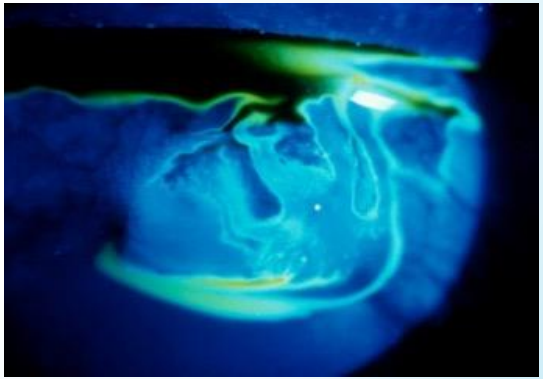
POAG, primary open-angle-glaucoma; XFG, exfoliative/pseudoexfoliative glaucoma; PDG, pigment dispersion glaucoma.

Incisional Glaucoma Surgery

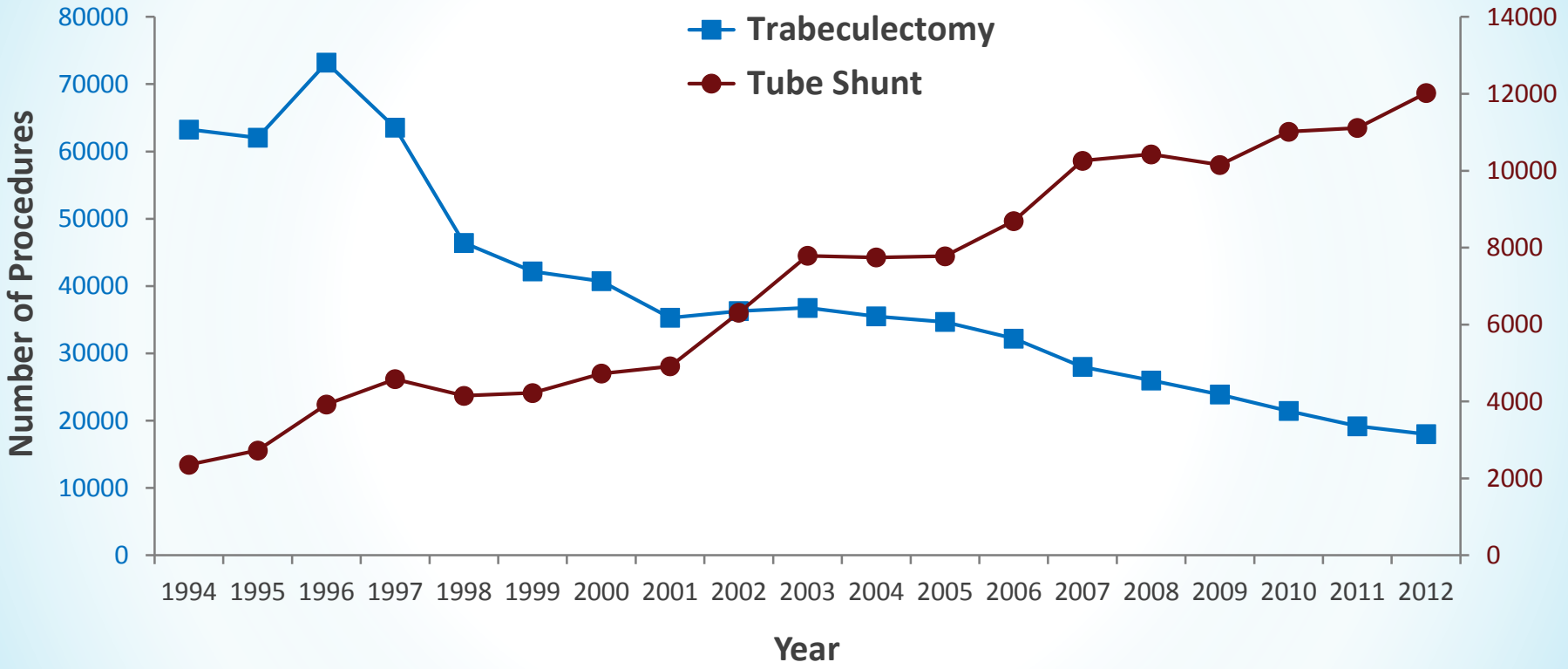
- Traditional glaucoma surgery
  - Trabeculectomy
  - Aqueous shunts
  - EX-PRESS® implant
- Nonpenetrating glaucoma surgery
  - Deep sclerectomy
  - Viscocanalostomy
  - Canaloplasty
- Endoscopic cyclophotocoagulation (ECP)
- Minimally invasive glaucoma surgery (MIGS)
  - Ab interno trabeculectomy (Trabectome®)
  - Trabecular microbypass stent (iStent®)
  - Gonioscopy-assisted transluminal trabeculotomy (GATT)
  - Kahook Dual Blade
  - CyPass® Micro-Stent
  - XEN® Gel Stent
  - Trab™360

Trabeculectomy

- Scleral fistula allows drainage of aqueous humor into subconjunctival space creating a filtering bleb
- Only titratable glaucoma procedure
- Success enhanced with use of antifibrotic agents (MMC, 5-FU)
- Growing concern about bleb-related complications (leaks, infection, dysesthesia)



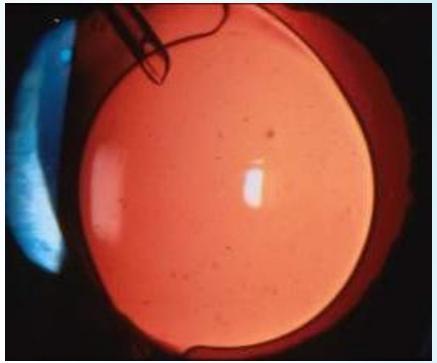
Surgical Trends



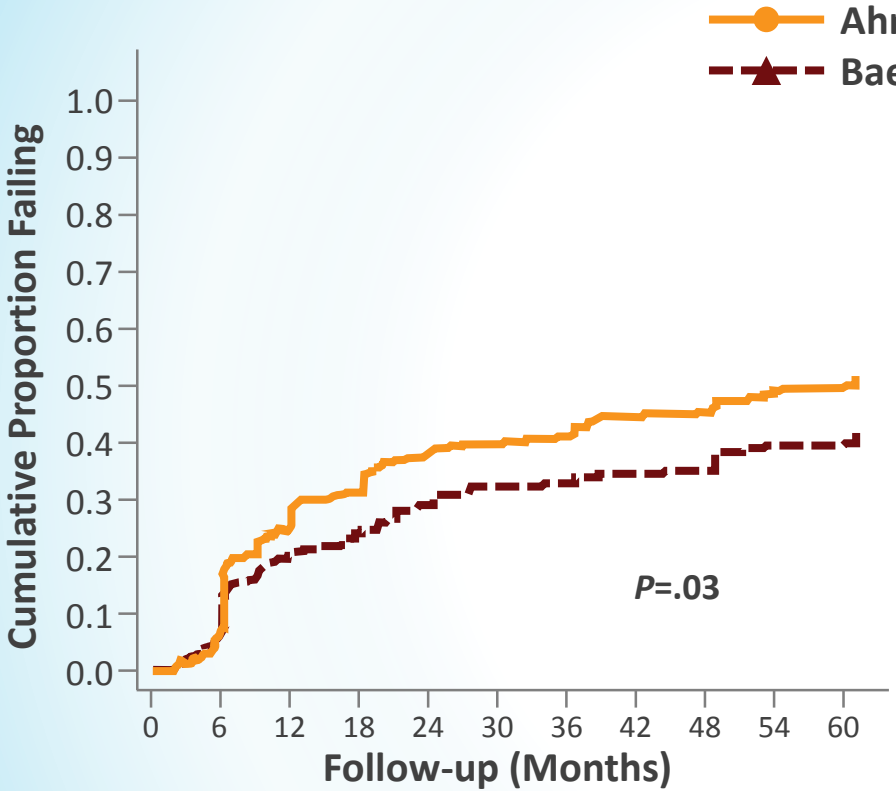
Arora KS, et al. *Ophthalmol*. 2015;122:1615-1624.

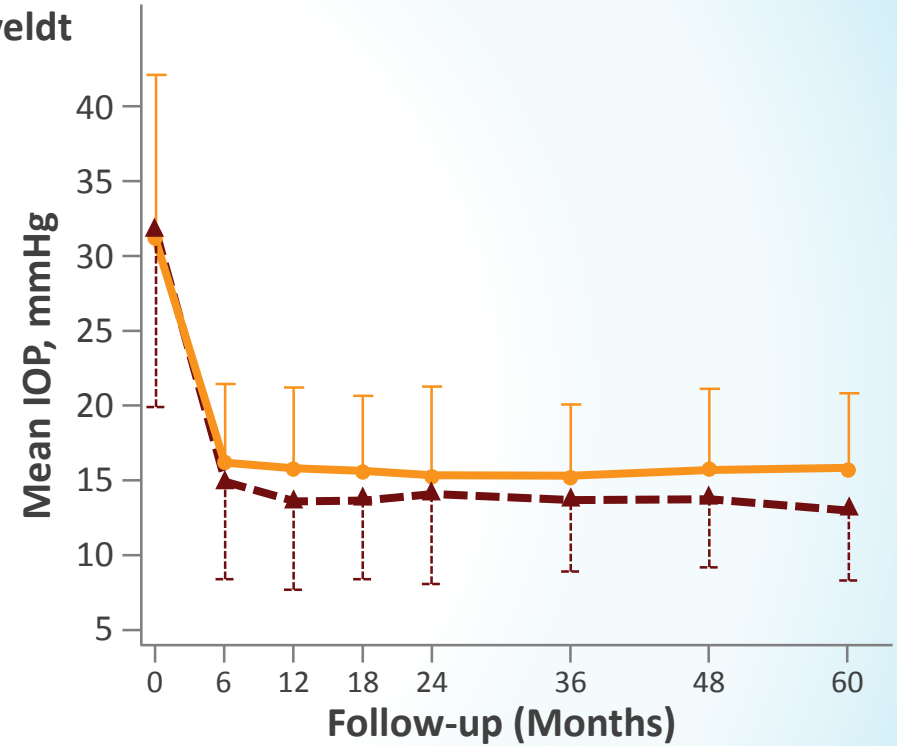
Aqueous Shunts

- Silicone tube shunts aqueous humor to end plate located in equatorial region of globe
- Design
  - Valved: Ahmed, Krupin
  - Nonvalved: Baerveldt, Molteno
- Traditionally used in eyes at high risk for filtration failure, but indications are expanding



ABC/AVB Studies

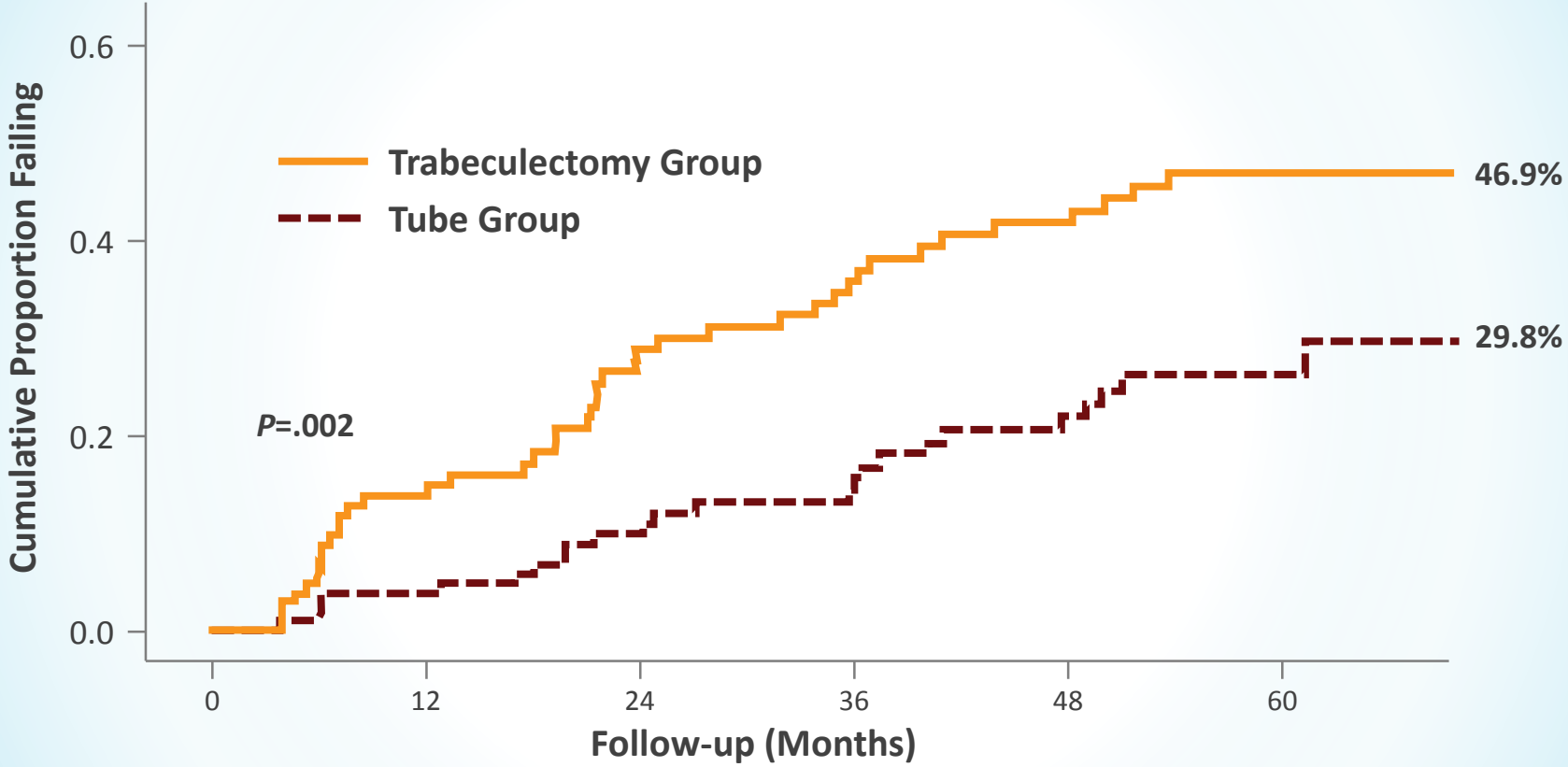




Ahmed (n)	267	222	221	189	193	174	147	133
Baerveldt (n)	247	212	205	179	178	161	137	133

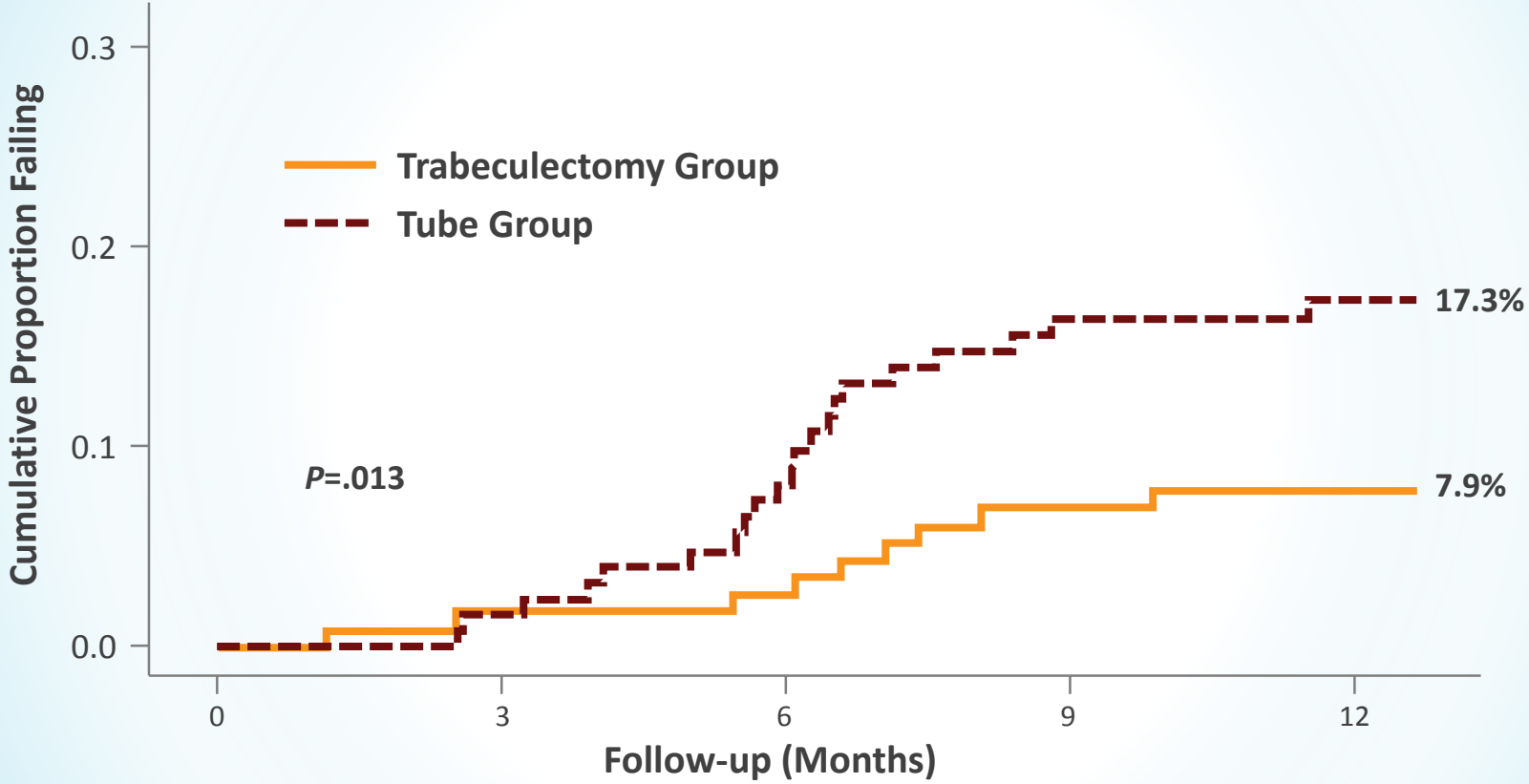
Christakis PG, et al. *Am J Ophthalmol*. 2017;176:118-126.

TVT Study



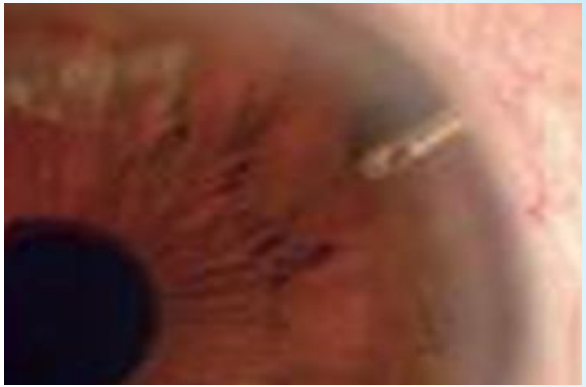
Gedde SJ, et al. *Am J Ophthalmol*. 2012;153:789-803.

PTVT Study


Cumulative Proportion Failing
0.3
0.2
0.1
0.0
Trabeculectomy Group
Tube Group
P=.013
17.3%
7.9%
0
3
6
9
12
Follow-up (Months)

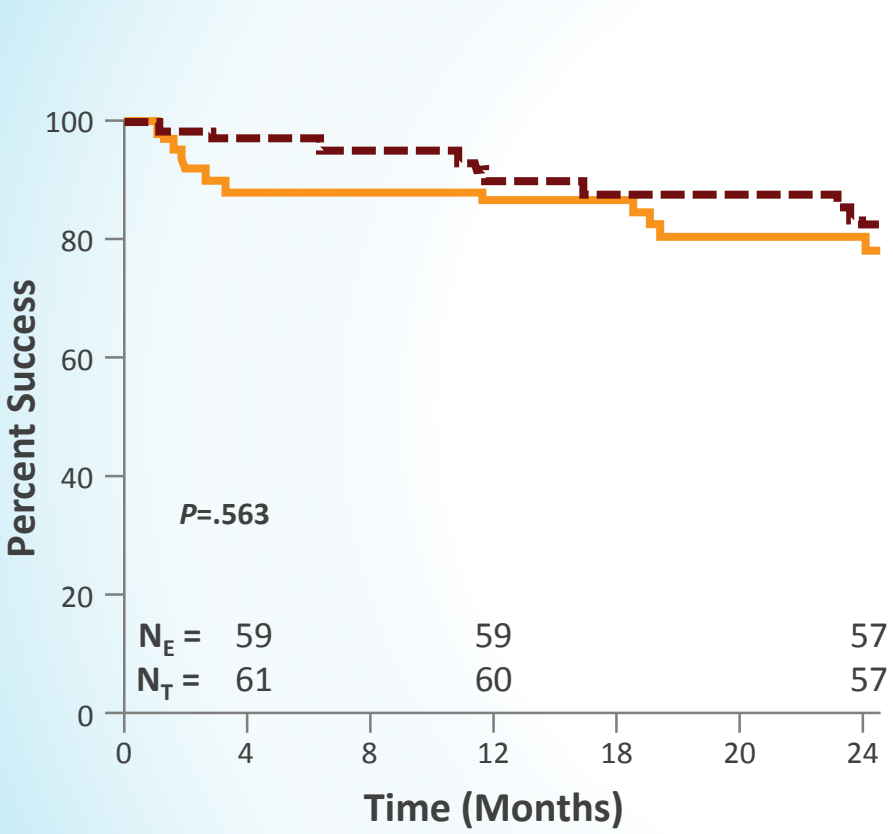
EX-PRESS® Implant

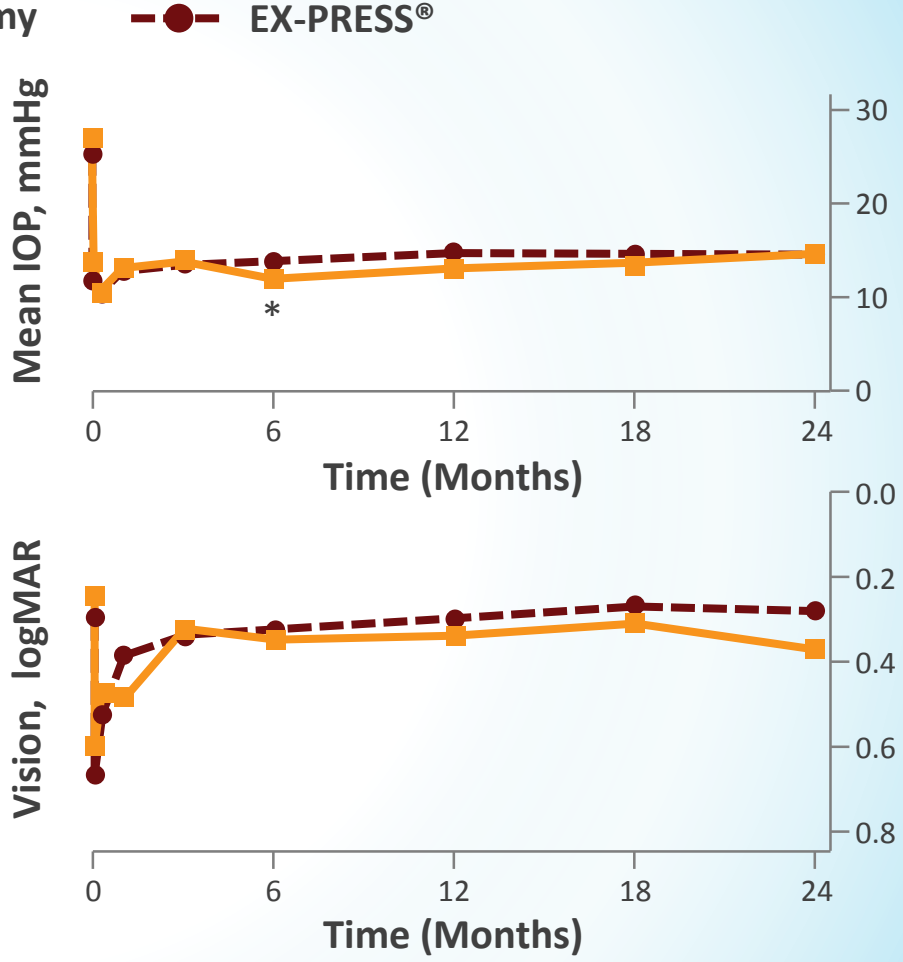
- Nonvalved, stainless steel tube
- No sclerostomy or iridectomy required
- High rate of hypotony and extrusion prompted placement under a scleral flap
- Similar long-term safety and efficacy compared with trabeculectomy



Courtesy of Marlene Moster.

XVT Study

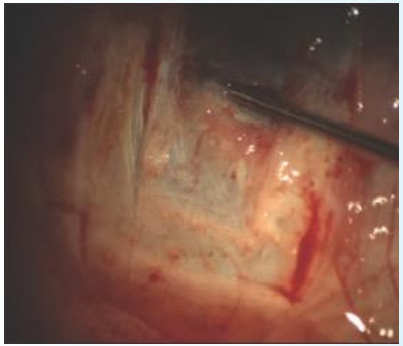




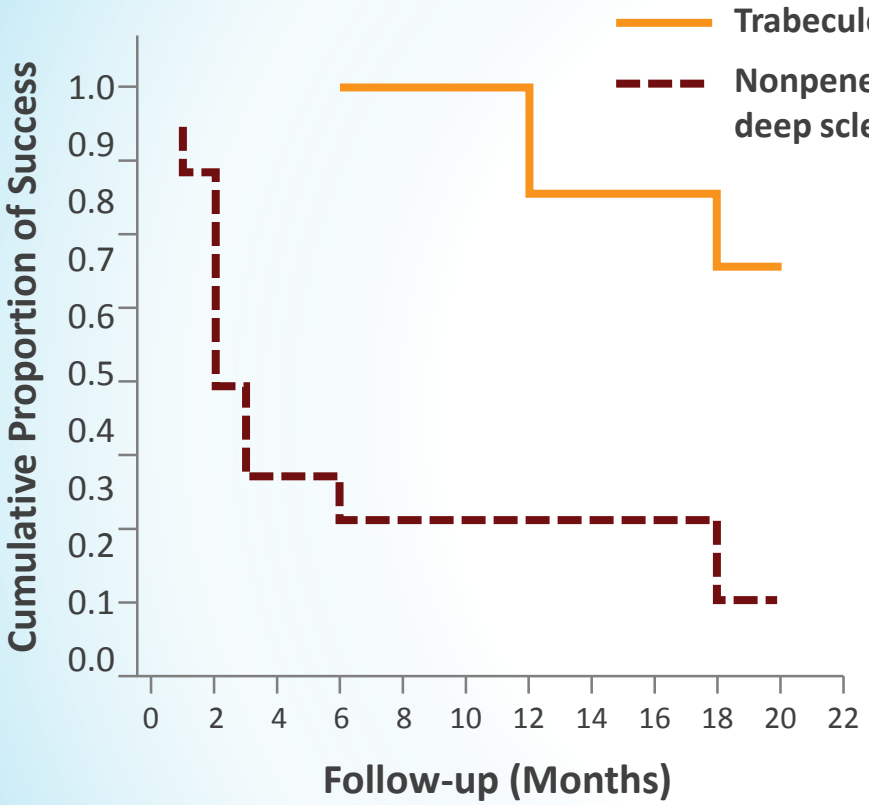
Netland PA, et al. *Am J Ophthalmol*. 2014;157:433-440.

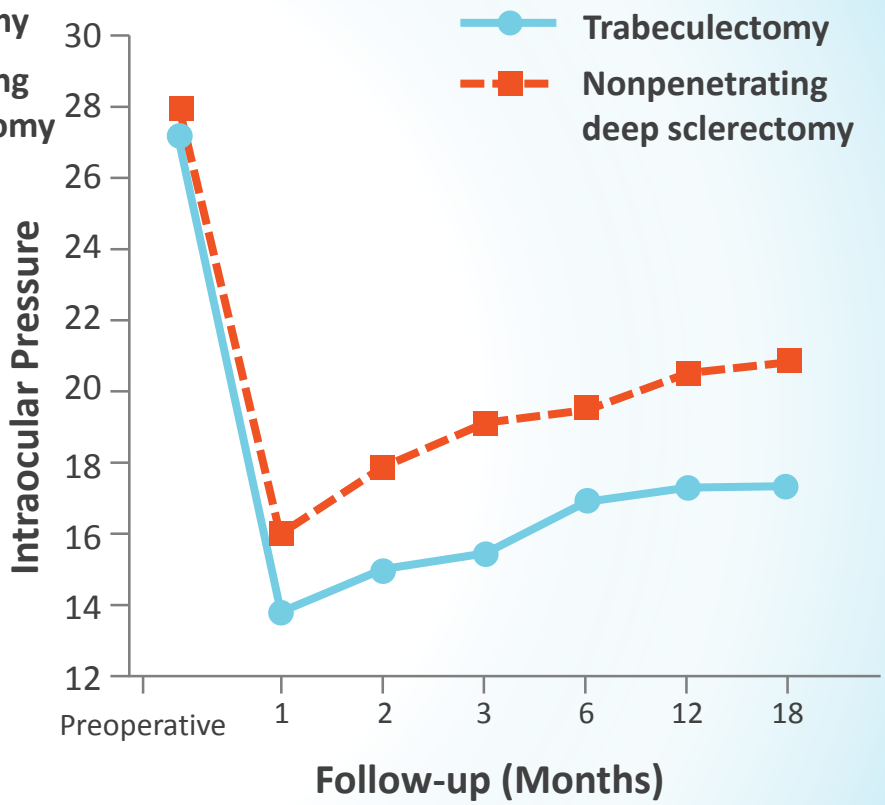
Nonpenetrating Glaucoma Surgery

- Excision of corneoscleral tissue under scleral flap leaves thin window of trabecular meshwork (TM) and Descemet's membrane to provide resistance to aqueous outflow
- Reduces risk of hypotony
- Technically difficult
- Types:
  - Deep sclerectomy
  - Viscocanalostomy
  - Canaloplasty



Nonpenetrating Glaucoma Surgery



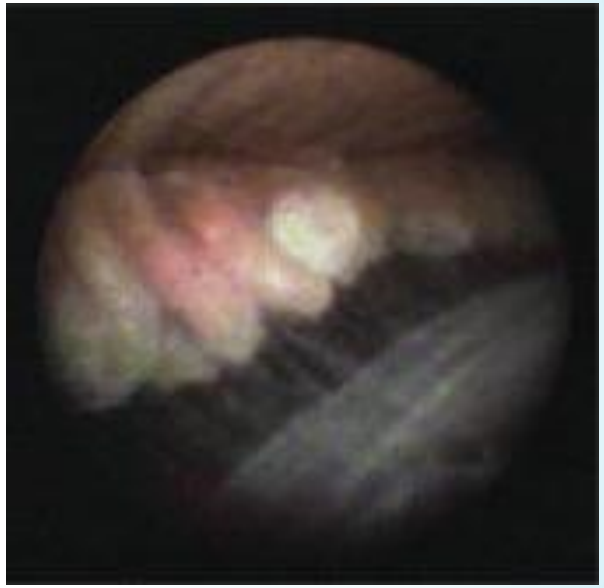


Chiselita D. *Eye (Lond).* 2001;15:197-201.

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

Endoscopic Cyclophotocoagulation (ECP)

- Treatment of ciliary processes under direct visualization with endoscopic camera and laser
- Frequently combined with phaco
- Provides moderate long-term IOP reduction
- CME is most common cause of vision loss



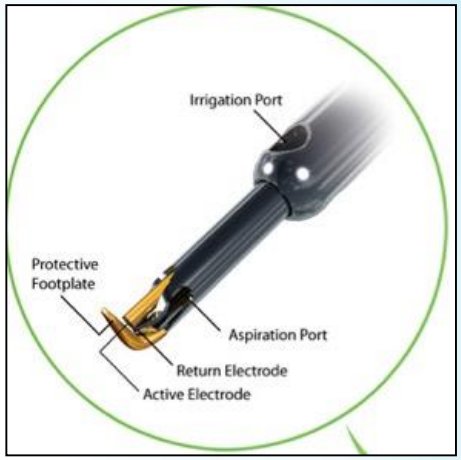
Minimally Invasive Glaucoma Surgery (MIGS)

- Newer group of glaucoma procedures characterized by:
  - Ab interno approach
  - Minimal trauma to tissue
  - Modest efficacy
  - Excellent safety profile
  - Rapid postoperative recovery
- Frequently performed in combination with phaco
- Growing in popularity

Saheb H, et al. *Curr Opin Ophthalmol*. 2012;23:96-104.

Ab Interno Trabeculectomy (Trabectome®)

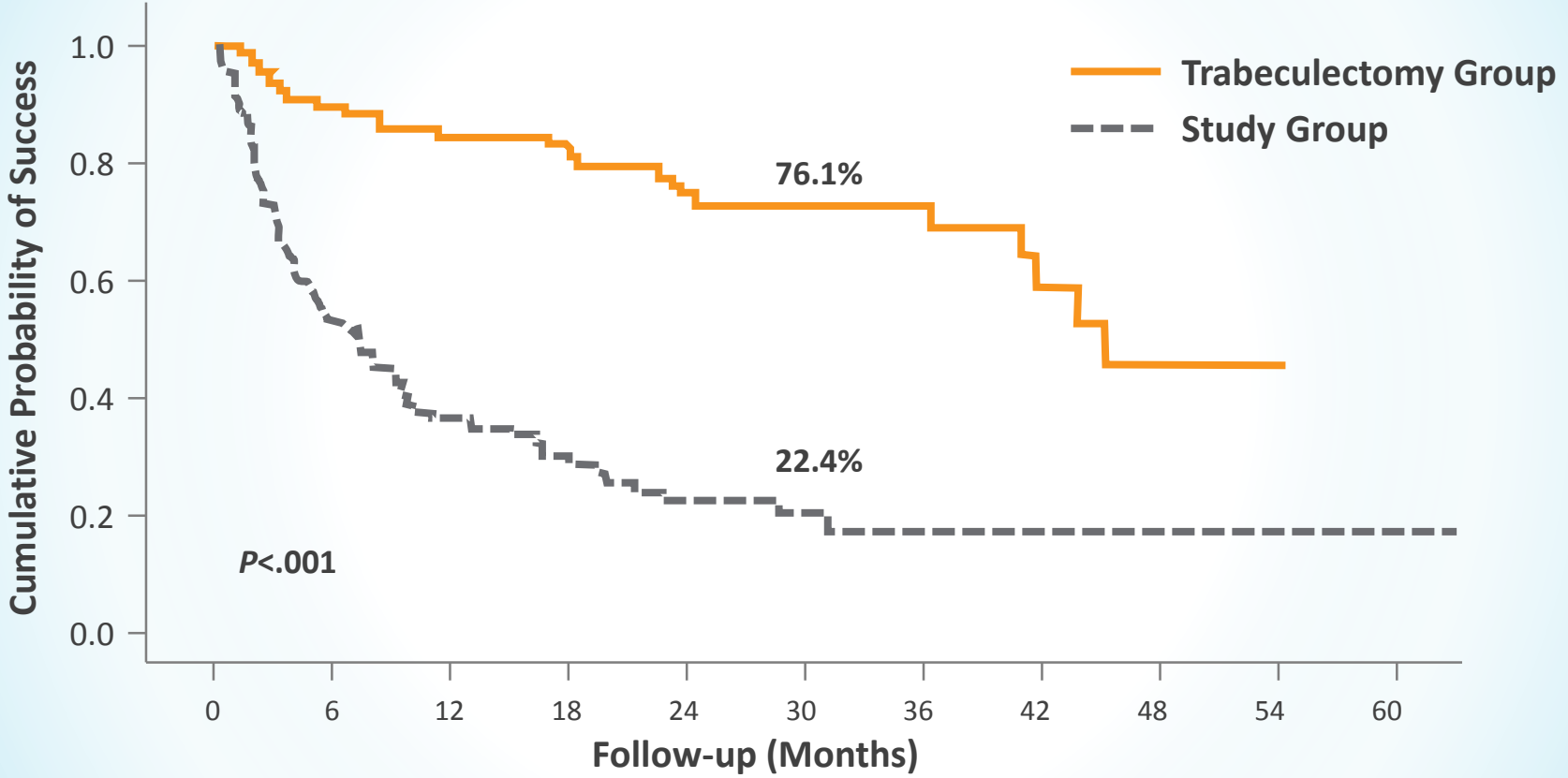
- Electrocautery removes a strip of TM and Schlemm's canal
- Meta-analysis
  - 31% reduction in IOP
  - 66% success rate at 2 years
- Prior laser trabeculoplasty and trabeculectomy does not appear to influence results



Courtesy of Brian Francis.

Kaplowitz K, et al. *Br J Ophthalmol*. 2016;100:594-600.

Ab Interno Trabeculectomy (Trabectome®)



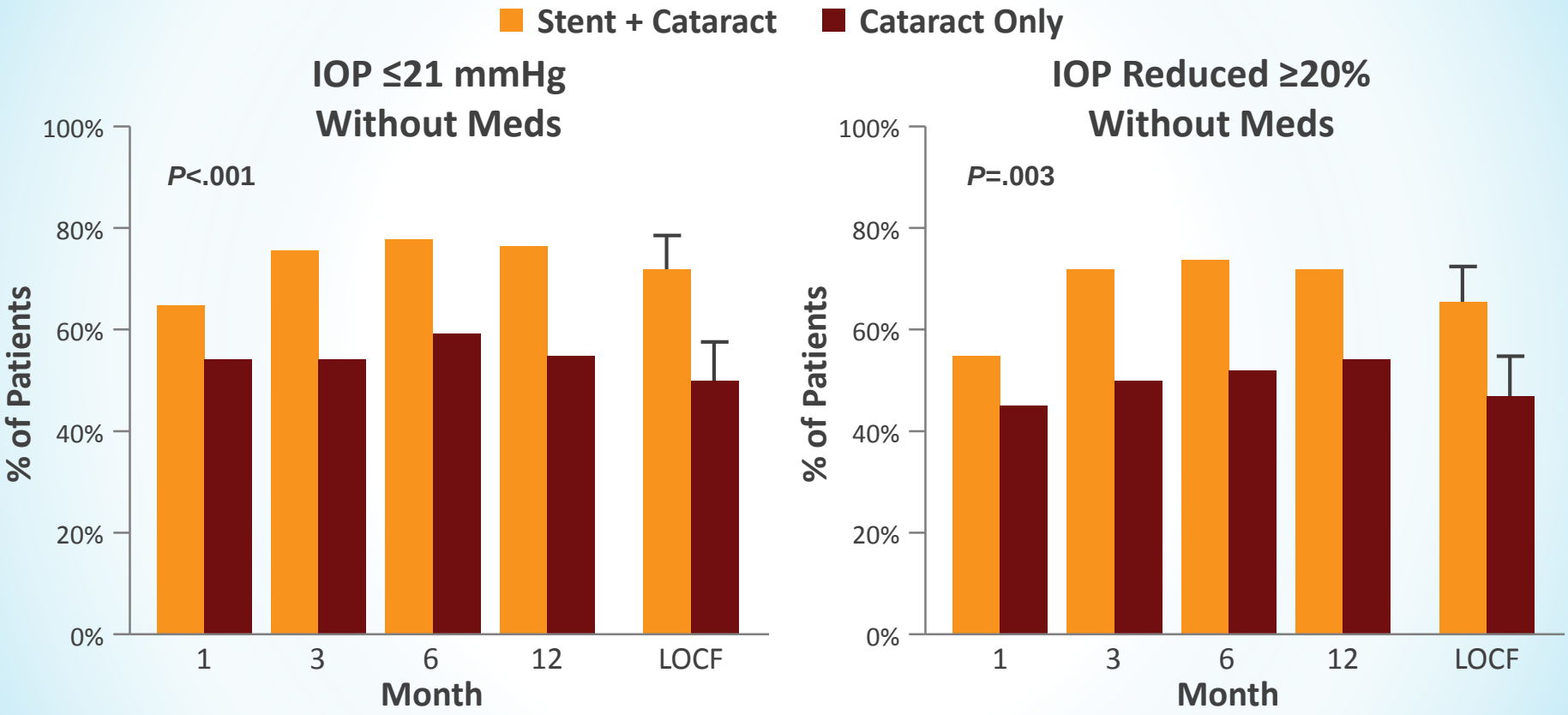
Jea SY, et al. *Ophthalmol*. 2012;119:36-42.

Trabecular Micro-Bypass Stent (iStent®)

- Snorkel-shaped device made of heparin-coated titanium is inserted into Schlemm's canal
- FDA-approved for use with CE in patients with mild-moderate glaucoma
- RCTs show greater reduction in IOP and medical therapy than phaco alone
- Multiple stents may provide greater IOP reduction than single stent

Courtesy of Ike Ahmed.

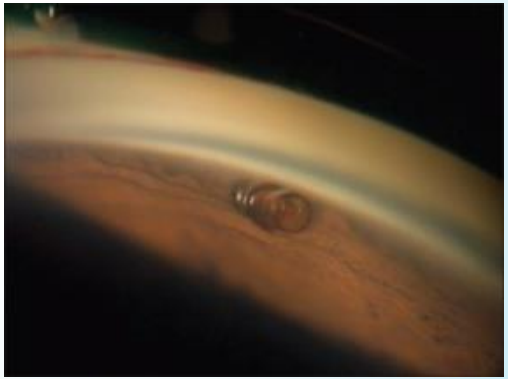
Trabecular Micro-Bypass Stent (iStent®)



Samuelson TW, et al. *Ophthalmol*. 2011;118:459-467.

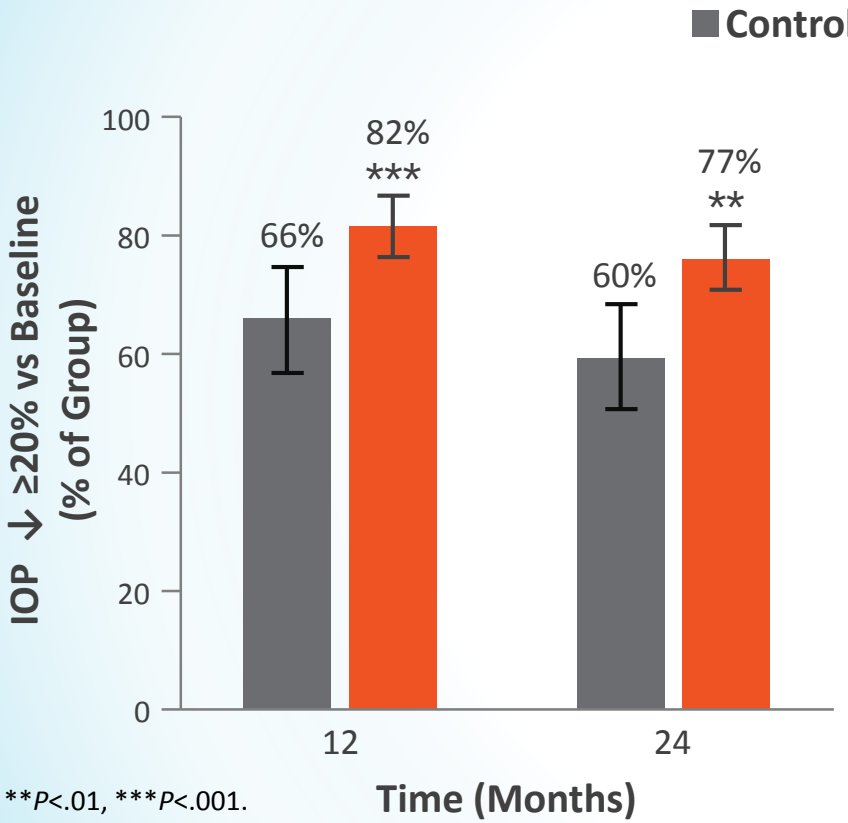
CyPass® Micro-Stent

- Flexible 6.35 mm fenestrated micro-stent with internal lumen of 300 micron
- Inserted with a guidewire
- Shunts aqueous humor from the AC to the suprachoroidal space
- Pressure gradient drives flow through device

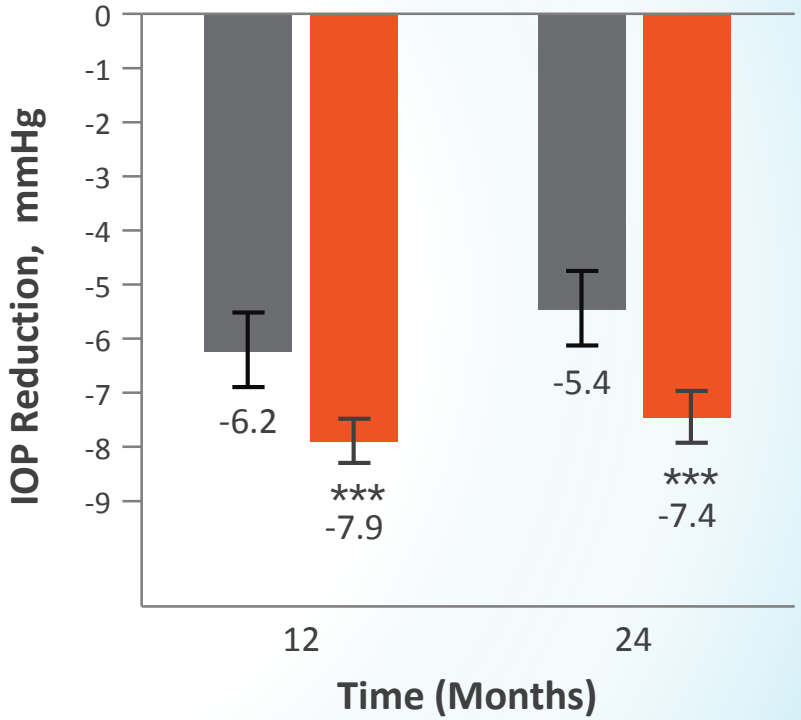


Courtesy of Ike Ahmed.

CyPass® Micro-Stent



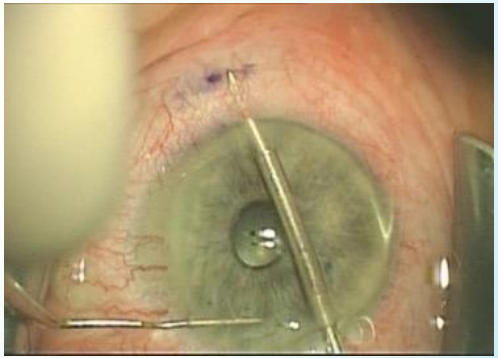
**P<.01, ***P<.001.



Vold S, et al. *Ophthalmol*. 2016;123:2103-2112.

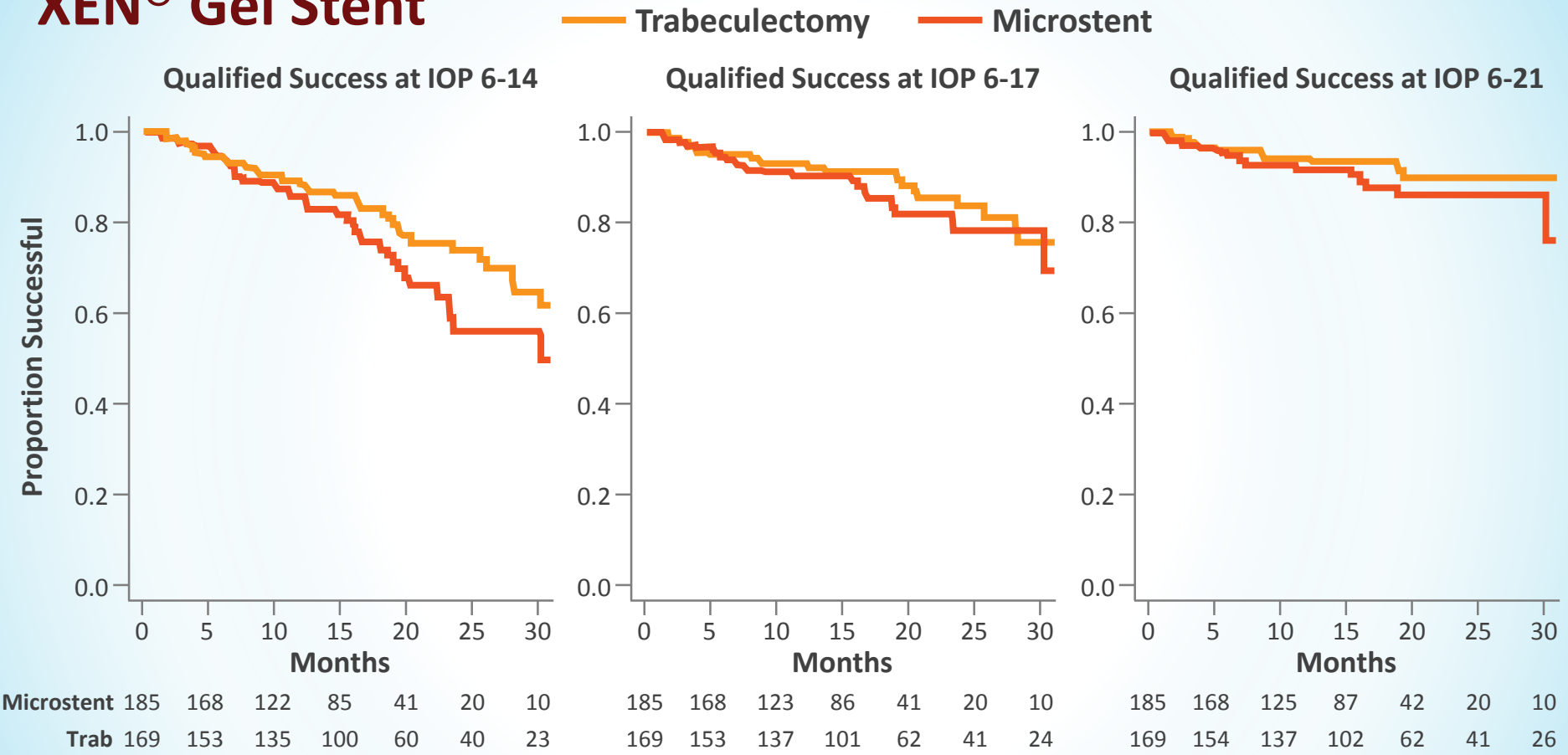
XEN® Gel Stent

- 6 mm tubular collagen implant placed translimbally
- 27-gauge needle inserter
- Drains aqueous into subconjunctival space
- High needling rate (32%-47%)



Courtesy of Joseph Panarelli.

XEN® Gel Stent



Schlenker MB, et al. *Ophthalmol*. 2017;124(11):1579-1588.

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

Gonioscopy-Assisted Transluminal Trabeculotomy (GATT)

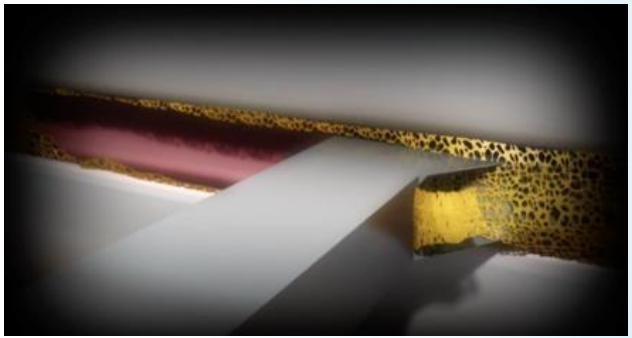
- Microcatheter or suture used to perform 360° trabeculotomy
- Hyphema is most common complication

Courtesy of Davinder Grover.

GATT, gonioscopy-assisted transluminal trabeculotomy.

Kahook Dual Blade

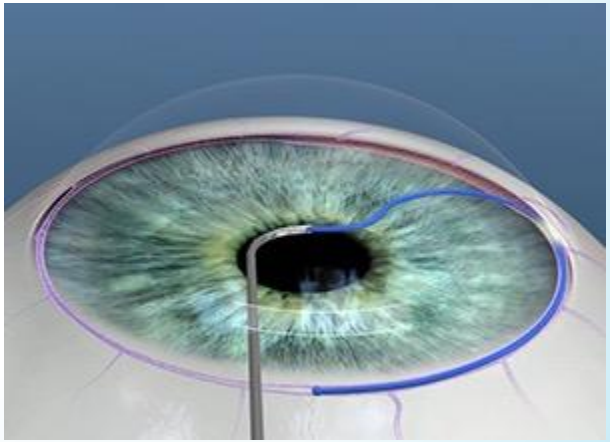
- Removal of TM using dual blade
- Single use ophthalmic blade
- Blade composition
  - Pointed tip easily pierces TM
  - Ramp elevates and stretches TM
  - Dual blade excises strip of TM
  - Foot plate prevents damage to collateral tissue



Courtesy of Malik Kahook.

TRAB™360

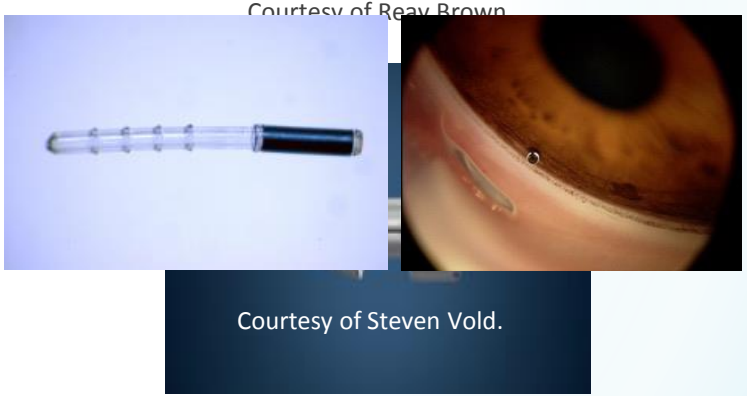
- Cannula used to incise TM and introduce flexible trabeculotome 180°
- Filament is retracted back into device and procedure is repeated in other direction
- 360° goniotomy performed



Investigational

- Translimbal implant
  - InnFocus MicroShunt®
- Schlemm's canal implants
  - Hydrus™ Microstent
  - iStent inject®
- Suprachoroidal shunts
  - Gold Micro Shunt
  - iStent Supra®

Courtesy of Reay Brown



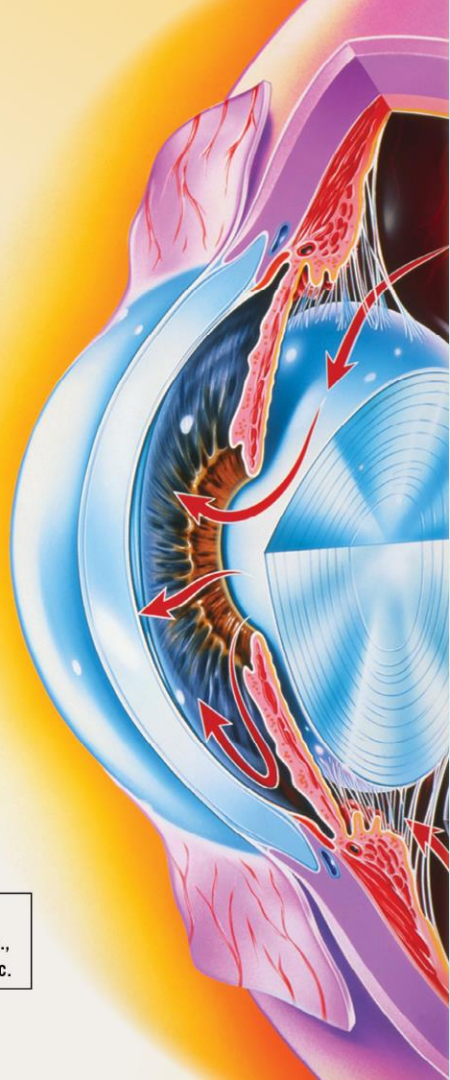
Courtesy of Ike Ahmed.

In Summary

- Surgical options for managing glaucoma are rapidly expanding
- Traditional glaucoma surgery (tubes and trabs) provide excellent IOP reduction, but surgical complications are common (generally transient and self-limited)
- MIGS are newer procedures that offer an improved safety profile, but reduced efficacy

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

PHARMACOLOGIC & SURGICAL ADVANCES FOR REFRACTORY POAG OR NON-ADHERENCE



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This activity is jointly provided by Postgraduate Institute for Medicine and HealthmattersCME.

This activity is supported by independent educational grants from **Aerie Pharmaceuticals, Inc.**, **Alcon Pharmaceuticals Ltd.** and **Bausch & Lomb, Inc.**

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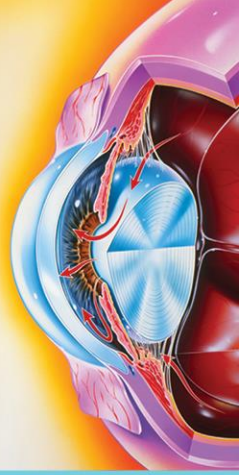


In the Pipeline: New Approaches to Drug Delivery for Glaucoma

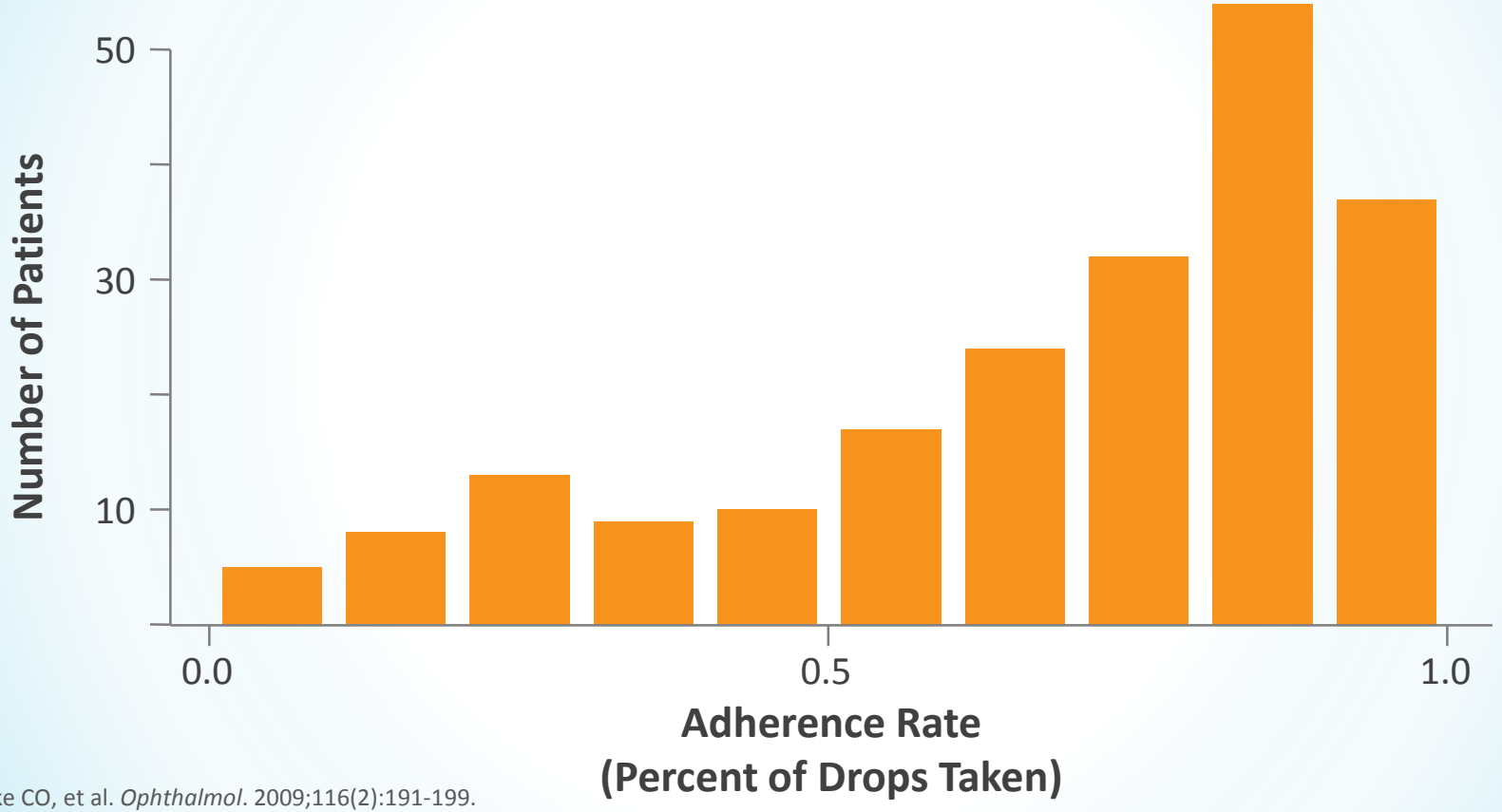
David S. Friedman, MD, MPH, PhD

Director, Dana Center for Preventive Ophthalmology
Wilmer Eye Institute, Alfred Sommer Professor of Ophthalmology
Johns Hopkins University School of Medicine
Professor, Department of International Health
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD

Modest Advances in Medical Therapy: Largely Stagnant Over Last 20 Years

- Combination therapies
- Preservative free

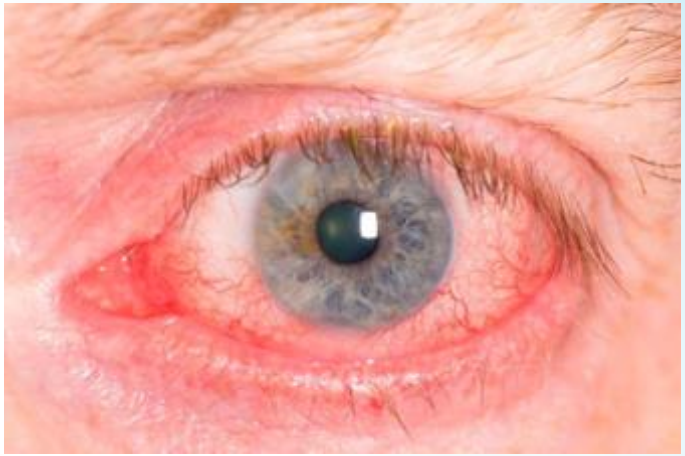
Adherence in Clinic Patients Monitored Electronically

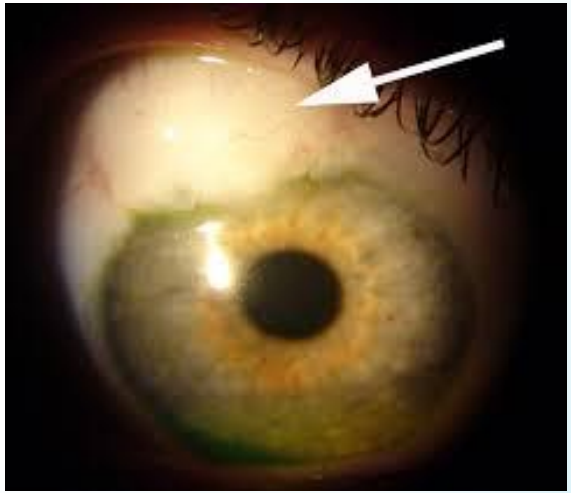


Okeke CO, et al. *Ophthalmol*. 2009;116(2):191-199.

Drops Are Not Ideal

- Half of new scripts are not filled after 6 months, low adherence
- Administrative errors
- Local and systemic side effects





Ideal Glaucoma Medical Treatment

- Patient-proof
- Few symptoms
- Can achieve the IOPs we need
- Cost effective

Drug Delivery Through a Scleral Ring

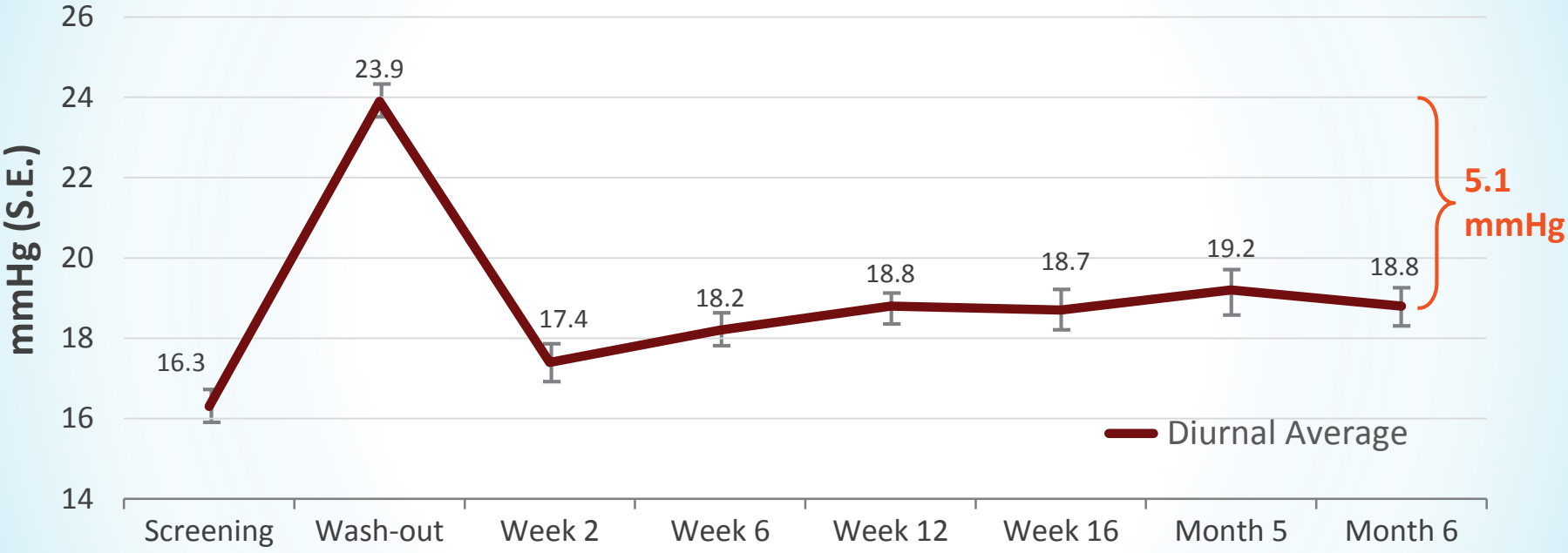
- Ability to incorporate drugs into polymer
- Phase 2 trials completed

Consistent Performance in Clinical Trials: Four Phase 1 (N = 73) and Four Phase 2 (N = 251)

Patient Acceptance	• Topical, comfortable (90%), well-retained (90% at 6 months)
Durable Efficacy	• One ring provides clinically significant IOP reduction for 6 months
Safety and Benefits	• Uneventful safety profile • Regulatory pathway: NDA in 2019
Market Value	• 85% of patient recommend insert • 80% of doctors prefer insert to drops
Future	• Validated platform for fixed combination glaucoma, allergy, dry eye, other pipeline

Goldberg I, et al. Poster presented at: World Glaucoma Congress; 2015 (Hong Kong).

Mean Diurnal IOP with Bimatoprost Insert: Phase I Efficacy Results (N = 26)



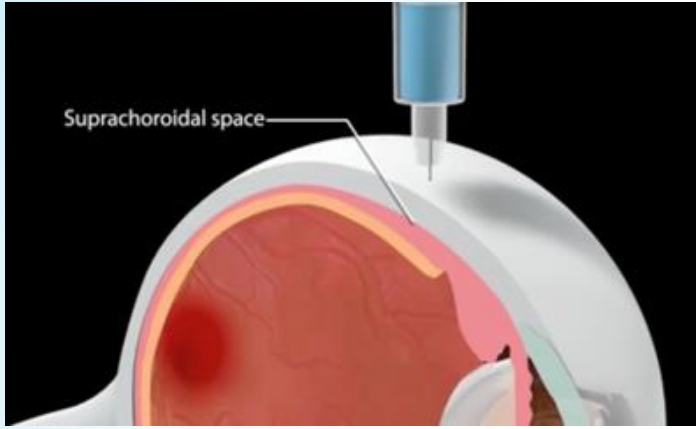
- Mean IOP reduction: 4.7 to 6.5 mmHg from washout

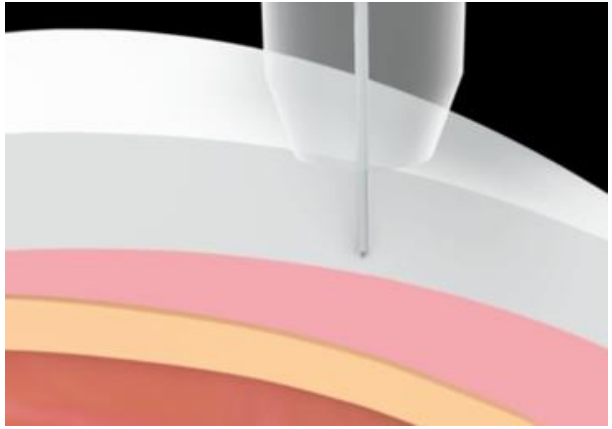
Goldberg I, et al. Poster presented at: World Glaucoma Congress; 2015 (Hong Kong).

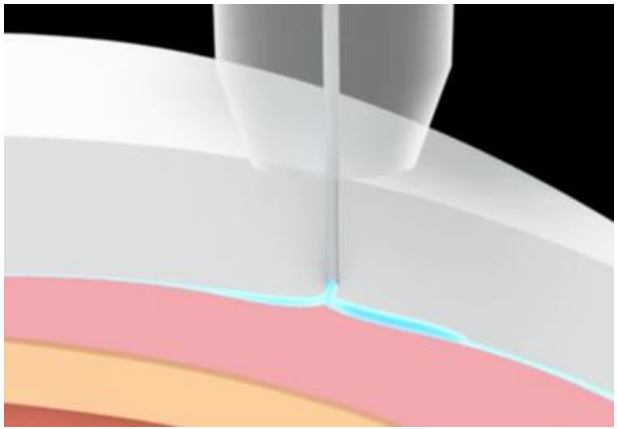
Scleral Ring Pros and Cons

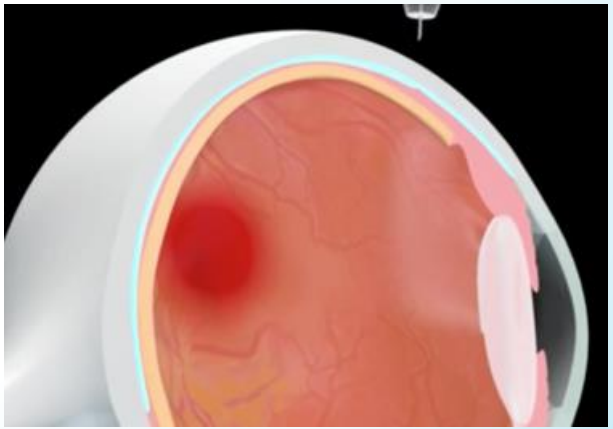
- Comfort???
- Cosmesis???
- Medication can be placed by the patient (no physician involvement needed)
- Possible compliance issues
- Local side effects???

Drug Delivery Into Suprachoroidal Space









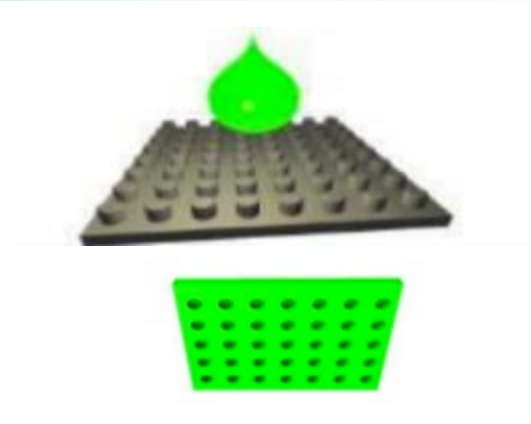
Ongoing Research

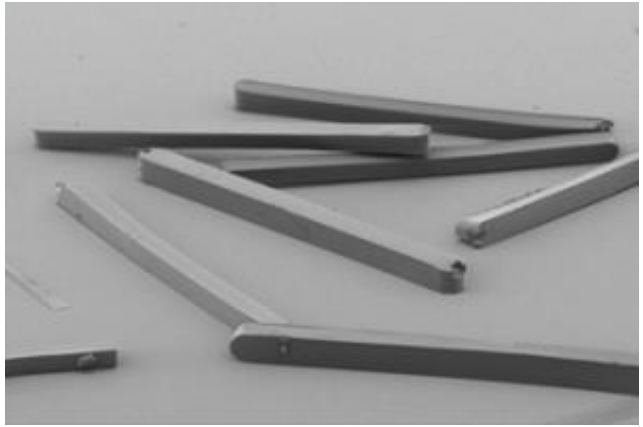
- Currently focused on macular edema and neovascular age-related macular degeneration
- One Phase I/II study completed
- Phase II and III studies on macular edema ongoing
- Injections **every 12 weeks**
- Planned research on delivery of glaucoma medicines using this technology

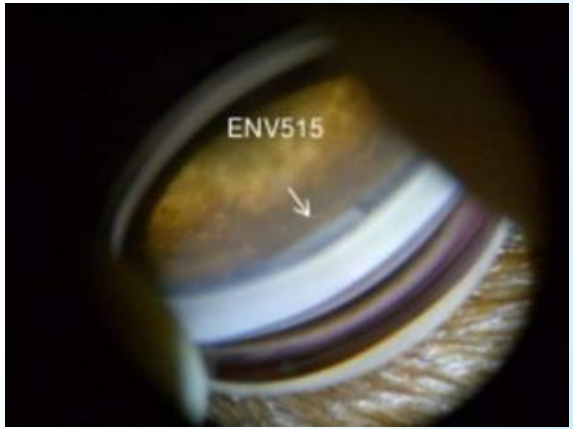
Suprachoroidal Delivery Pros and Cons

- Likely to eliminate many local side effects
- Low drug requirement
- Harm to retina and choroid unknown???
- Dosing frequency may exceed visit frequency
- Patient acceptance of “injection” unknown

Intracameral Injection of Printed Particles

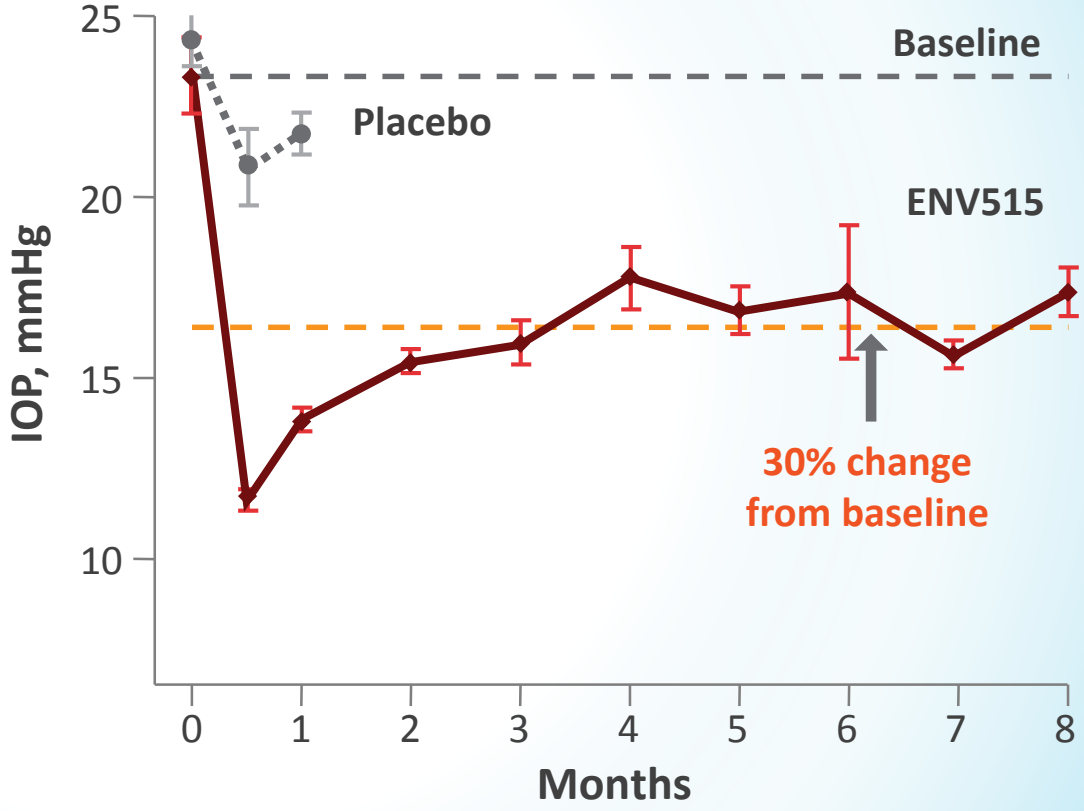






Intracameral Injection of Printed Particles: Early Development

- Current product includes printed travoprost
- Ongoing Phase II study
- Novel design: enrolling patients scheduled for phaco within 60 days
- Evidence of efficacy >6 months in dogs

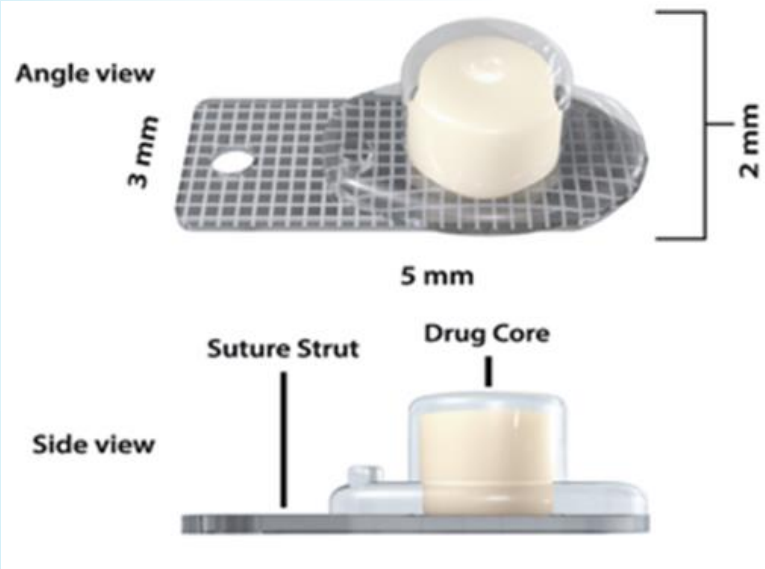


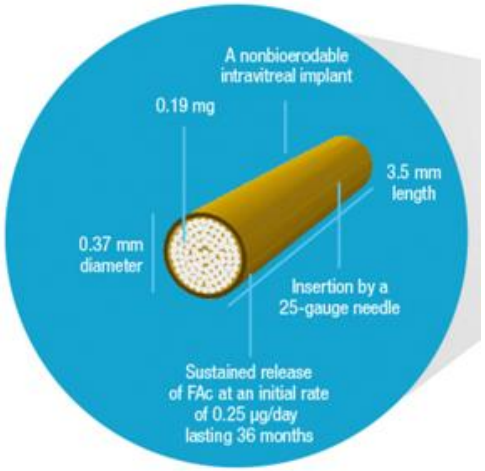
Intracameral Delivery Pros and Cons

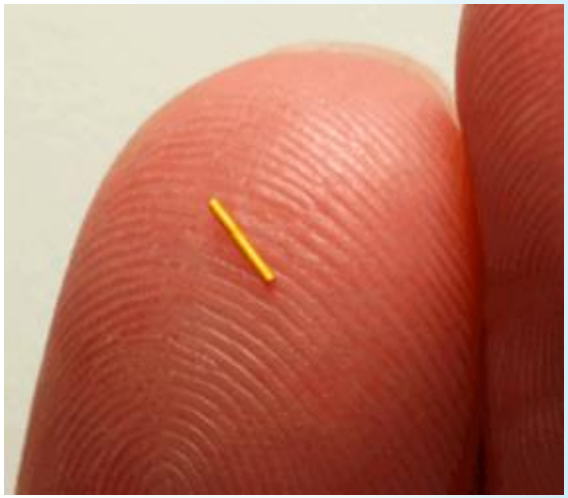
- Likely to eliminate many local side effects
- Evidence of long duration of action
- Possibility of infection, harm to cornea, other?
- Difficulty removing implant if side effects occur
- Patient acceptance of “injection” unknown

Bioerodible Subconjunctival Implant

Two views and their delivery system







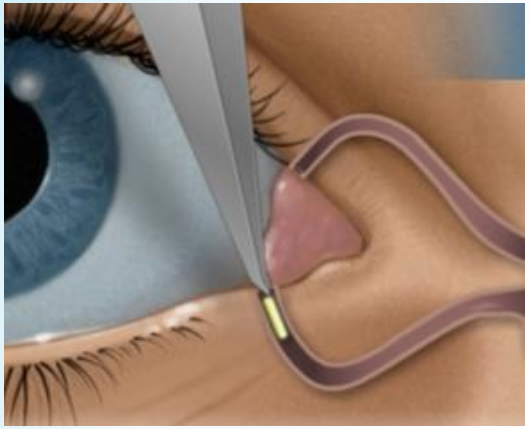
Bioerodible Subconjunctival Implant

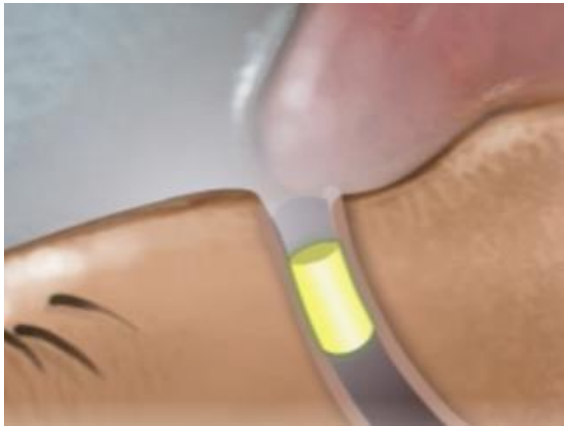
- Ongoing Phase I/II study
- Retinal products: duration of action as long as three years

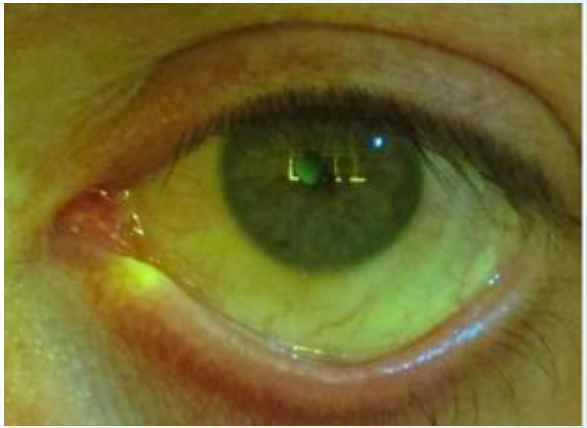
Bioerodible Subconjunctival Implant: Pros and Cons

- Potentially long duration of action
- Avoids intraocular injection
- Possibility of removing implant if side effects occur
- May still have normal drug side effects
- Patient acceptance of “injection” unknown
- Possible adverse effect on later glaucoma surgeries

Bioerodible Tear Duct Plug







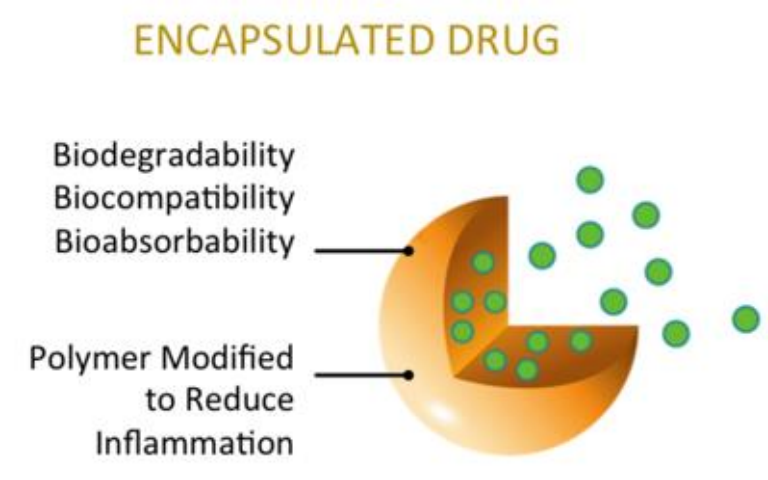
Bioerodible Tear Duct Plug

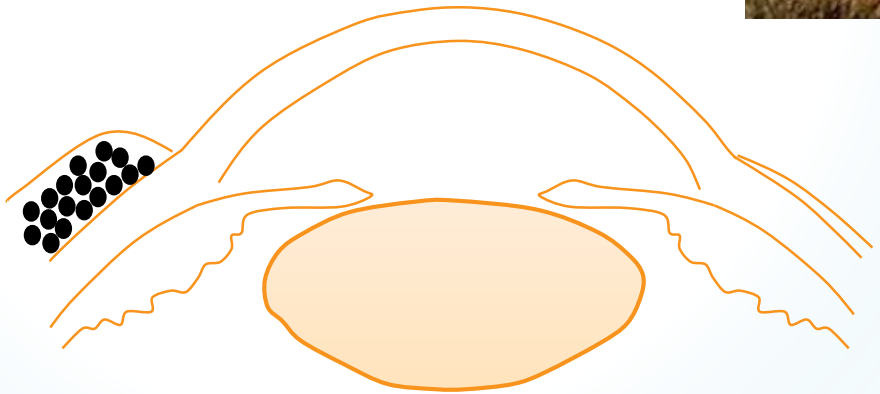
- Phase III trial completed for dexamethasone implant after cataract extraction
- Completed Phase I study comparing travoprost plug vs timolol
- IOP lowering noted for 3 months with minimal side effects

Bioerodible Tear Duct Plug: Pros and Cons

- Easy to insert
- Likely to be accepted by patients
- No possibility of removing implant if side effects occur
- May still have normal drug side effects, could fall out
- Dosing frequency may be > visit frequency

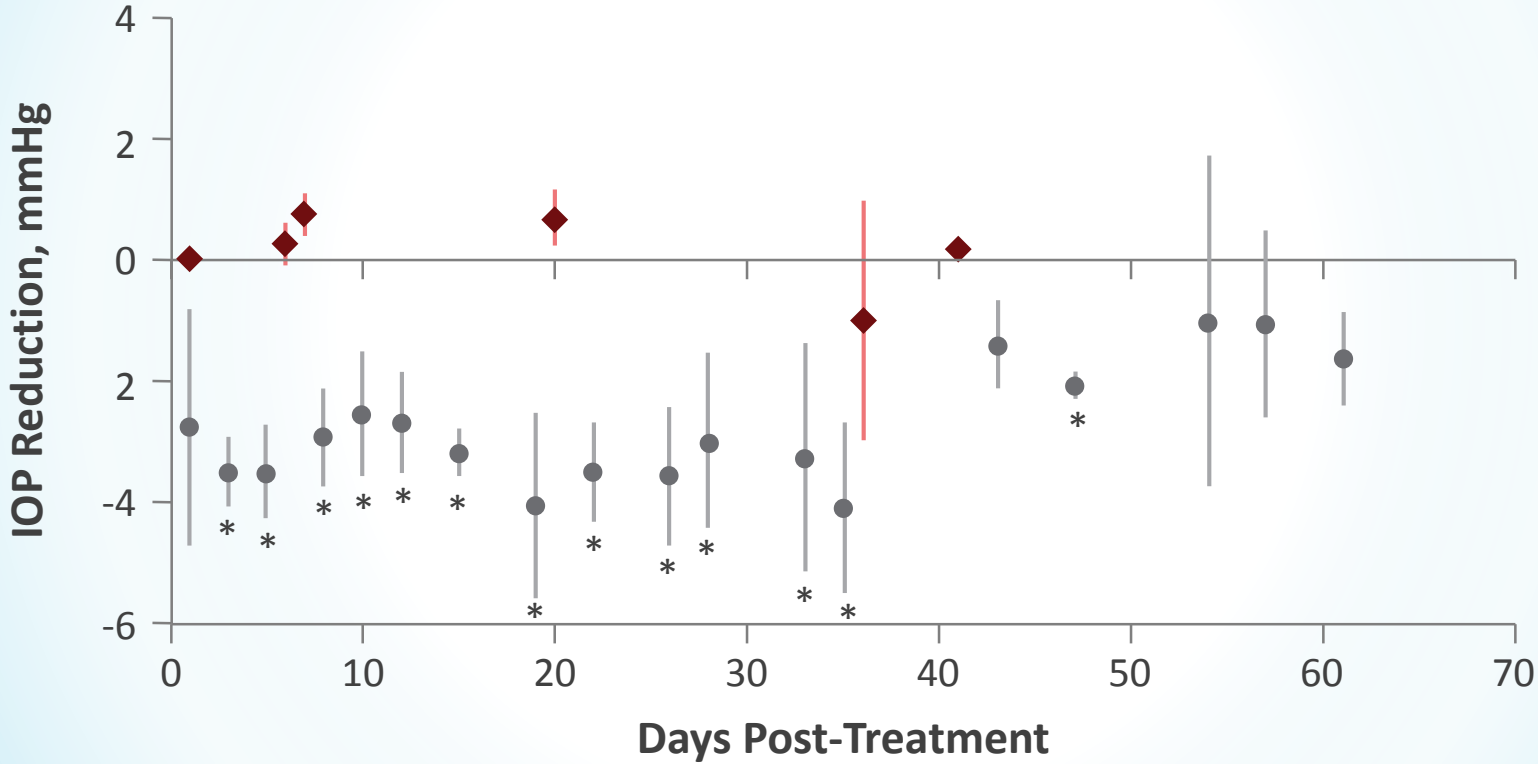
Biodegradable Nanoparticles





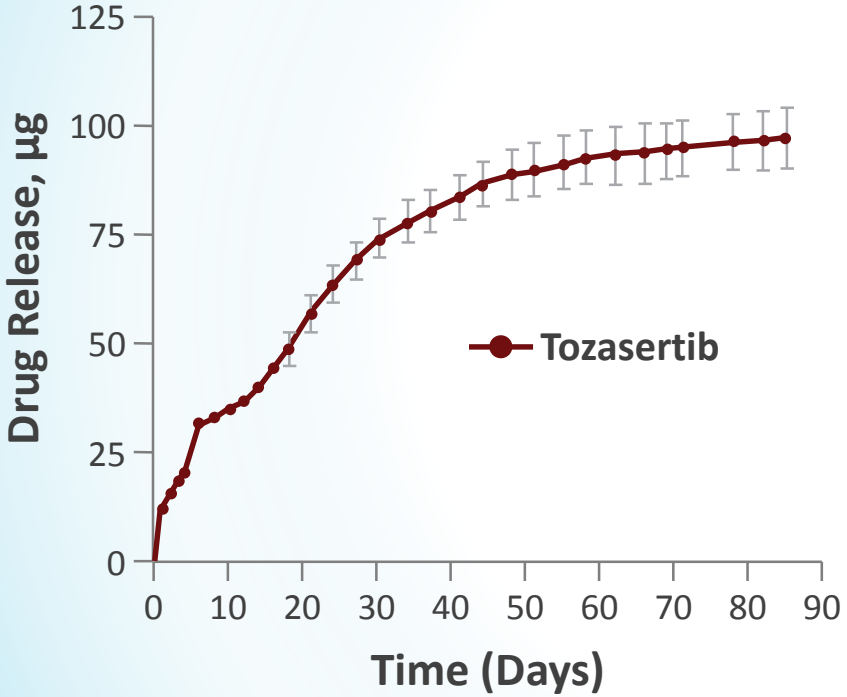
MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

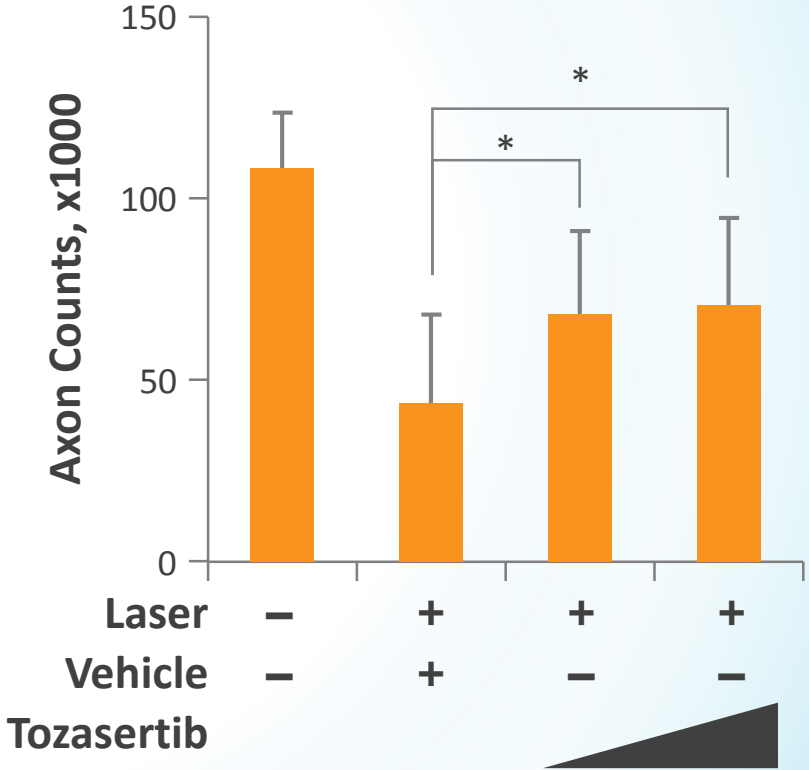
Subconjunctival Dorzolamide Particles Lowered IOP for 30 Days in Normotensive Rabbits



*Outliers more than 1.5x the interquartile range from the median.

Particles Potentially Useful for Delivering Neuroprotective Agents as Well





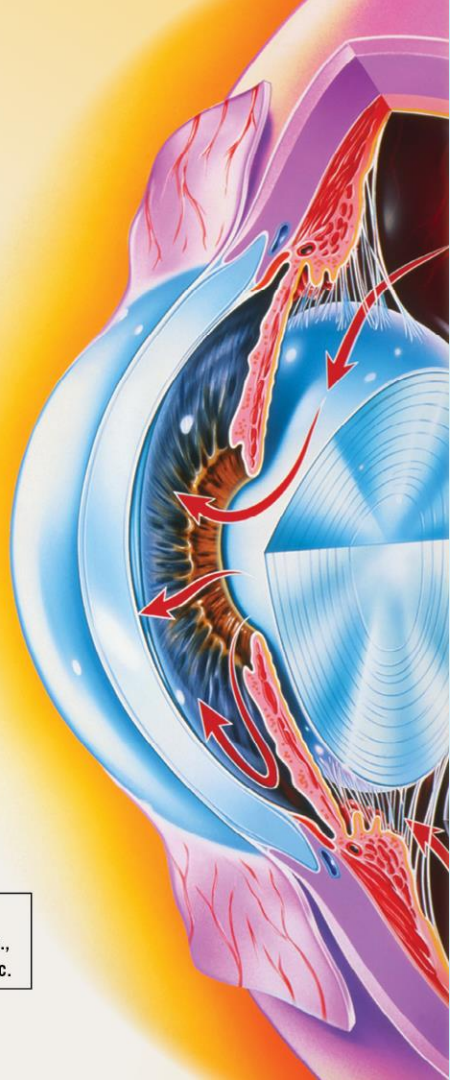
Welsbie DS, et al. *Proc Natl Acad Sci USA*. 2013;110(10):4045-4050.

Medical Therapy Likely to Be a Rapidly Evolving Field

- Multiple new drug delivery platforms emerging
- Doctor and patient acceptance as well as business models will influence uptake

MECHANISMS OF PRESSURE RELIEF IN GLAUCOMA

PHARMACOLOGIC & SURGICAL ADVANCES FOR REFRACTORY POAG OR NON-ADHERENCE



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