Controversies in Glaucoma Therapy

J. James Thimons, O.D.,FAAO
Chairman, National Glaucoma Society
Director, Glaucoma Institute @ Ophthalmic Consultants of Connecticutt

1. To Sleep Perchance to Dream! The Role of Sleep Dysfunction in Glaucoma

To Sleep Perchance to Dream

- Sleep Dysfunction: It's Role in patient Health
- Sleep Apnea: The Impact of sleep dysfunction in glaucoma

TO SLEEP PERCHANCE TO DREAM

- MOJON DS, etal
  - OPTIC NEUROPATHY / SLEEP APNEA
  - OPHTH 105:874-77 1998
    - SEVEN PATIENTS
      - 3 SEVERE / NASAL STEPS 2 /ARCUATE DEFECT 3
      - 2 MODERATE / ARCUATE DEFECT
      - 1 MILD
      - ETIOLOGY- DECREASED BLOOD FLOW

Obstructive Sleep Apnea

- Bendel, R et al.(Mayo Clinic, Jacksonville)
- OAS- Repeated apnea episodes
- Daytime symptoms
  - Daytime sleepiness
  - Chronic fatigue
  - Decreased cognitive function
- Etiology
  - Collapse of the pharyngeal airway
  - Last 10-60 seconds

OSA

- Diagnosis
  - Overnight polysomnography
  - EEG, EMG, EOG EKG, Nasal buccal airflow,and pulse oximetry(arterial oxygen)
- Respiratory Disturbance Index 10 >= OASS
- 83 patients with apnea
- Outcomes
  - Median age 62
  - Median RDI 37
  - Median IOP 16mmHg

OSA

- Outcomes
- 2.4% patients with OHTN
- 33% COAG
- No relation to gender , age, or BMI
- Relation between IOP increase and BMI level

Sleep Apnea & NTG

- Mojon DS et al; Ophthalmologica 2002
- 16 patients with NTG had PSN
- RDI > defined as mild
- < 45 - 0%
- 46-64 - 50%
- 65 & > 63%

Sleep Apnea: The Silent Assassin

- Co-Morbidities of Sleep apnea
  - Increased risk of CVA
  - Irregular Menstrual Cycles (40%)
  - Children May exhibit " Failure to Thrive": T & A removal
  - Psychologic Dysfunction (32%)

2. Will The Real IOP Please Stand Up!
Dr Goldmann Please Take a Seat!

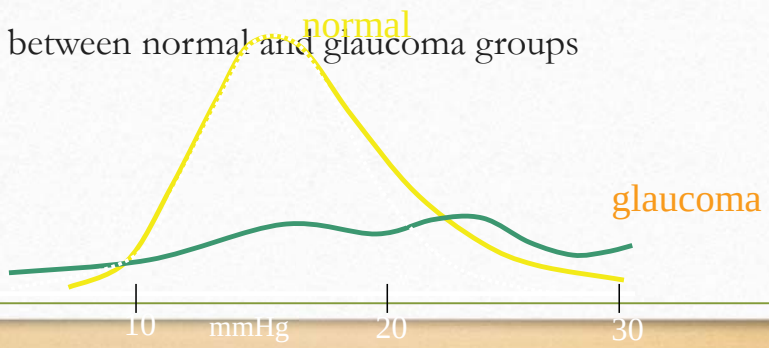
WHAT IS THE ROLE OF IOP IN GLAUCOMA?

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

IOP in glaucoma

- A risk factor
- Poor for diagnosing POAG

- Poor predictor of disc and field damage
- Used for management (AGIS - target IOP)
- Normal population distribution skewed (non-bell shaped)
- Overlap between normal and glaucoma groups
-



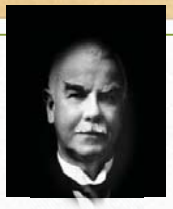
Lowering IOP Reduces the Risk of Glaucomatous Progression

- Results of major studies on established glaucoma
  - Collaborative Normal-Tension Glaucoma Study[1]
  - Collaborative Initial Glaucoma Treatment Study[2]
  - Advanced Glaucoma Intervention Study[3]

1. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol.* 1998;126:487-497. **2.** Lichter PR et al. *Ophthalmology.* 2001;108:1943-1953. **3.** The AGIS Investigators. *Am J Ophthalmol.* 2000;130:429-440.

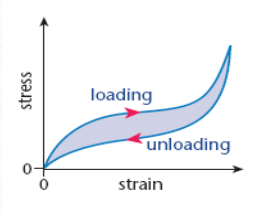
Ocular Response Analyzer

Corneal Hysteresis: A New Ocular Parameter



Sir James Alfred Ewing
Identified the phenomenon of hysteresis and coined the term in 1890

Classic "Hysteresis Loop"



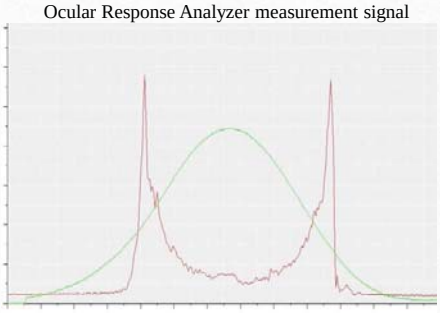
- A measurement that characterizes response to application and removal of force (load/unload)[1]
  - Found in materials or systems that do not instantly follow forces applied to them but react slowly, *or dissipate a portion of the applied energy* [1]
- More than 7500 papers published on hysteresis in a variety of medical fields[2]
  - Various tissues and structures (tendon, lung, arteries, etc)
  - The importance of Corneal visco-elasticity had been discussed and explored (*EX-VIVO*) prior to the ORA[3]

1. Vincent J. Basic elasticity and viscoelasticity. In: Vincent J, ed. *Structural Biomaterials.* 3rd ed. Princeton, NJ: Princeton University Press; 2012:1-28.
2. PubMed Search for "hysteresis" on October 3, 2014 returned 7696 results.
3. Hjortdal JO1. On the biomechanical properties of the cornea with particular reference to refractive surgery. Acta Ophthalmol Scand Suppl. 1998;(225):1-23.

Corneal Hysteresis (CH)

- The only in-vivo measurement of corneal/ocular biomechanics
  - CH specifically refers to the output of the measurement process performed by the Ocular Response Analyzer (ORA)[1,2]
- Corneal Hysteresis reflects the ability of the corneal tissue to dissipate energy [1]
  - Function of viscoelastic damping[2]
  - Not a characterization of stiffness[3]
- Provides insight into ocular properties that were not previously understood or conceived of

Ocular Response Analyzer measurement signal

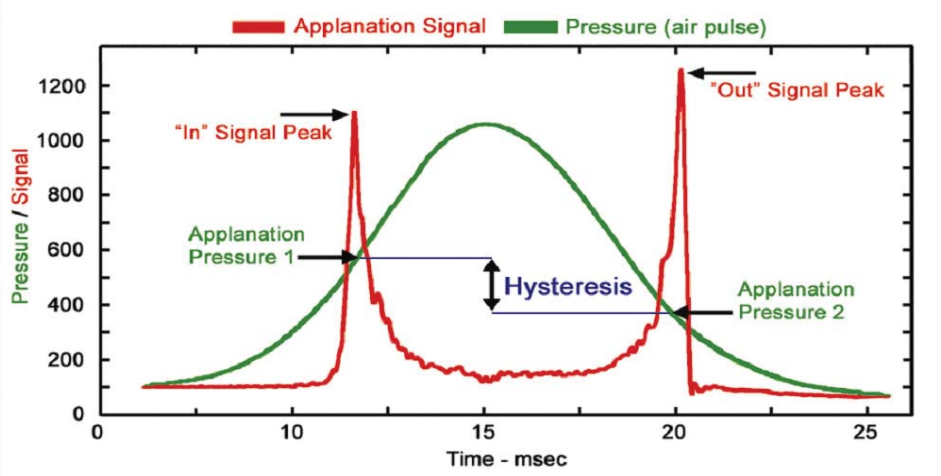


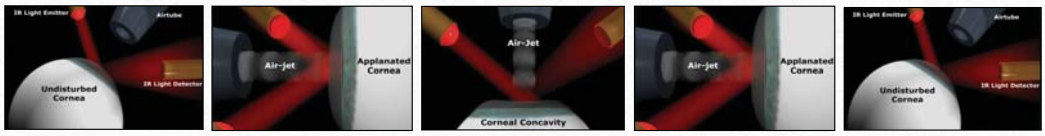
David Luce, PhD
Invented the concept of Corneal Hysteresis

1. Luce DA. *J Cataract Refract Surg.* 2005;31:156-162.
2. Dupps WJ Jr. *J Cataract Refract Surg.* 2007;33:1499-1501.
3. Glass DH et al. *Invest Ophthalmol Vis Sci.* 2008;49:3919-3926.

Ocular Response Analyzer Technology

Bi-direction Applanation Signal





Ocular Response Analyzer Technology

The instrument

- **2002: Clinical research with ORA commences**
- **2005: The 1st generation ORA was made commercially available**
- **2012: Generation II ORA was launched**
- **3rd Generation "ORA G3" introduced September 2015**

Measures:

- Corneal Hysteresis (CH)
- Goldmann-correlated IOP (IOP_g)
- Corneal compensated IOP (IOP_{CC})

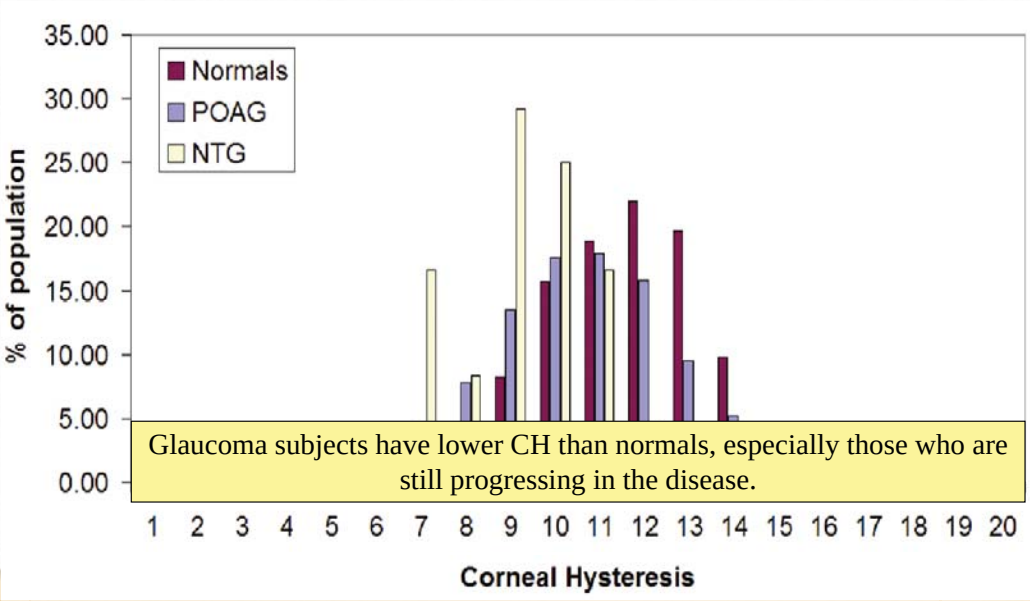
CH: Average Values in Normal Subjects

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

4. Kamiya Et Al. J Refract Surg. 2009 Oct;25(10):888-93
5. Ortiz Et Al. J Cataract Refract Surg. 2007 Aug;33(8):1371-5
6. John Et. Al. 2007 Spring;39(1):9-14

CH distribution - Normals & Glaucoma



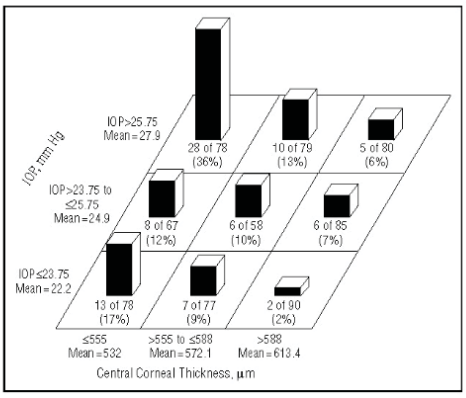
Glaucoma subjects have lower CH than normals, especially those who are still progressing in the disease.

Data courtesy New England College of Optometry and Mitsugu Shimmyo, MD

The Cornea and Glaucoma

- 2001 OHTS publication – the largest and longest glaucoma study in history
- CCT was the strongest independent indicator of conversion from ocular hypertension to POAG in the OHTS[1,2]
- As a result, CCT has become an essential metric in glaucoma risk assessment
  - **Not** as an IOP correction factor
  - "Low," "Medium," "High" stratification system

% of Patients Who Developed POAG by IOP[2]



1. Pensyl D et al. *Eye (Lond).* 2012;26:1349-1356.
2. Gordon MO et al. *Arch Ophthalmol.* 2002;120:714-720.

Section 1: Introduction to Corneal Hysteresis

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

6. John Et. Al. 2007 Spring;39(1):9-14

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.

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

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

Clinical Evidence – Study 3

CH Associated with Asymmetric Glaucoma Progression

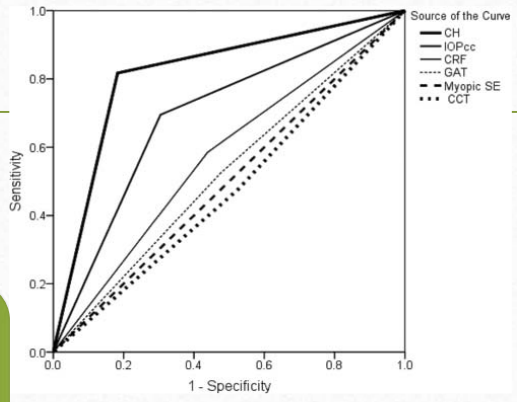
- Investigated the relationship between CH and asymmetric POAG
- In a prospective cross-sectional study, ORA parameters were measured in 117 POAG patients with asymmetric visual fields (VF).
  - VF testing was performed with a static, automated, achromatic perimetry (24–2 test pattern, Mk II, model 750; Carl Zeiss Meditec, Inc.) using the SITA-standard program.
  - Asymmetry was defined as a 5-point difference between OD and OS using the (AGIS) scoring system.
  - Pearson correlation coefficients were used to determine correlation of various parameters with the AGIS scores. Receiver operating characteristic (ROC) curves were plotted for ORA and other glaucoma risk factors. Area under the curve (AUC) for each parameter was compared to determine the best predictor for the worse eye in POAG with asymmetric VF.

Anand A et al. *Invest Ophthalmol Vis Sci.* 2010;51:6514-6518

Clinical Evidence – Study 3

CH Associated with Asymmetric Glaucoma Progression

	Worse Eye	Better Eye	P
AGIS II VF Score	8.1 ± 4.3	1.0 ± 1.6	<0.001
GAT mmHg	14 (12-17)	14 (12-16)	0.3
CCT (µm)	531.8 ± 34.7	532.3 ± 34.9	0.6
Drops (#)	2.2 ± 0.9	2.1 ± 2.6	0.9
CH (mmHg)	**8.2 ± 1.9**	**8.9 ± 1.9**	**<0.001**

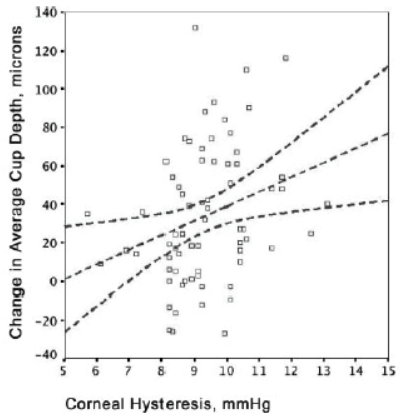


CH was the best discriminative index for the worse eye in asymmetric OAG.
- CH lower in 80% of worse eyes

Anand A et al. *Invest Ophthalmol Vis Sci.* 2010;51:6514-6518

Section 3: CH and the structural continuum

CH is Associated with ONH Deformation in Glaucoma



- Prospective experimental study of 100 subjects (38 with glaucoma, 62 without glaucoma)
- Data collected included SE, optic disc diameter, CCT, axial length, cylinder, GAT, Pascal IOP, OPA and CH.
- Elevation of IOP (approx 64 mm, 30 seconds) was induced OD on each subject with a modified LASIK suction ring.
- HRT-II was used to map the optic nerve surface before and during IOP elevation. Mean cup depth was calculated using built-in HRT data analysis software.
- Change in optic disc depth during IOP elevation was calculated for all right eyes, and tests for correlation with the parameters listed were performed.

CH, but not CCT or other anterior segment parameters, is associated with increased deformation of the optic nerve during transient IOP elevations in glaucoma patients but NOT in normal controls.[1]

1. Weils AP et al. *Invest Ophthalmol Vis Sci.* 2008;49:3262-3268.

Clinical Evidence- Study 2

CH associated with progression in NTG eyes

Logistic regression with VF progression as a binary outcome

Baseline VF MD (dB)	1.18 (0.96 to –1.44)	0.12
CCT (μm)	0.99 (0.97 to 1.01)	0.35
Subfoveal choroidal thickness	0.99 (0.98 to 1.00)	0.08
RNFL thickness (average)	0.96 (0.92 to 0.99)	0.04
RNFL thickness (temporal)	0.97 (0.94 to 1.01)	0.09
RNFL thickness (inferior)	0.98 (0.96 to 1.01)	0.13

- Of the 39 eyes with low CH, 26 (66.7%) showed progression of VF damage while 13 (33.3%) showed no progression.
- Of the 43 eyes with high CH, 15 (34.9%) showed progression of VF damage, whereas 28 (65.1%) showed no progression.

These findings suggest that CH can be used as one of the prognostic factors for progression, independent of corneal thickness or IOP

Park Et. Al Br J Ophthalmol. 2015 Jan 2. pii: bjophthalmol-2014-305962. doi: 10.1136/bjophthalmol-2014-305962.

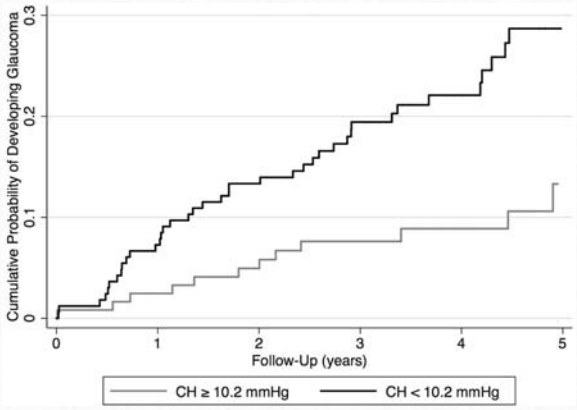
Corneal Hysteresis in Glaucoma

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

Reimbursement

As of January 1, 2015, the measurement of Corneal Hysteresis is reimbursable by Medicare in the USA

CPT code 92145: Corneal hysteresis determination, by air impulse stimulation, unilateral or bilateral with interpretation and report

Surgical Continuous IOP Monitoring Device

- Nature Medicine 2014
  - Yossi Mandel, Bar-Ilan/ Stephen Quake, Stanford
  - Utilizes a variable float tube in the IOL
  - Smart Phone app allows acquisition of data
  - Anticipated in 2-3 years

ANOTHER REASON NOT TO BE A COUCH POTATOE !

- PASSO, M etal; Arch Ophth-Vol 109 Aug 1991
- EXERCISE TRAINING REDUCES IOP AMOUNG GLAUCOMA SUSPECTS
  - 13 SEDENTARY ADULTS/25-60 Y/O
  - < 1 HOUR/WEEK OF EXERCISE PRIOR TO STUDY FOR 6 MONTHS
  - IOP > 22mmHg MULTIPLE MEASUREMENTS

EXERCISE AND IOP

- BASELINE COMPREHENSIVE EXAM
- 12 WEEKS/ 40 MINUTES /DAY/4 DAYS
- OUTCOMES
  - BASELINE IOP 23.8 mmHg
  - POST TRAINING IOP 19.2 mmHg
- SYSTEMIC RESPONSE SIMILAR(BP, HEART RATE)
- IOP AFTER DECONDITIONING 24mmHg

3. Alternate Day Therapy in Glaucoma

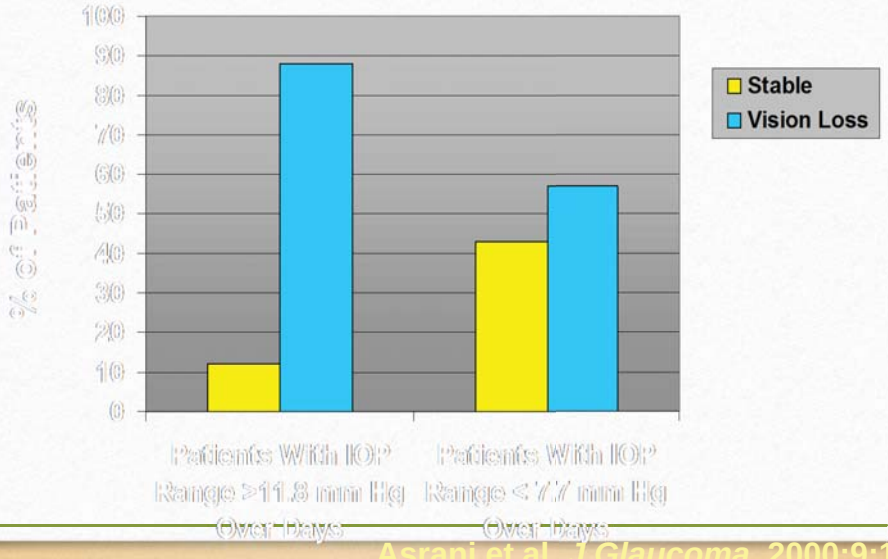
Diurnal IOP Fluctuation & Visual Field Loss

- Greater diurnal IOP fluctuation resulted in greater visual field progression

  - Home applanation tonometry by 64 patients 5X daily for 5 days
  - Visual field progression of patients was tracked over 8 years

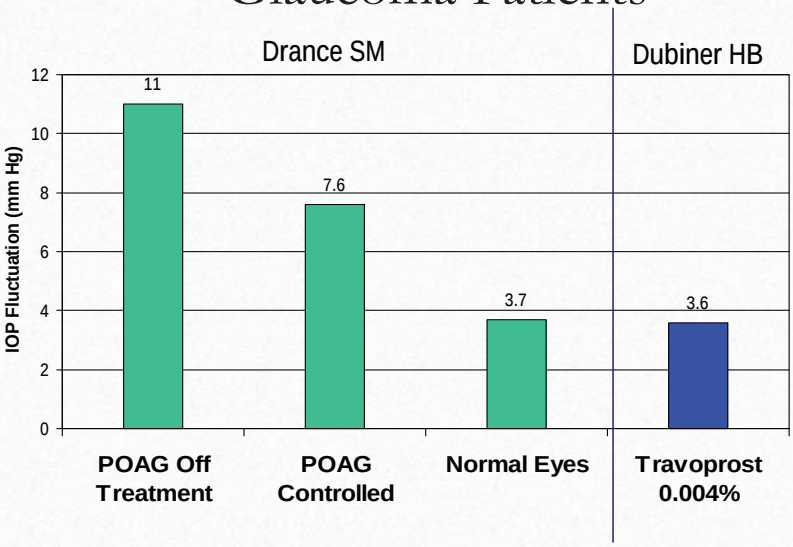
Asrani, et. al. ***Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma,*** **J.Glaucoma, 9, 134-142, 2000**

Diurnal IOP Fluctuations and Glaucomatous Progression



Asrani et al. *J Glaucoma.* 2000;9:134-142.

Diurnal IOP Fluctuation in Glaucoma Patients



Drance SM. Arch Ophth, 1963;70: 302-311
Drance SM. Arch Ophth, 1960; 64: 494-501
H.B. Dubiner Travatan Administration Results in Effective Diurnal Reduction in Intraocular Pressure Over 36 Hoursand Lower Pressures Up to 3.5 Days Without Further Dosing; Presented at ARVO Meeting; May 2002

Alternate Day Therapy

- Twice daily dosing increases IOP relative to once daily dosing
- Xalatan and Lumigan combined can increase IOP, even to 50s
- anytime IOP is >30 with prostaglandin, it is overdosed
- Once daily can be overdose if there is inflammation/endogenous prostaglandin

Persistence of IOP Response

- Labovitz RA et al; Arch Ophth 2001
- Comparison of Lumigan vs: Timolol
- Maintenance of IOP at 48 hours post D/C 5.6mmHg
- 7.2 - 8.2 mmHg at peak effect
- 28 Day control showed less than
- Timolol was 3.4-3.9 mmHg at peak.

Alternate Day Therapy

- 30% reduction first day, 25% reduction second day
- IOP will be one point higher on second day
  - Gross. Journal of Glaucoma 2008
  - Doro. ARVO 2007

Alternate Day Therapy

- Reduced cost
- Reduced hyperemia, ache, dry eye
- Reduced long term conjunctival inflammation promoting trabeculectomy scarring

Alternate Day Therapy: Practical Tips

- Starting every other day improves tolerability in prostaglandin novices
- Aching and high IOP suggest overdose
- Wash face after instillation

Alternate Day Therapy: Compliance

- Not a problem for organized patients
- Some keep a calendar
- Some choose 3 or 4 days of the week
- Some choose odd or even days

Alternate Day Therapy Post SLT

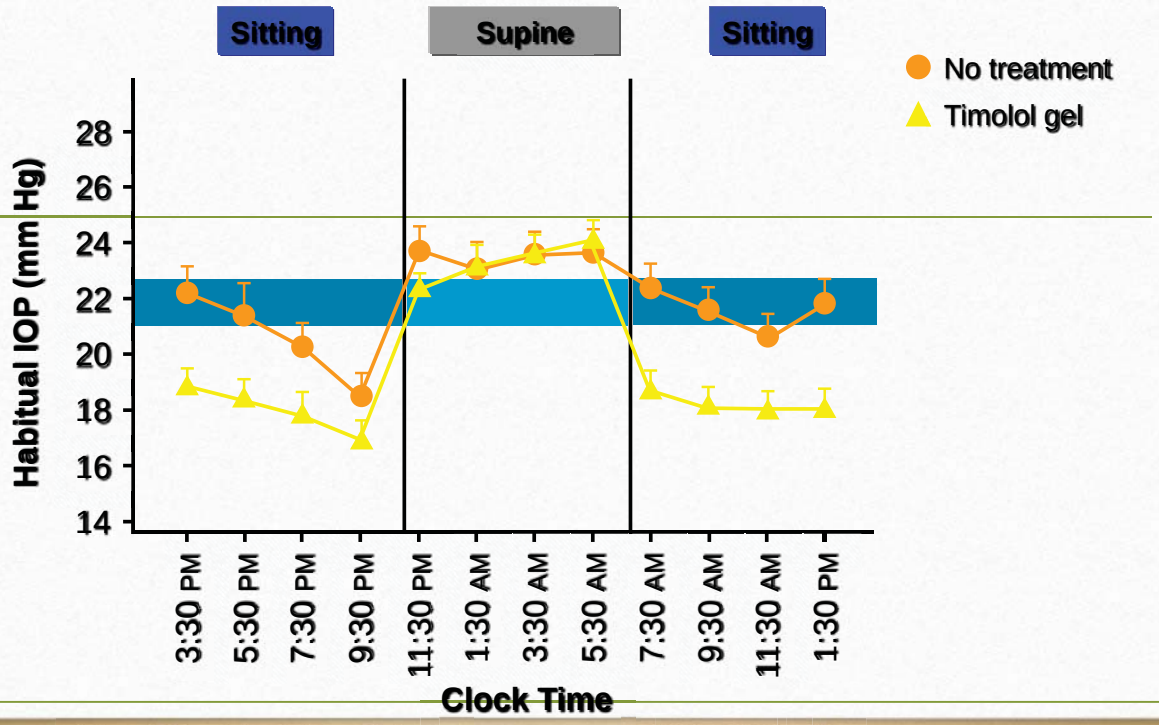
- SLT somewhat less effective in patients already on prostaglandin
  - Suggesting that part of SLT induces prostaglandin like effects
- QD prostaglandin could be an overdose after SLT
  - Especially first year after laser

Alternate Day Therapy: Initial Review

- 22 patients with well controlled glaucoma over a two year period.
- Switched from daily therapy to alternate day treatment following complaints of cosmetic/ anterior segment problems
- Average IOP pre-switch: 16.2 mmHg
- Post switch IOP at 1 week, 1month and 3 months average: 16.67 mmHg

Diurnal Pressure: All Talk, No Action?

Nocturnal and Diurnal Habitual IOP



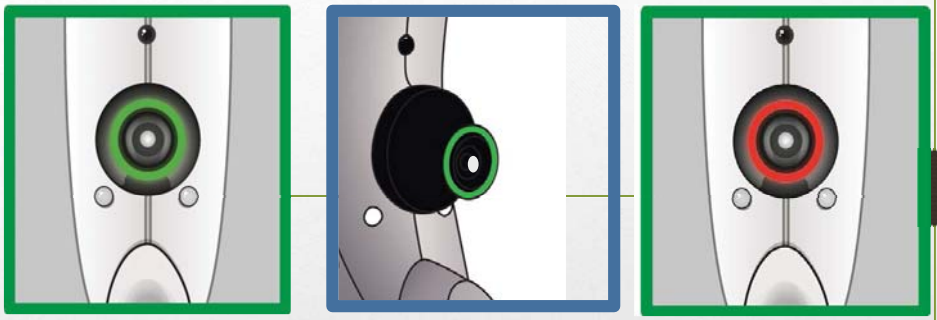
Adapted from Liu, Kripke, Weinreb. *Am J Ophthalmol*. 2004;138:389-395.

Icare HOME tonometer

- IOP, date, time, eye recognition (right/left) and measurement quality are all stored in the internal memory.
- Data is transferred to a PC for further analysis by the prescribing physician.
- New features: positioning light, automatic eye recognition system, series or single measurements, new user interface panel.

Icare® EasyPos: Positioning Light

Red and green light signals help patients correctly position the tonometer.



Correct alignment | **Incorrect alignment** | **Incorrect alignment**

Icare® EyeSmart: Automatic Eye Recognition

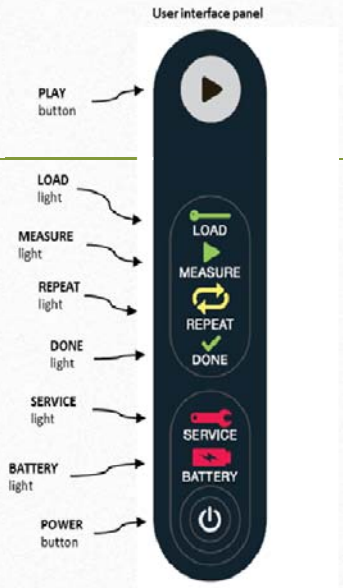
The tonometer includes an automatic eye recognition system that identifies which eye is being measured.

- Two infrared LED transmitters below probe (1)
- One infrared LED sensor above probe (2)
- The infrared light is reflected from nose back to the sensor
- The sensor knows from which transmitter the reflected infrared light came from and thus which eye, right or left, was measured
- The resulting eye indication is stored into the memory of the tonometer

2/4/2019

New User Interface Panel

- Simple Indicator Lights and Audible Alerts
- Interpretation only by a health care professional
- Does not display the IOP measurement
  - Mitigating concerns that the patient or caregiver might improperly use the information provided by the device




icare

The Role of Perfusion Pressure in Glaucoma

Hypoperfusion

- flow = pressure/resistance
- perfusion pressure = BP - IOP
- mean arterial BP = diastolic + 1/3 syst-diastolic
- nocturnal hypotension is greatest risk

Nocturnal Hypotension: Another Reason to Get a Good Nights Sleep

- TIBA Medical
- ABPM 2400
- 24 hour Serial BP Monitoring
- Role in Glaucoma Management

Nocturnal Hypotension

- TIBA Medical
- Reimbursement
  - Commercial
  - Medicare
- ICD-9 Codes
- www.tibamedical.com

Ocular Perfusion Pressure and Glaucoma Progression

Ocular Perfusion Pressure (OPP) = BP – IOP
(BP is mean arterial pressure, diastolic BP, or systolic BP)

Low ocular perfusion pressure has been shown to be strongly associated with the prevalence of glaucoma progression in multiple population-based surveys

Tielsch JM, et al. *Arch Ophthalmol.* 1995.

Leske MC, et al. *Arch Ophthalmol.* 1995.

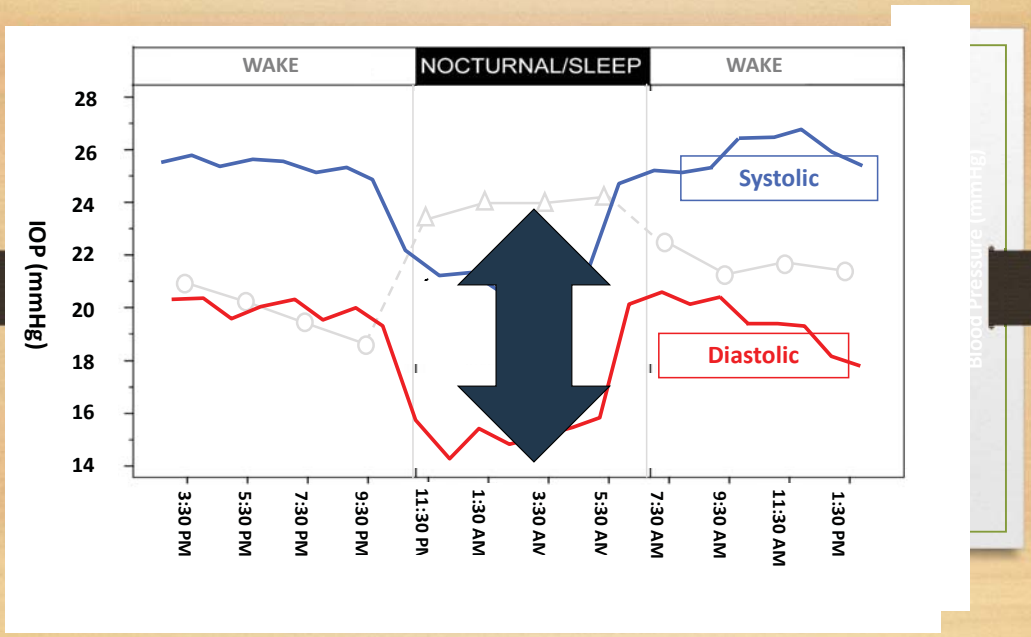
Leske MC, et al. *Arch Ophthalmol.* 2002.

Quigley HA, et al. *Arch Ophthalmol.* 2001.

Bonomi L, et al. *Ophthalmol.* 2000.

Leske et al.Ophthalmology 114 (11), November 2007

Habitual IOP and Pulse Pressure



An Evidence-Based Review of Prognostic Factors for Glaucomatous Visual Field Progression

Paul J. Ernest, MD,[1,2] Jan S. Schouten, MD, PhD,[1] Henny J. Beckers, MD, PhD,[1] Fred Hendrikse, MD, PhD,[1] Martin H. Prins, MD, PhD,[2] Carroll A. Webers, MD, PhD[1]

Purpose: To examine which prognostic factors are associated with glaucomatous visual field progression.

Design: Knowledge of prognostic factors helps clinicians to select patients at risk of glaucomatous visual field progression and intensify their treatment.

Methods: By consulting relevant databases, we identified 2733 articles published up to September 2010, of which 85 articles investigating prognostic factors for visual field progression in patients with open-angle glaucoma (OAG) were eligible. We summarized results for each factor in tables, noting the direction of the association between the prognostic factor and progression, and the accompanying *P* value. Four authors, working blind to the factors, independently judged the extent to which a prognostic factor was associated with glaucomatous visual field progression. If there were different associations for normal-tension glaucoma (NTG) studies, they were judged separately. Consensus was reached during group meetings.

Main Outcome Measures: A ranking of all studied prognostic factors for glaucomatous visual field progression according to their likelihood of being prognostic.

Results: A total of 103 different prognostic factors were investigated in 85 articles. The following factors were clearly associated with glaucomatous visual field progression: age, disc hemorrhages (for NTG), baseline visual field loss, baseline intraocular pressure (IOP), and exfoliation syndrome. An association was unlikely for family history of glaucoma, atherosclerosis, systemic hypertension, visual acuity, sex (for NTG), systolic blood pressure, myopic refractive error (for NTG), and Raynaud's phenomenon.

Conclusions: The factors we found clearly associated with progression could be used in clinical practice and for developing clinical prediction models. For many other factors, further research is necessary.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2013;120:512–519*

EMGT RFs for Progression

Table 2. Baseline and Follow-up Factors for Progression in the Early Manifest Glaucoma Trial, All Patients (n = 255)

Variables	Reference	Hazard Ratio (95% Confidence Interval)	P Value*
Baseline factors†			
Treatment group	Control	0.53 (0.39–0.72)	<0.0001
Higher intraocular pressure (IOP), mmHg	<21	1.77 (1.29–2.43)	0.0005
Exfoliation	None	2.12 (1.30–3.46)	0.0026
No. of eligible eyes	1	1.88 (1.35–2.63)	0.0002
Older age (yrs)	<68	1.51 (1.11–2.07)	0.0095
Lower systolic perfusion pressure (mmHg)	>125	1.42 (1.04–1.94)	0.0268
Worse mean deviation (dB)	>−4	1.38 (1.00–1.91)	0.0510
Systolic blood pressure (mmHg)‡	≤160	0.69 (0.44–1.07)	0.0971
Follow-up factors§			
a. Initial change in IOP (baseline − 3-mo IOP)	Per mmHg lower	0.92 (0.89–0.96)	0.0001
b. IOP at first follow-up visit (3-mo IOP)	Per mmHg higher	1.13 (1.08–1.18)	<0.0001
c. Mean IOP at follow-up (time dependent)	Per mmHg higher	1.12 (1.07–1.16	<0.0001
d. Percent of visits with disc hemorrhages (time dependent)	Per % higher	1.02 (1.01–1.02)	0.0014
e. Central corneal thickness (μm)‖	Per 40 μm lower	1.25 (1.01–1.55)	0.0422

Ophthalmology 2007;*114:11*,

Drance Hem and Progression

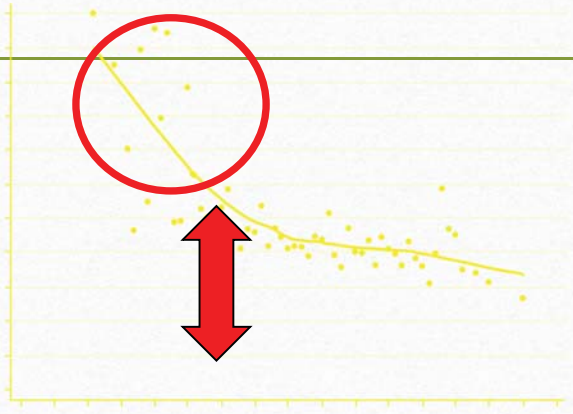
The Relationship between Intraocular Pressure Reduction and Rates of Progressive Visual Field Loss in Eyes with Optic Disc Hemorrhage

Felipe A. Medeiros, MD, PhD,[1,2] Luciana M. Alencar, MD,[1,2] Pamela A. Sample, PhD,[1] Linda M. Zangwill, PhD,[1] Remo Susanna Jr., MD,[2] Robert N. Weinreb, MD[1]

Purpose: To evaluate rates of visual field progression in eyes with optic disc hemorrhages and the effect of intraocular pressure (IOP) reduction on these rates.
Design: Observational cohort study.
Participants: The study included 510 eyes of 348 patients with glaucoma who were recruited from the Diagnostic Innovations in Glaucoma Study (DIGS) and followed for an average of 8.2 years.
Methods: Eyes were followed annually with clinical examination, standard automated perimetry visual fields, and optic disc stereophotographs. The presence of optic disc hemorrhages was determined on the basis of masked evaluation of optic disc stereophotographs. Evaluation of rates of visual field change during follow-up was performed using the visual field index (VFI).
Main Outcome Measures: The evaluation of the effect of optic disc hemorrhages on rates of visual field progression was performed using random coefficient models. Estimates of rates of change for individual eyes were obtained by best linear unbiased prediction (BLUP).
Results: During follow-up, 97 (19%) of the eyes had at least 1 episode of disc hemorrhage. The overall rate of VFI change in eyes with hemorrhages was significantly faster than in eyes without hemorrhages (−0.88%/year vs. −0.38%/year, respectively, $P<0.001$). The difference in rates of visual field loss pre- and post-hemorrhage was significantly related to the reduction of IOP in the post-hemorrhage period compared with the pre-hemorrhage period ($r = -0.61$; $P<0.001$). Each 1 mmHg of IOP reduction was associated with a difference of 0.31%/year in the rate of VFI change.
Conclusions: There was a beneficial effect of treatment in slowing rates of progressive visual field loss in eyes with optic disc hemorrhage. Further research should elucidate the reasons why some patients with hemorrhages respond well to IOP reduction and others seem to continue to progress despite a significant reduction in IOP levels.
Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2010;xx:xxx

Los Angeles Latino Eye Study

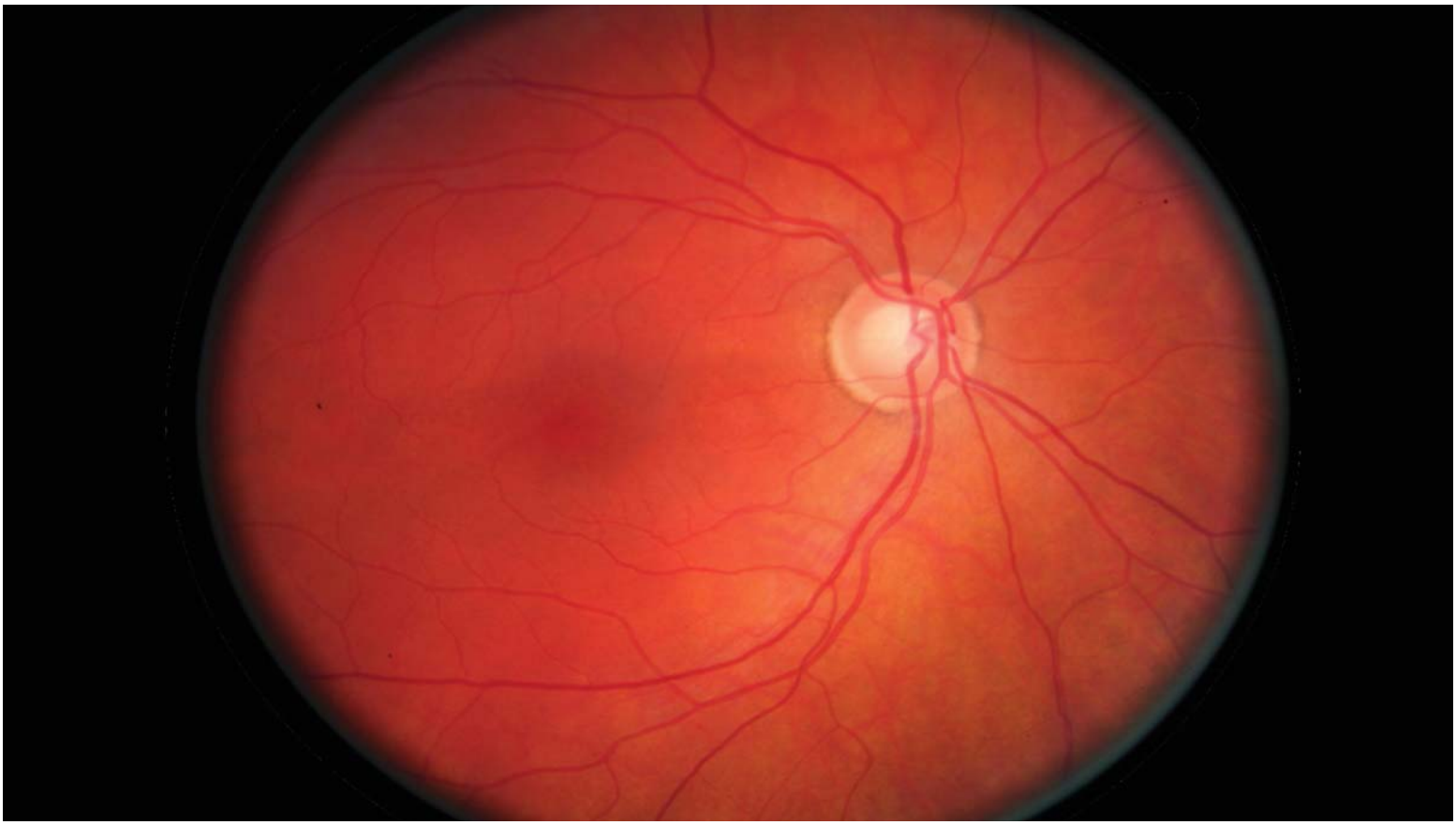
- Cross-sectional study of 6,357 Latinos, >40 years in Los Angeles, CA.
- Persons with low diastolic and systolic perfusion pressures had a higher risk of POAG.
- DOPP <50 mmHg, the prevalence of glaucoma rapidly increases linearly.

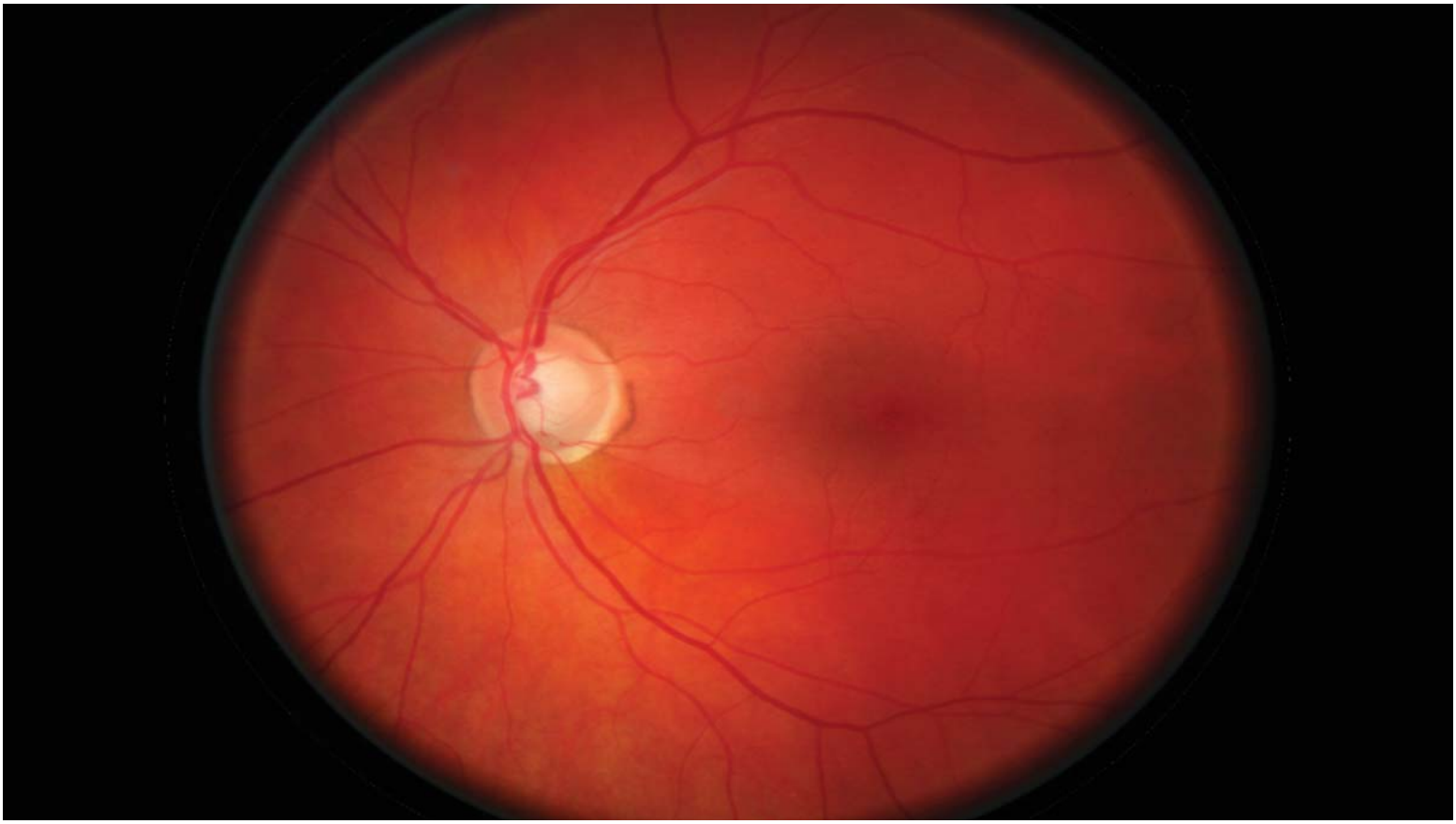


Varma R, et al. *Ophthalmology.* 2004;111:1439-1448.

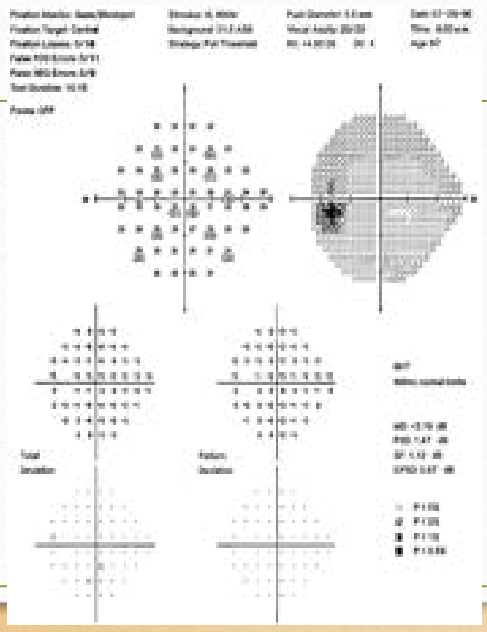
How Low Can You Go!

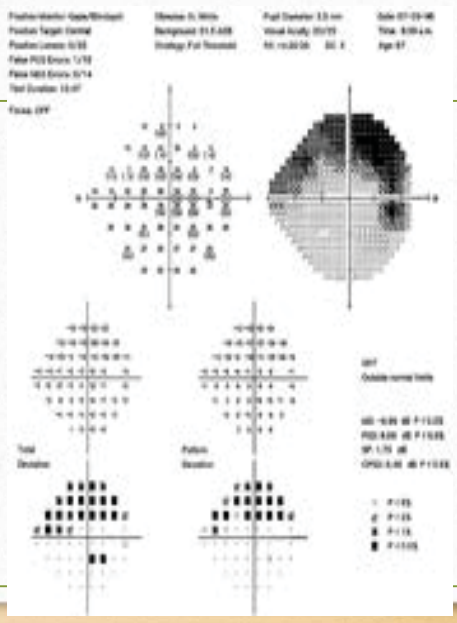
- SM a 40 y/o white female was referred for evaluation of glaucoma. Current Tx was Timolol and Alphagan.
- VA 20/20 OD/OS
- Ta 12/12 @ 10
- SLE: wnl
- DFE: 0.7 OD / 0.9 OS
- VF: Early near fixation loss OS
- Gonioscopy: CB 360 OU
- Medical Hx: LBP (100/65), pulse 54, Raynaud's, Migraine HA
- Family Hx: Negative

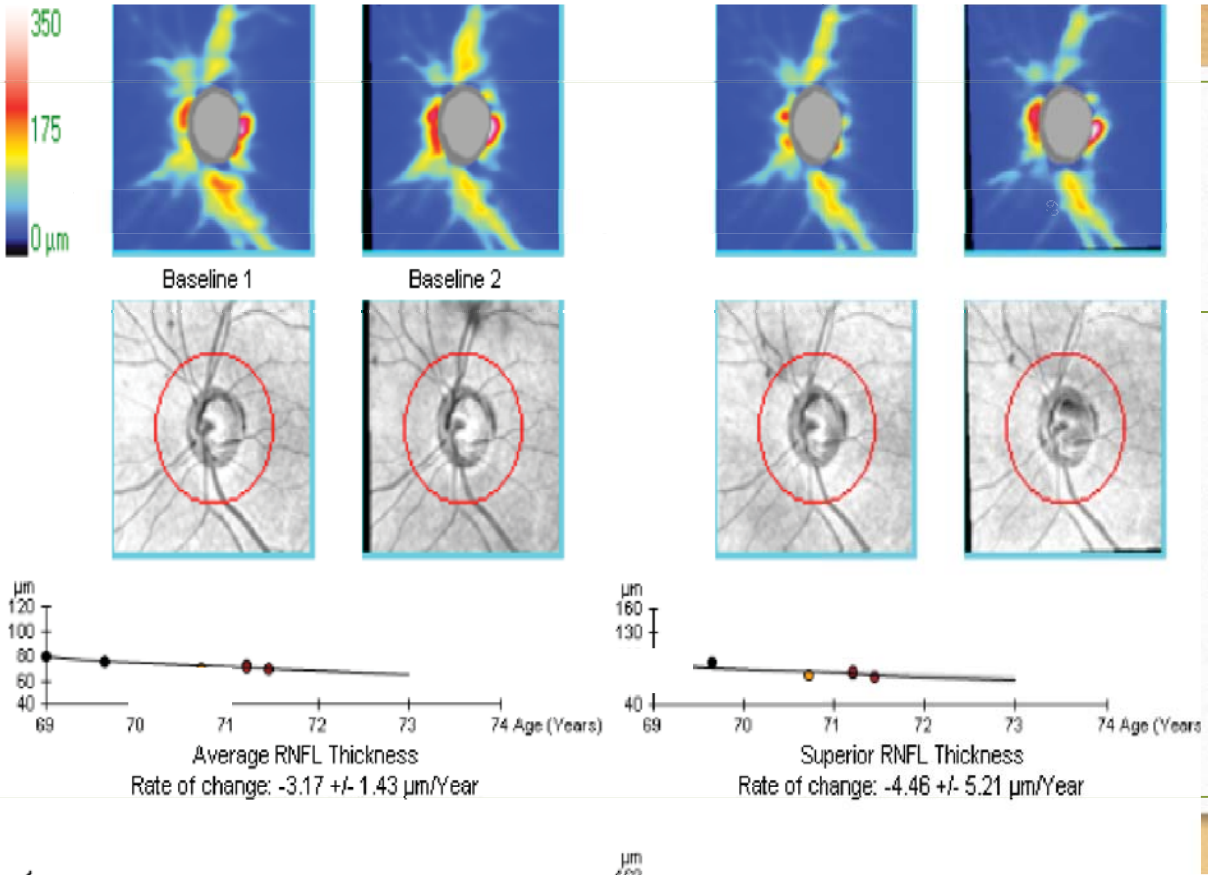




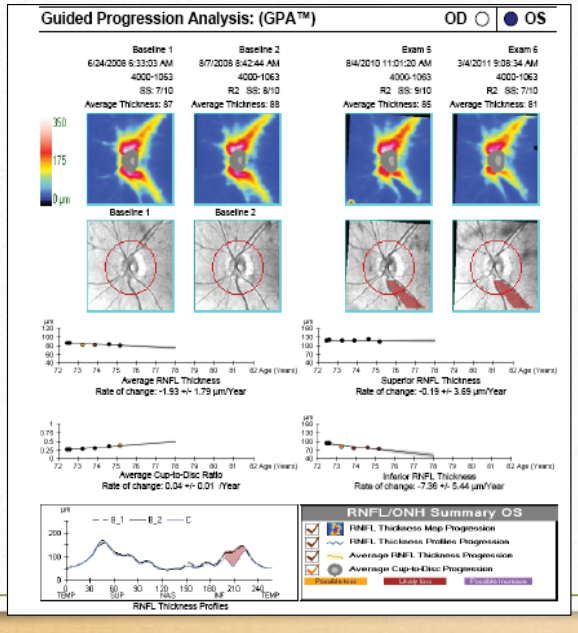
Visual Field Loss



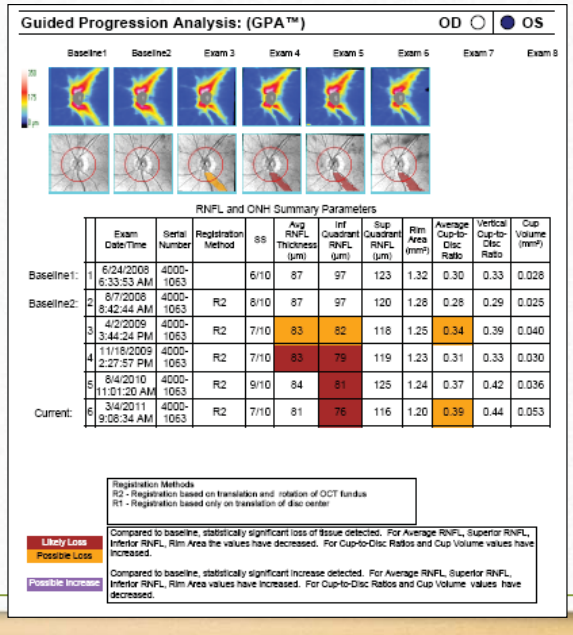




Page 1



Page 2



		Exam Date/Time	Serial Number	Registration Method	SS	Avg RNFL Thickness (µm)	Inf Quadrant RNFL (µm)	Sup Quadrant RNFL (µm)	Rim Area (mm²)	Average Cup-to-Disc Ratio	Vertical Cup-to-Disc Ratio	Cup Volume (mm³)
Baseline1:	1	6/24/2008 6:33:53 AM	4000-1063		6/10	87	97	123	1.32	0.30	0.33	0.028
Baseline2:	2	8/7/2008 8:42:44 AM	4000-1063	R2	8/10	87	97	120	1.28	0.28	0.29	0.025
	3	4/2/2009 3:44:24 PM	4000-1063	R2	7/10	83	82	118	1.25	0.34	0.39	0.040
	4	11/18/2009 2:27:57 PM	4000-1063	R2	7/10	83	79	119	1.23	0.31	0.33	0.030
	5	8/4/2010 11:01:20 AM	4000-1063	R2	9/10	84	81	125	1.24	0.37	0.42	0.036
Current:	6	3/4/2011 9:08:34 AM	4000-1063	R2	7/10	81	76	116	1.20	0.39	0.44	0.053

Registration Methods
R2 - Registration based on translation and rotation of OCT fundus
R1 - Registration based only on translation of disc center

Likely Loss
Possible Loss

Compared to baseline, statistically significant loss of tissue detected. For Average RNFL, Superior RNFL, Inferior RNFL, Rim Area the values have decreased. For Cup-to-Disc Ratios and Cup Volume values have increased.

Possible Increase

Compared to baseline, statistically significant increase detected. For Average RNFL, Superior RNFL, Inferior RNFL, Rim Area values have increased. For Cup-to-Disc Ratios and Cup Volume values have decreased.

How Low Can You Go!

- Meds: Alphagan P, Lumigan, Ginkgo
- Ta:14/11 @ 9:30
- Migraines increased x 4 weeks, episode of syncope x 1 week
- Serial BP 2 AM 58/30/ pulse 54

NTG- Differential Diagnosis

- Diurnal Variation
- Vasculitis
- Optic Atrophy
  - Old AION
  - Previous RBON
- Compressive ON
- Chronic marijuana use
- Prior Hypotensive episodes
- Systemic Beta-Blocker
- "Burned out" Glaucoma
- Sub-acute angle closure
- History steroid use
- Ocular Ischemic Syndrome

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

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

THE BIG DIPPER

- STIMADA K etal, CIRCULATION 1990 COLLIGNON N etal INT OPH 1998
  - NOCTURNAL HYPOTENSION OCURS IN 10% OF POPULATION
  - “BIG DIPPERS” > 10%
  - INCREASED RISK OF MI AND LOWER LIMB ISCHEMIA
  - INCREASED RISK OF VF LOSS AND DISC DAMAGE

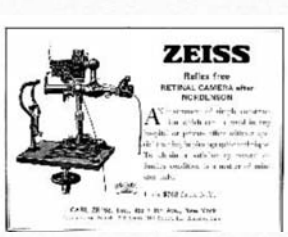
Treatment of Low Blood Flow

- middle aged women with history of low BP
  - increase salt
  - licorice extract (glycerrhinic acid) is aldosterone agonist
- elderly patients taking BP meds with BP <130/75
  - if no heart disease or stroke, discuss reduced anti-hypertensive therapy

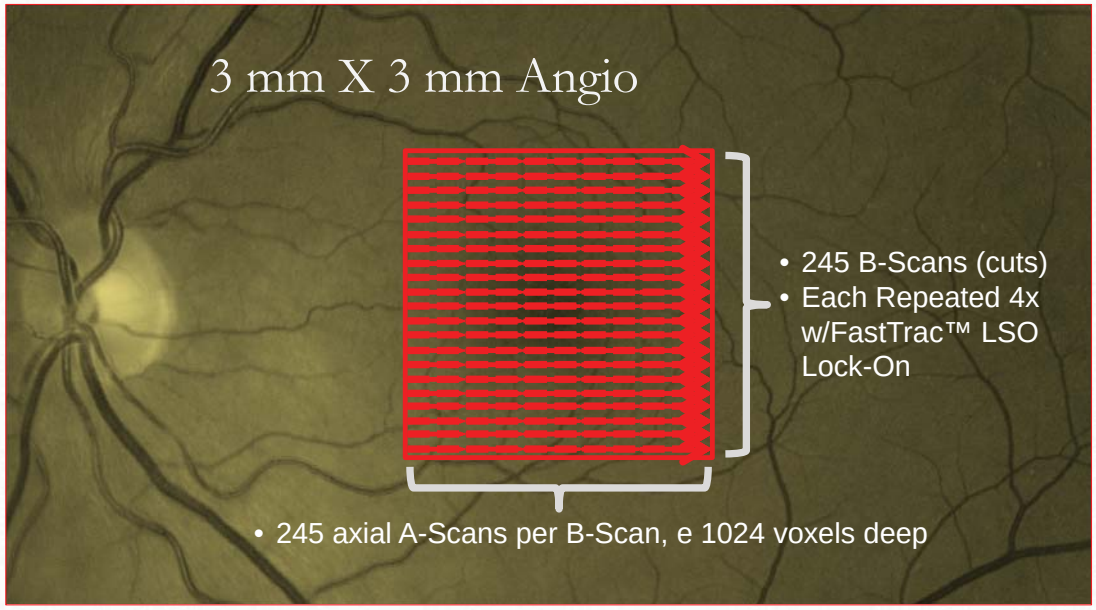
90 Years of ZEISS and Retinal Imaging

1. **First commercial Retina Camera** in the early 1920s.
2. **First commercial OCT** TWENTY YEARS AGO in 1996-1997.
3. **First FDA-Cleared OCTA** in late 2015

ZEISS is a **revered brand** worldwide, not just in Eye Care.
We are involved in dozens of other markets at the highest levels.

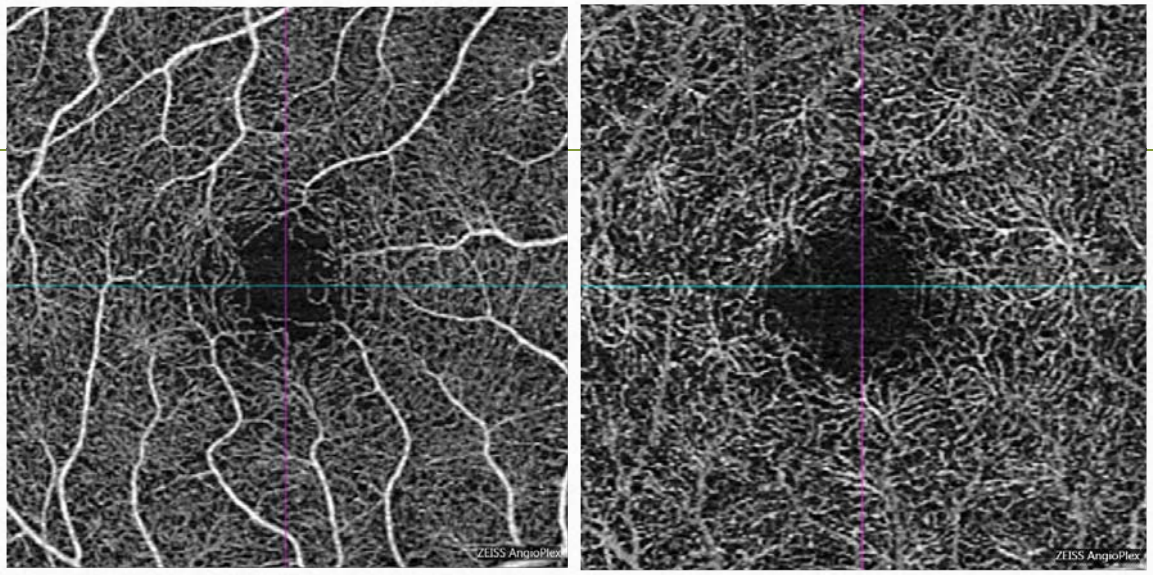


Zeiss AngioPlex™ = One Fast Cubic Scan x4

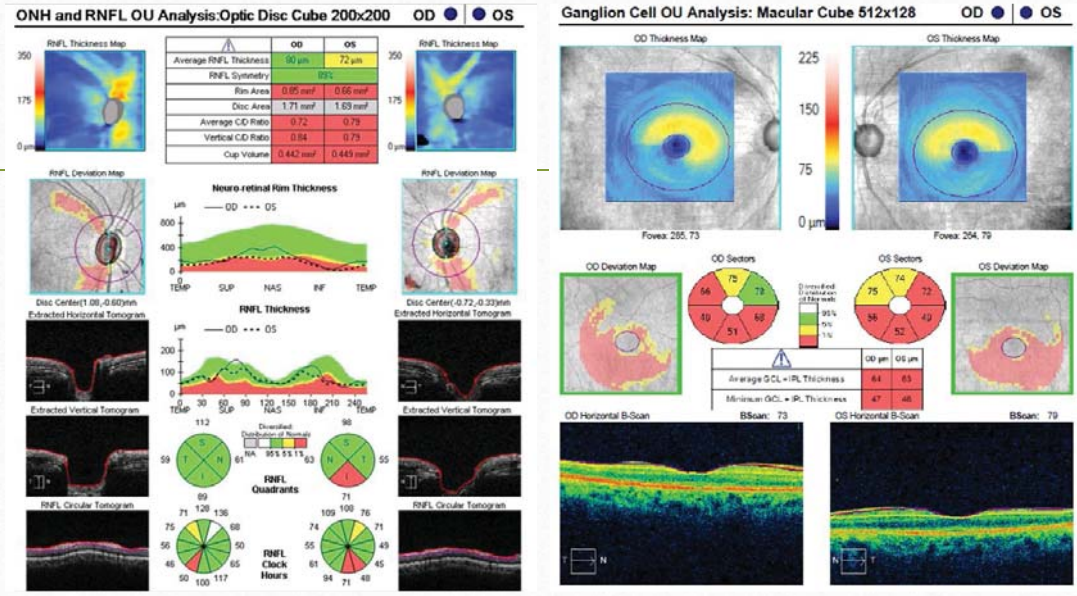


Total = **240,000 A-scans,** ~ 5.0 secs

Normal 3x3 Angio Cube OD - Full Retina (L) and Deep Plexus (R)

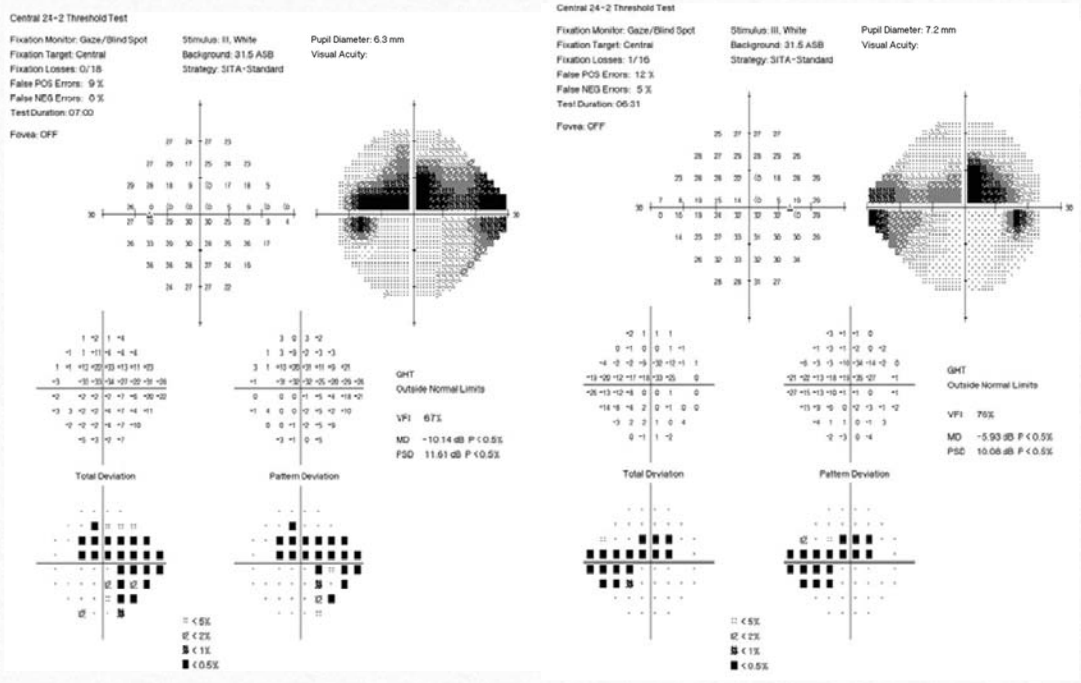


Glaucoma



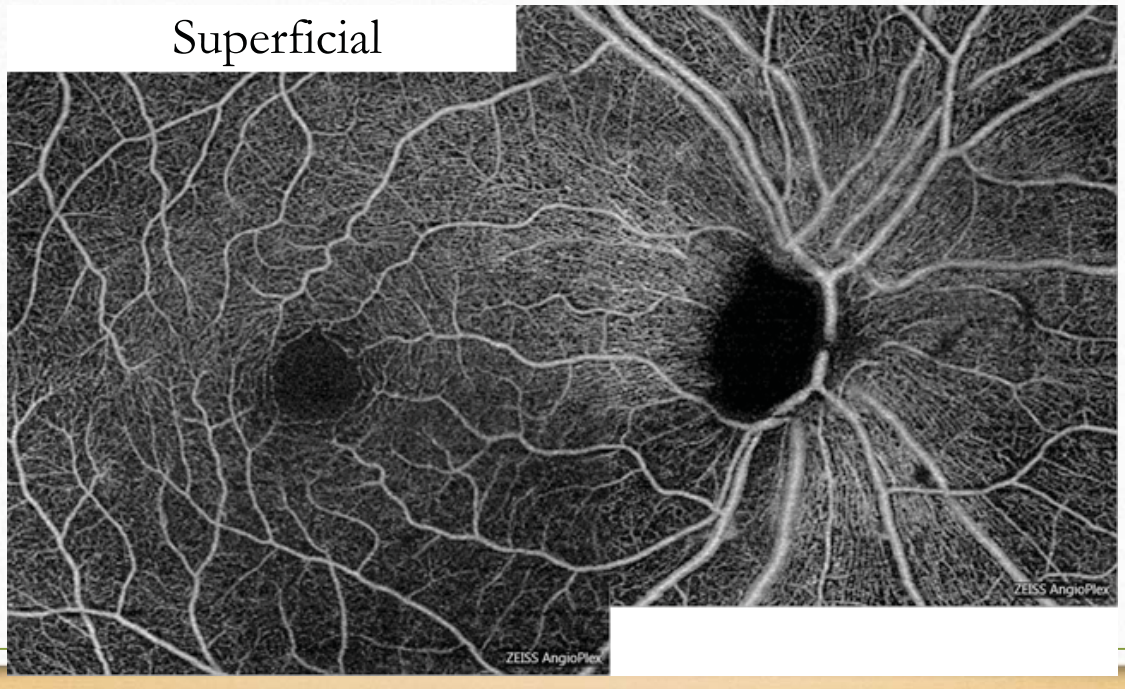
This case courtesy of **Carolyn Majcher, OD**. Incarnate Word, San Antonio

Glaucoma



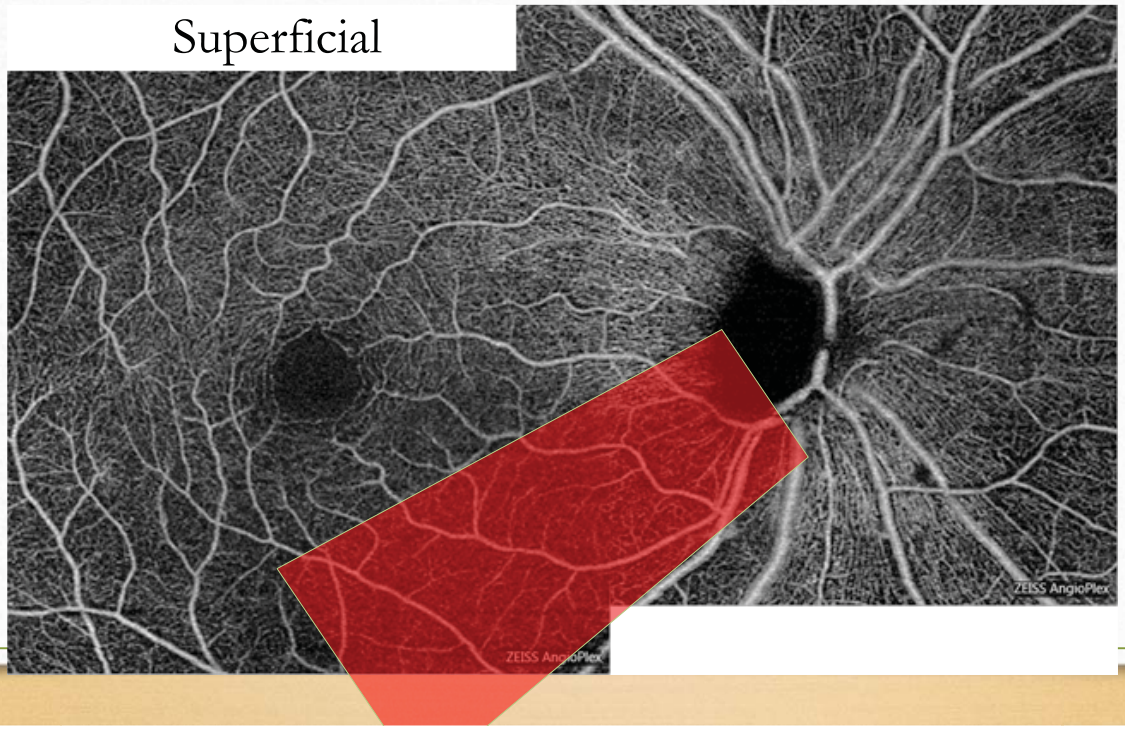
Glaucoma

Superficial



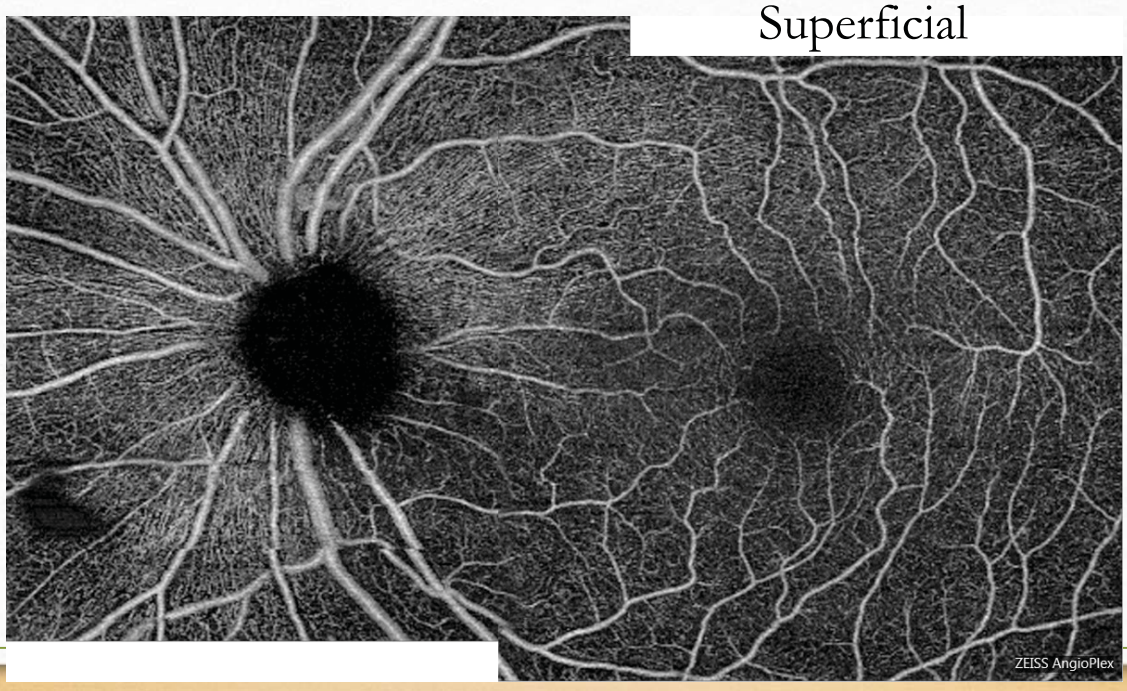
Glaucoma

Superficial



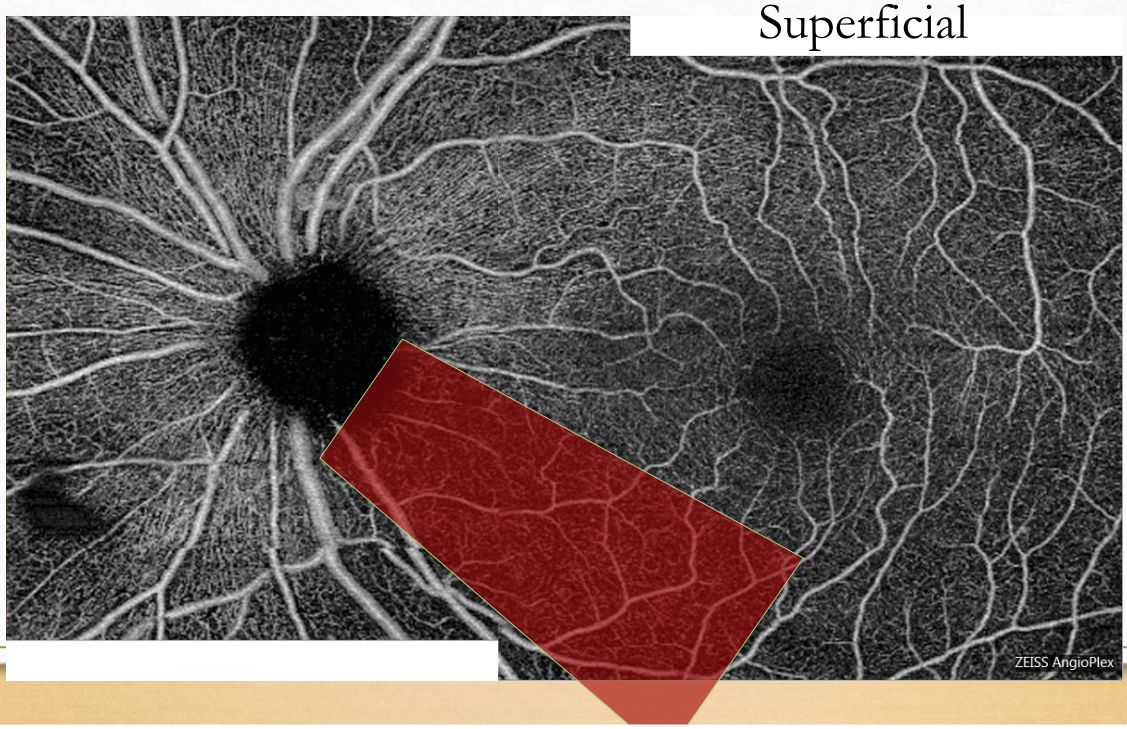
Glaucoma

Superficial



Glaucoma

Superficial



Dry Eye Syndrome in Glaucoma

I Tear Deficiency

II Evaporative 2º to Goblet Cell Deficiency/ Mucin Deficiency

III Blepharitis/ Meibomian Gland Disease

IV Exposure Keratopathy

Dry Eye Syndrome
Co-Conspirators
Exacerbate or Masquerade DES

1. SLK (superior limbic keratoconjunctivitis)
2. Medicomentosa (topical medication toxicity)
3. SPK of Thygeson
4. Mucous Fishing Syndrome
5. Contact Lens Related Toxicity
6. Chemical Toxicity (eg hairspray toxicity)
7. Allergic / Atopic Conjunctivitis
8. Conjunctivochalasis (CCh)
9. Floppy Lid Syndrome

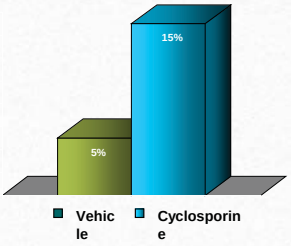
Current and Emerging Therapies

- Established
  - Cyclosporine A (Restasis)
  - Thermal pulsation therapy (LipiFlow)
- Emerging
  - Lifitegrast (Xiidra)
  - Nasal neurostimulation (Allergan/Oculeve)
- Pipeline – Phase II-III
  - New delivery vehicles
  - Nanoparticle technology
  - New small-molecule therapies

Cyclosporine A (Restasis)

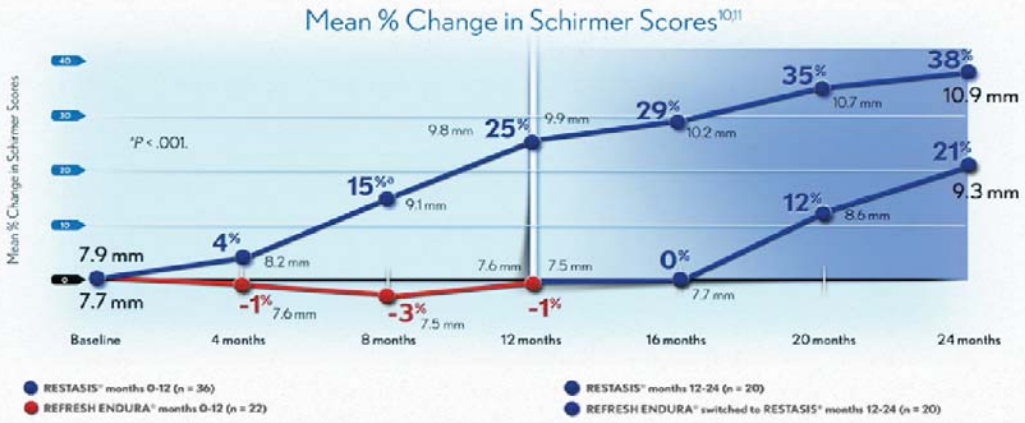
- Immunosuppressive agent when administered systemically
- Inhibits T-cell activation, enabling patients to produce their own tears[1]
- In clinical trials:
  - Increased tear production (superior Schirmer scores)
  - Reduced corneal staining
  - Increased goblet cell density
  - Reduced reliance on artificial tears

% of Subjects with Improvement of ≥10 mm



1. Nelson et al. *Adv Ther.* 2000.

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% Helped Moderate and Severe Patients Make More of Their Own Real Tears[1,2]



1. Rao. *J Ocul Pharmacol Ther*. 2010; 2. Rao. *J Ocul Pharmacol Ther*. 2011.

Thermal Pulsation Therapy (LipiFlow)

- Only approved treatment for MGD
- Heats inner lid to 42.5°C combined with simultaneous pulsation for gland evacuation
  - Protects cornea and globe from heat and pressure
- Outcomes:
  - Sustained effects over 12 months with 1 treatment[1]
    - 50% reduction in symptoms
    - 3x improvement in MG secretions
  - Improves comfort & MG function after cataract Sx[2]
  - Increases comfortable CL wear time[3]

1. Blackie CA, Holland,EJ et al. Curr Opin Ophthalmol 2015, 26:306–313.; 2. Jackson M. ASCRS 2015. 3. Kading D. VEW, 2015

Emerging Treatments

Lifitegrast

- First prescription FDA approved drop to treat signs AND symptoms of DED
- Lifitigrast versus vehicle was evaluated for safety and efficacy in four clinical trials with a total of 2,133 patients, Age range 19–97 yrs (mean 59)
- Primary Endpoints
  - Improvement in the signs (measured by Inferior Corneal Staining Score)
  - Symptoms of dry eye disease (measured by Eye Dryness Score)

Integrins and the Immunological Synapse: Role in Inflammation

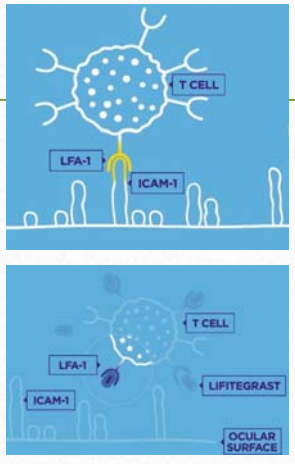
- Integrins are transmembrane receptors that bridge the cell-cell interactions
- LFA-1
  - Cell-surface protein on T cell
- ICAM-1
  - Cell surface protein on APC
  - Also present on conjunctival endothelial and epithelial cells
  - Expressed at higher levels in patients with dry eye disease

APC = antigen-presenting cell.

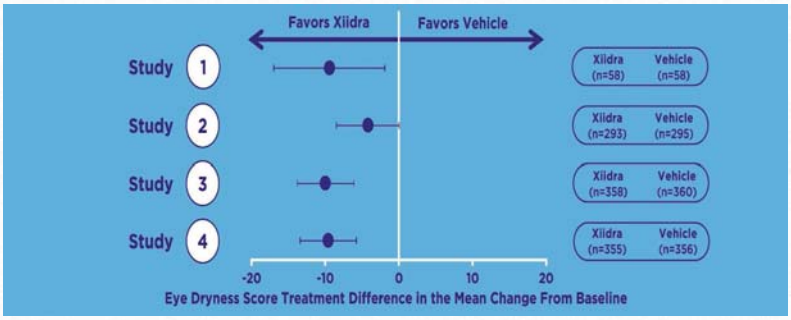
LFA-1 and ICAM-1 binding is central to the immunological response

Lifitegrast: MOA

- Lifitegrast binds to integrin receptor LFA-1
- Blocks the interaction of LFA-1 with ICAM-1 that signals the start of the inflammatory cycle. May inhibit:
  - T-cell activation
  - T-cell migration
  - Secretion of inflammatory cytokines



Primary End Point: Eye Dryness Score

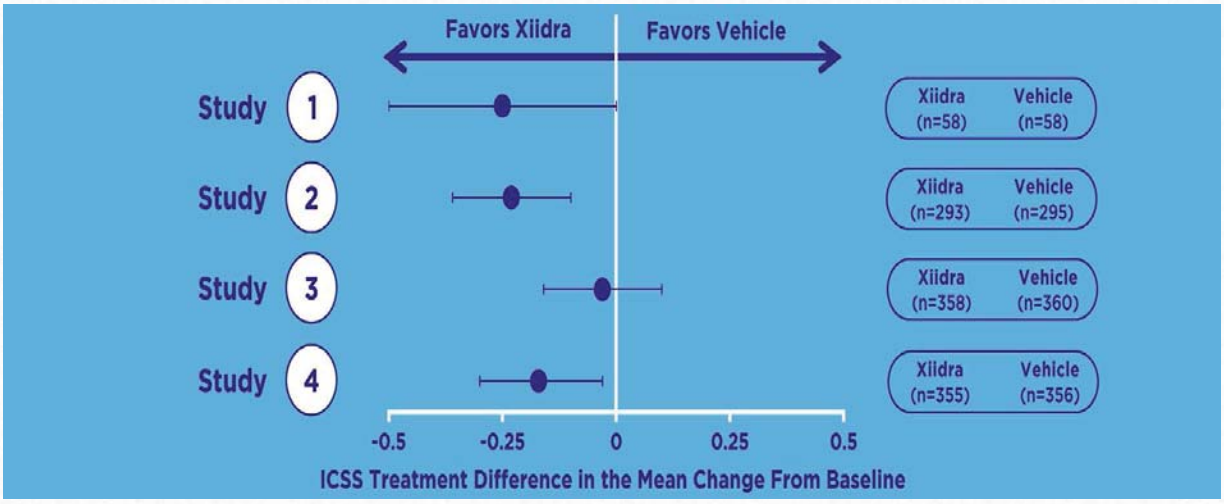


Lifitigrast Effects on Signs/Symptoms

- Onset of action in as early as 2 weeks[1]
  - Larger reduction in dryness observed at week 6
  - Larger reduction in inferior corneal staining at week 12
- Initiate treatment for signs or symptoms of Dry Eye

1. Semba CP, Gadek TR. Development of lifitegrast: a novel T-cell inhibitor for the treatment of dry eye disease. Clin Ophthalmol. 2016;10:1083-1094-

Primary End Point: Inferior Corneal Staining



OPEN

Safety of Lifitegrast Ophthalmic Solution 5.0% in Patients With Dry Eye Disease: A 1-Year, Multicenter, Randomized, Placebo-Controlled Study

Eric D. Donnenfeld, MD, FAAO, Paul M. Karpecki, OD, FAAO,† Parag A. Majmudar, MD,‡ Kelly K. Nichols, OD, MPH, PhD,§ Aparna Raychaudhuri, PhD,¶ Monica Roy, OD, MPH, FAAO,¶ and Charles P. Semba, MD¶*

Purpose: To evaluate the 1-year safety of lifitegrast ophthalmic solution 5.0% in patients with dry eye disease compared with placebo.

Methods: SONATA (Safety Of a 5.0% coNcentrATion of lifitegrAst ophthalmic solution) was a multicenter, randomized, prospective, double-masked, placebo-controlled phase 3 study (NCT01636206). Adults (≥18 years) with dry eye disease (Schirmer test score ≥1 and ≤10 mm; corneal staining score ≥2.0) were randomized 2:1 to lifitegrast ophthalmic solution 5.0% or placebo twice daily for 360 days. The primary objective was percentage and severity of treatment-emergent adverse events (TEAEs). Secondary objectives were ocular safety measures: corneal fluorescein staining, drop comfort, best-corrected visual acuity, slit-lamp biomicroscopy, and intraocular pressure over 7 visits. Exploratory objectives included concentration of lifitegrast in plasma.

Results: The safety population comprised 331 participants (220 lifitegrast; 111 placebo). There were no serious ocular TEAEs. Overall, 53.6% of participants receiving lifitegrast experienced ≥1 ocular TEAE versus 34.2% in the placebo group; most TEAEs were mild to moderate in severity. Rates of discontinuation because of TEAEs were 12.3% (lifitegrast) versus 9.0% (placebo). The most common (≥5%) TEAEs occurring in either treatment group were instillation site irritation (burning), instillation site reaction, visual acuity reduced, dry eye, and dysgeusia (change in taste). Ocular safety parameters for lifitegrast were similar to placebo. The mean plasma lifitegrast concentration at 360 days (n = 43) was below the limit of detection. There was no indication of systemic toxicity or localized infectious complications secondary to chronic immunosuppression.

Conclusions: Lifitegrast ophthalmic solution 5.0% seemed safe and well tolerated in this study, with no unexpected adverse events.

Key Words: adverse drug reactions, dry eye disease, randomized controlled trial, safety

(*Cornea* 2016;35:741–748)

Lifitegrast is a small-molecule integrin antagonist that was developed as a treatment for dry eye disease (DED) by targeting an inflammatory pathway associated with DED. The efficacy and safety of lifitegrast ophthalmic solution 5.0%, when administered twice daily for 84 days in participants with DED, have been demonstrated in 3 randomized controlled studies. These are 1 phase 2 study[1] and 2 phase 3 studies (OPUS-1[2] and OPUS-2[3]). In OPUS-1, the coprimary sign endpoint of change from baseline to day 84 in inferior corneal staining score was significantly improved in patients with DED treated with lifitegrast compared with placebo. However, the coprimary symptom endpoint of change from baseline to day 84 on the visual-related function subscale was not met.[2] The results of the OPUS-2 study were recently published; they showed that in lifitegrast-treated patients with DED with a recent history of artificial tear use and at least moderate baseline symptomology (eye dryness score ≥40), there was a significant improvement in the coprimary symptom endpoint of eye dryness score compared with placebo. The coprimary sign endpoint of inferior corneal staining score was not met in OPUS-2.[3] In the phase 2 study, and in OPUS-1 and OPUS-2, lifitegrast was generally well tolerated, and no serious ocular adverse events (AEs) were reported.

Lifitegrast is designed to target the inflammation associated with DED by blocking the binding of the integrin, lymphocyte function–associated antigen 1 (LFA-1), to its cognate ligand, intercellular adhesion molecule 1 (ICAM-1). Inflammation at the cellular level of the lacrimal gland and ocular surface plays a major role in DED and is associated with symptoms of eye dryness and discomfort.[4] T-cell activation is critical in the inflammatory process and is influenced by LFA-1/ICAM-1 binding.[5] The interaction of

Received for publication October 16, 2015; revision received December 8, 2015; accepted January 8, 2016. Published online ahead of print April 7, 2016.

From the *Ophthalmic Consultants of Long Island, Garden City, NY; †Koffler Vision Group, Lexington, KY; ‡Chicago Cornea Consultants, Ltd., Hoffman Estates, IL; §University of Alabama at Birmingham, School of Optometry, Birmingham, AL; and ¶Shire, Lexington, MA.

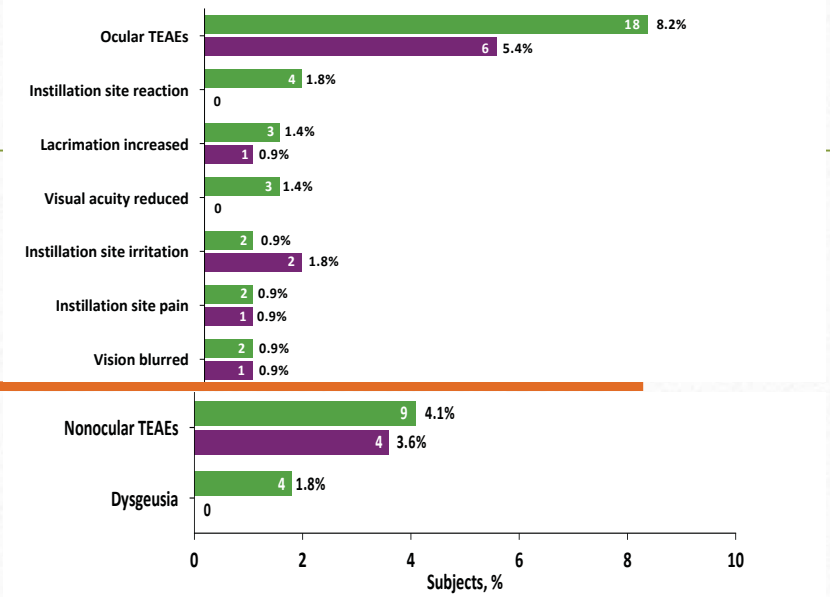
This study was funded by SAReode Bioscience (now a wholly owned subsidiary of Shire) and Shire.

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.corneajrnl.com).

Reprints: Eric D. Donnenfeld, MD, 711 Stewart Avenue, Suite 160, Garden City, NY 11530 (e-mail: ericdonnenfeld@gmail.com).

TEAEs Leading to Discontinuation



OPEN

Effect of Oral Re-esterified Omega-3 Nutritional Supplementation on Dry Eyes

Alice T. Epitropoulos, MD, Eric D. Donnenfeld, MD,† Zubin A. Shah, MPH,‡ Edward J. Holland, MD,§ Michael Gross, MD,‡ William J. Faulkner, MD,§ Cynthia Matossian, MD,¶ Stephen S. Lane, MD,‖ Melissa Toyos, MD,** Frank A. Bucci, Jr, MD,†† and Henry D. Perry, MD†*

Purpose: To assess the effect of oral re-esterified omega-3 fatty acids on tear osmolarity, matrix metalloproteinase-9 (MMP-9), tear break-up time (TBUT), Ocular Surface Disease Index (OSDI), fluorescein corneal staining, Schirmer score, meibomian gland dysfunction (MGD) stage and omega-3 index in subjects with dry eyes and confirmed MGD.

Methods: This was a multicenter, prospective, interventional, placebo-controlled, double-masked study. Subjects were randomized to receive 4 softgels containing a total of 1680 mg of eicosapentaenoic acid/560 mg of docosahexaenoic acid or a control of 3136 mg of linoleic acid, daily for 12 weeks. Subjects were measured at baseline, week 6, and week 12 for tear osmolarity, TBUT, OSDI, fluorescein corneal staining, and Schirmer test with anesthesia. MMP-9 testing and omega-3 index were done at baseline and at 12 weeks.

Results: One hundred five subjects completed the study. They were randomized to omega-3 ($n = 54$) and control group ($n = 51$). Statistically significant reduction in tear osmolarity was observed in the omega-3 group versus control group at week 6 (-16.8 ± 2.6 vs. -9.0 ± 2.7 mOsm/L, $P = 0.042$) and week 12 (-19.4 ± 2.7 vs. -8.3 ± 2.8 mOsm/L, $P = 0.004$). At 12 weeks, a statistically significant increase in omega-3 index levels ($P < 0.001$) and TBUT (3.5 ± 0.5 s vs. 1.2 ± 0.5 s, $P = 0.002$) was also observed. Omega-3 group experienced a significant reduction in MMP-9 positivity versus control group (67.9% vs. 35.0%, $P = 0.024$) and OSDI scores decreased significantly in omega-3 (-17.0 ± 2.6) versus control group (-5.0 ± 2.7, $P = 0.002$).

Conclusions: Oral consumption of re-esterified omega-3 fatty acids is associated with statistically significant improvement in tear osmolarity, omega-3 index levels, TBUT, MMP-9, and OSDI symptom scores.

Key Words: dry eyes, omega-3 fatty acid, tear osmolarity, re-esterified omega-3, meibomian gland dysfunction

(*Cornea* 2016;0:1–7)

Dry eye disease (DED) is a common, yet complex, multifactorial progressive condition that can lead to visual loss, damage to the ocular surface, discomfort, and overall reduction in quality of life.[1,2] Meibomian gland dysfunction (MGD) results in inadequate and dysfunctional lipid production, which leads to evaporative DED.[3] MGD has, also, recently been shown to be a sign of hypercholesterolemia.[4,5] Because MGD is associated with altered lipid composition, dietary supplementation with omega-3 fatty acids has been recommended in both the International Dry Eye Workshop and International Workshop on Meibomian Gland Dysfunction as primary therapy.[2,3] With increased tear film evaporation, tear film osmolarity is elevated and results in ocular surface damage: epithelial cell desiccation, loss in glycocalyx,[6] inflammation, and cell apoptosis.[7] Essential fatty acids, including the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), perform numerous roles in the human body and are considered essential nutrients.[8–10] They are important in the treatment and prevention of DED.[11–13]

The rationale for treatment with oral omega-3 supplementation in the management of meibomian gland disease may be explained by 2 different mechanisms of action. The breakdown of omega-3 fatty acids results in anti-inflammatory molecules that suppress the inflammatory pathways that are found in meibomian gland disease. In addition, the unstable tear film associated with meibomian gland disease results in evaporative dry eye. The oral supplementation of omega-3 fatty acids changes the fatty acid composition of the meibomian gland secretions resulting in a secretion that contains increased levels of unsaturated fatty acids, which are in a liquid state at body temperature preventing the blockage of

Received for publication January 13, 2016; revision received May 18, 2016; accepted May 19, 2016.

From the *Ophthalmic Surgeons & Consultants of Ohio, The Eye Center of Columbus; and Department of Ophthalmology, The Ohio State University Wexner Medical Center, Columbus OH; †Ophthalmic Consultants of Long Island, Long Island, NY; ‡PRN Physician Recommended Nutraceuticals, Plymouth Meeting, PA; §Cincinnati Eye Institute, Cincinnati, OH; ¶Matossian Eye Associates, Pennington, NJ; ‖Associated Eye Care, Stillwater, MN; **Toyos Clinic, Nashville, TN; and ††Bucci Laser Vision Institute, Wilkes-Barre, PA.

A. T. Epitropoulos, E. D. Donnenfeld, Z. A. Shah, E. J. Holland, M. Gross, W. J. Faulkner, C. Matossian, S. S. Lane, M. Toyos, and F. A. Bucci Jr received compensation from PRN Physician Recommended Nutraceuticals for participating in the study. The remaining author has no funding or conflicts of interest to disclose.

Reprints: Alice T. Epitropoulos, MD, The Eye Center of Columbus, and The Ohio State University Wexner Medical Center, Columbus, OH 43215 (e-mail: aepitrop@columbus.rr.com).

Dosing Protocol – Dry Eye Omega Benefit

Indications:
- Ocular Surface Inflammation
- Pre-surgical Patients

Therapeutic Dose -Four capsules daily with meals

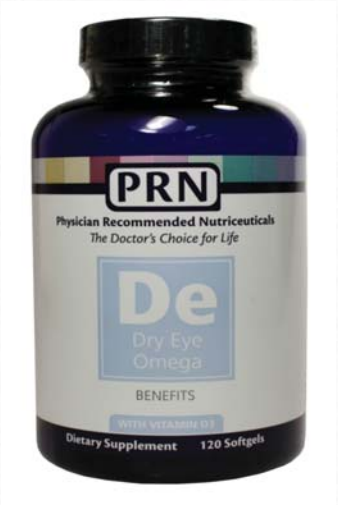
Supplement Facts

Serving Size: 4 Softgels
Servings Per Container: XX

Four Softgels Contain		% Daily Value
Calories (energy)	45	
Calories from Fat	40	
Total Fat	4.5 g	7%*
Polyunsaturated Fat	3 g	†
Monounsaturated Fat	1 g	†
Cholesterol	10 mg	3%*
Protein	<1 g	
Vitamin D (as D_3 Cholecalciferol)	1000 IU	250%
Omega-3 Fatty Acids as TG**	2668 mg	†
EPA (Eicosapentaenoic acid) as TG**	1680 mg	†
DHA (Docosahexaenoic acid) as TG**	560 mg	†
Additional Omega-3 Fatty Acids as TG**	428 mg	†

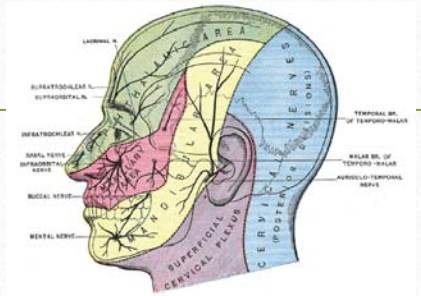
* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.
** Superior Triglyceride Form

Ingredients: Highly Refined and Concentrated Omega-3 Fish Oil (anchovy, sardine, mackerel), Capsule Shell (gelatin, glycerin, purified water), Natural Mixed Berry/Orange Flavor, Natural Mixed Tocopherols (soy), and Cholecalciferol.

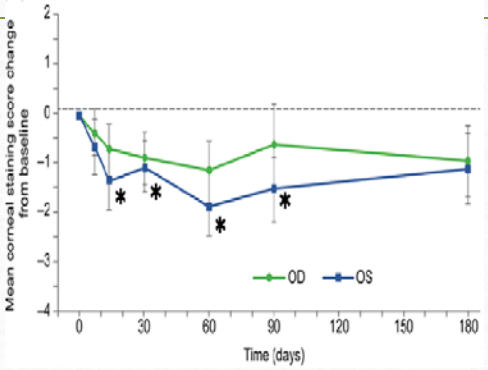


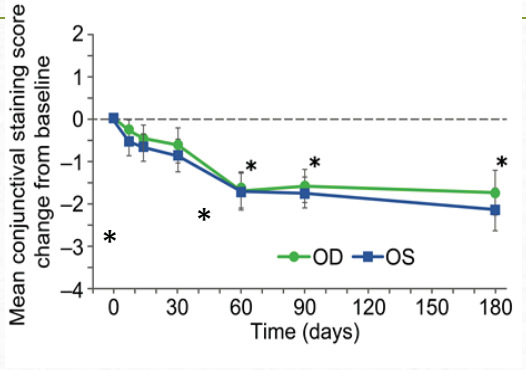
Nasal Neurostimulation

- Targets the nasolacrimal reflex by stimulating an ophthalmic branch of afferent trigeminal nerve fibers in nasal cavity
- Results in upregulation of parasympathetic activity in the superior salivatory nucleus of the brain
- Stimulates the lacrimal glands to increase tear production
- Immediate response to stimulation



Nasal Neurostimulation: Corneal & Conjunctival Staining

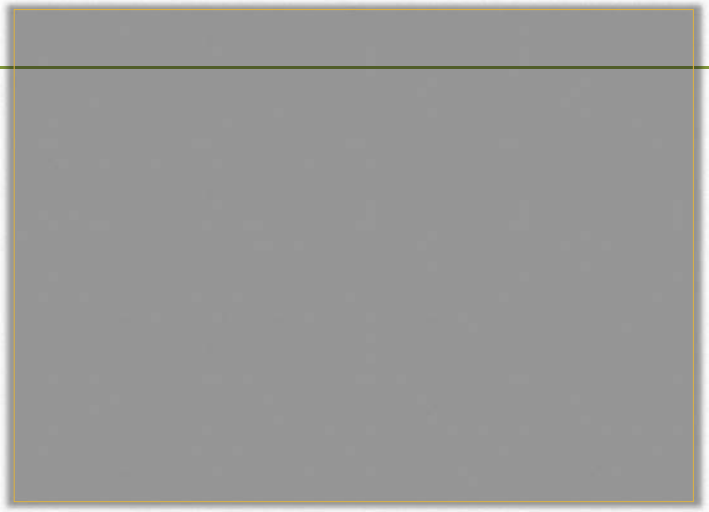




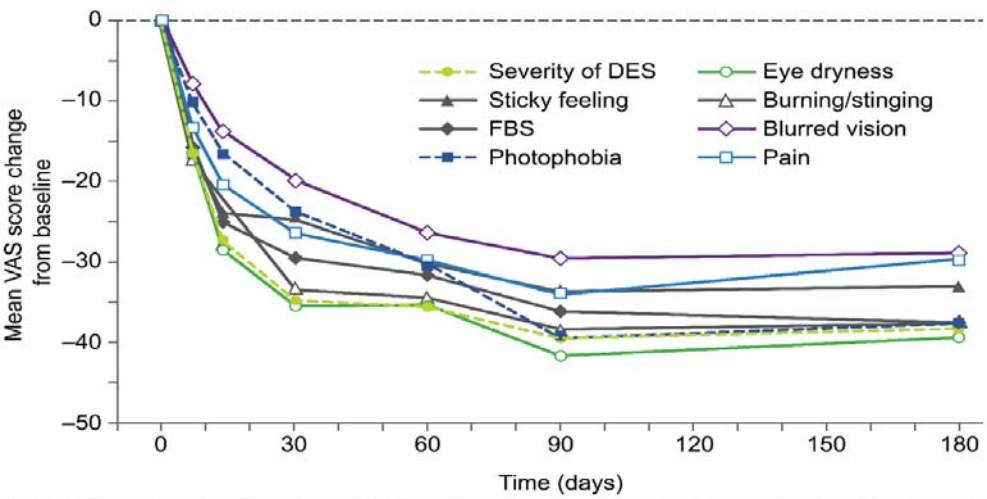
- Corneal staining was reduced relative to baseline in both eyes
- Conjunctival staining was reduced relative to baseline in both eyes

* $P < 0.05$

Nasal Neurostimulation

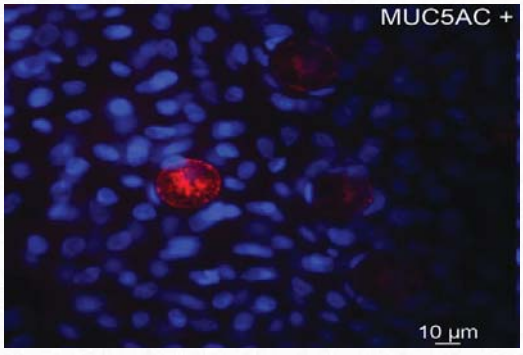


Nasal Neurostimulation: Symptoms Reduced

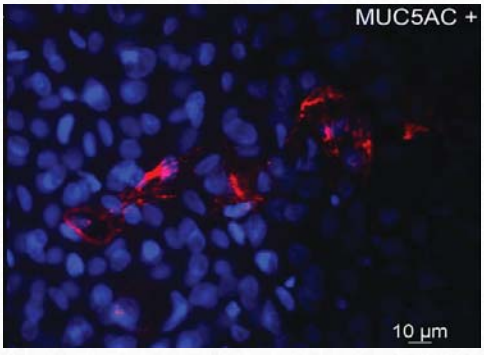


Nasal Neurostimulation: Mucin Secretion

- Nasal neurostimulation induces mucin secretion from goblet cells



Pre-stimulation



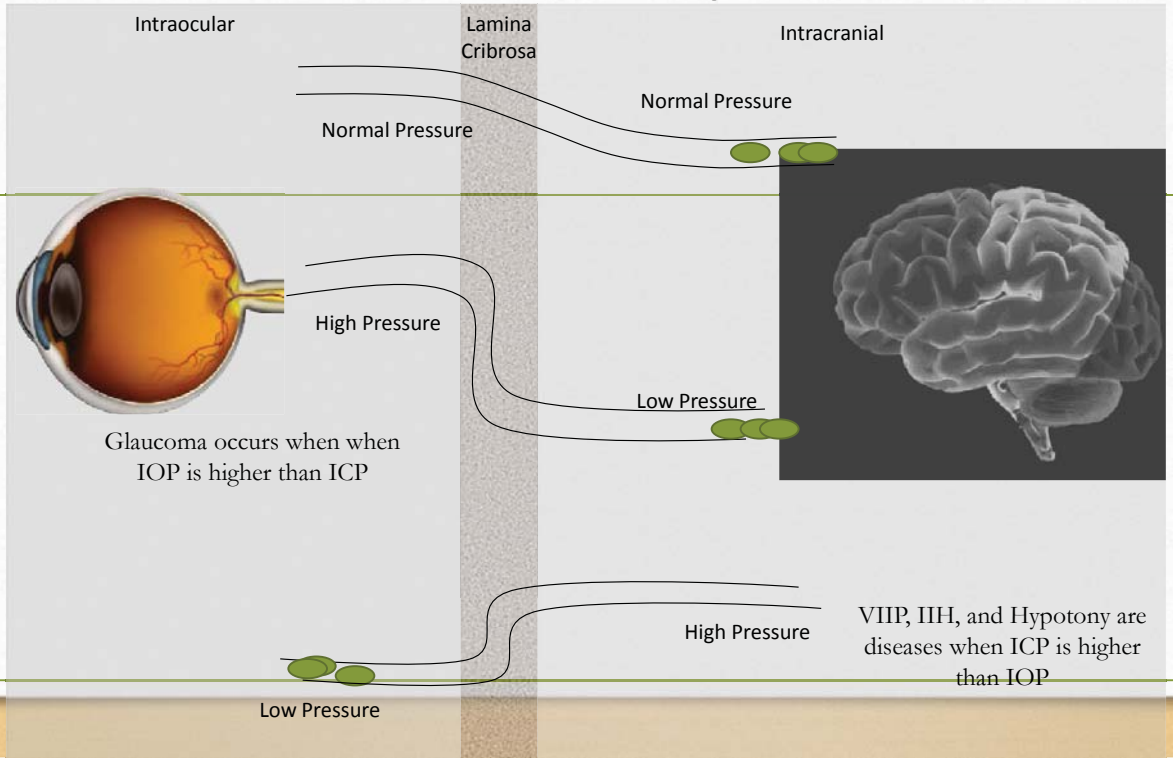
5 min post-stimulation

Visual Impairment and Intracranial Pressure - VIIP

Optic Disc Edema, Globe Flattening, Choroidal Folds, and Hyperopic Shifts Observed in Astronauts after Long-duration Space Flight

Thomas H. Mader, MD,[1] C. Robert Gibson, OD,[2] Anastas F. Pass, OD, JD,[3] Larry A. Kramer, MD,[4] Andrew G. Lee, MD,[5] Jennifer Fogarty, PhD,[6] William J. Tarver, MD,[6] Joseph P. Dervay, MD,[6] Douglas R. Hamilton, MD, PhD,[7] Ashot Sargsyan, MD,[7] John L. Phillips, PhD,[8] Duc Tran, DO,[2] William Lipsky, MD,[2] Jung Choi, OD,[2] Claudia Stern, MD, PhD,[9] Raffi Kuyumjian, MD,[10] James D. Polk, DO[6]

Axonal Transport



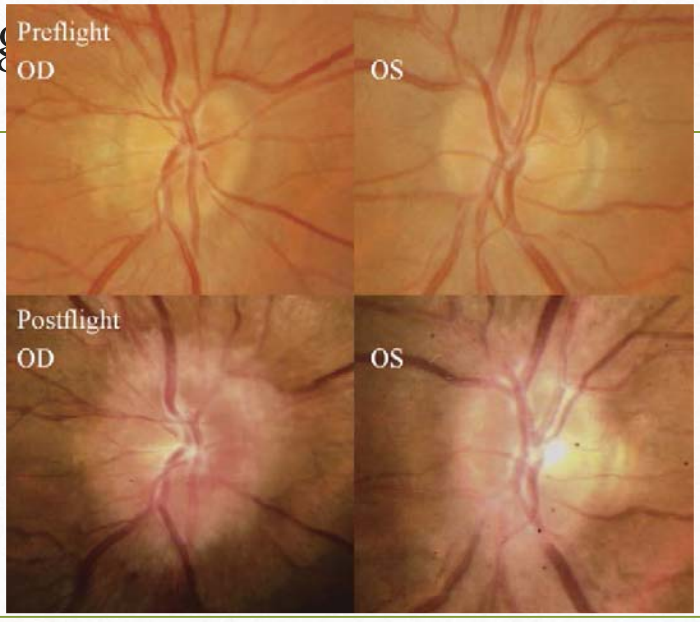
4 Sig

Papilledema

Globe flattening

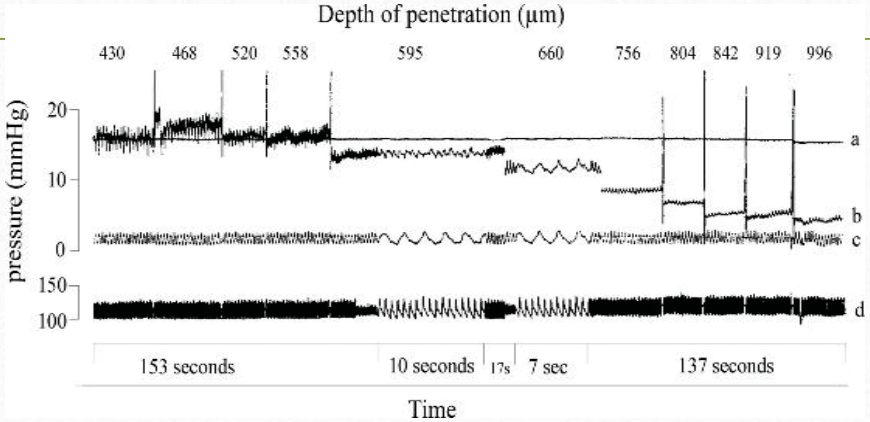
Choroidal Folds

Hyperopic Shift



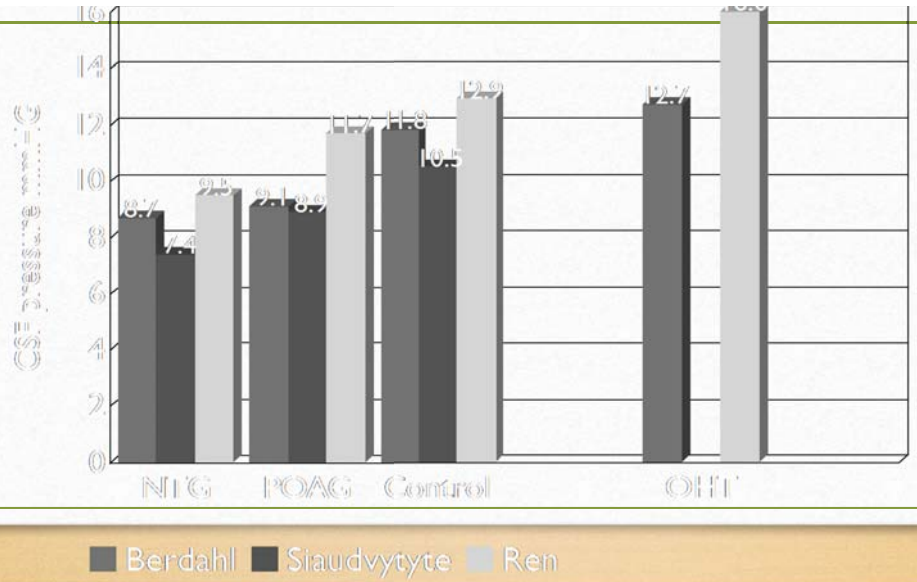
The Clinical Data Story

Micropipette tissue pressure measurements in dog (B) as the micropipette is passed from the vitreous region, the prelaminar region, the lamina and into the retrolaminar optic nerve.

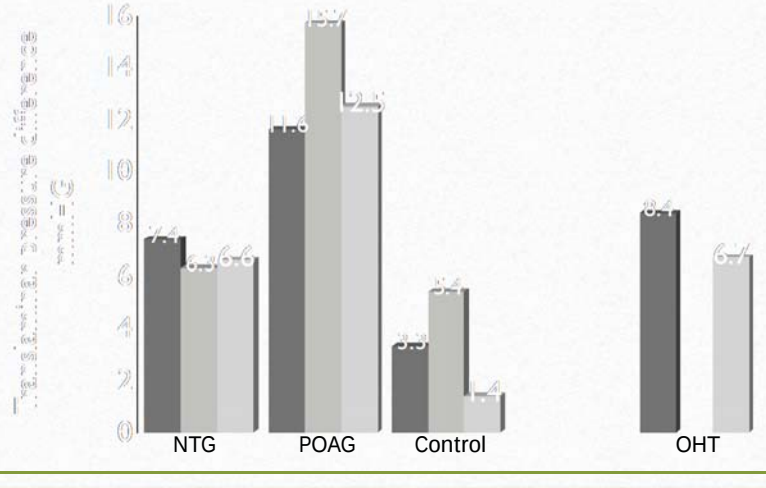


Morgan, W.H., Yu, D.Y., Cooper, R.L., Alder, V.A., Cringle, S.J., Constable, I.J., 1995. The influence of cerebrospinal fluid pressure on the lamina cribrosa tissue pressure gradient. Invest. Ophthalmol. Vis. Sci. 36, 1163–1172.
Morgan, W.H., Yu, D.Y., Alder, V.A., 1998. The correlation between cerebrospinal fluid pres- sure and retrolaminar tissue pressure. Invest. Ophthalmol. Vis. Sci. 39, 1419–1428. Morgan, W.H., Chauhan, B.C., Yu, D.Y., 2002. Optic disc movement with variations in in-
traocular and cerebrospinal fluid pressure. Invest. Ophthalmol. Vis. Sci. 43, 3236–3242. Morgan, W.H., Yu, D.Y., Balaratnasingam, C., 2008a. The role of cerebrospinal fluid pressure in glaucoma pathophysiology: the dark side of the optic disc. J. Glaucoma 17, 408–413. Morgan, W.H., Cringle, S.J., Balaratnasingam, C., Yu, D.Y., 2008b. Impaired cerebrospinal fluid
circulation and its relationship to glaucoma. Clin. Experiment. Ophthalmol. 36, 802–803. Morgan, W.H., Lind, C.R., Kain, S., Fatehee, N., Bala, A., Yu, D.Y., 2012. Retinal vein pul- sation is in phase with intracranial pressure and not intraocular pressure. Invest. Ophthal-
mol. Vis. Sci. 53, 4676–4681.
Morgan, W.H., Balaratnasingam, C., Lind, C.R.P., Colley, S., Kang, M.H., House, P.H., Yu, D.Y., 2015. Cerebrospinal fluid pressure and the eye. Br J Ophthalmol. 2015 Apr 15. http://dx.doi.org/10.1136/bjophthalmol-2015-306705. pii: bjophthalmol-2015- 306705 [Epub ahead of print].

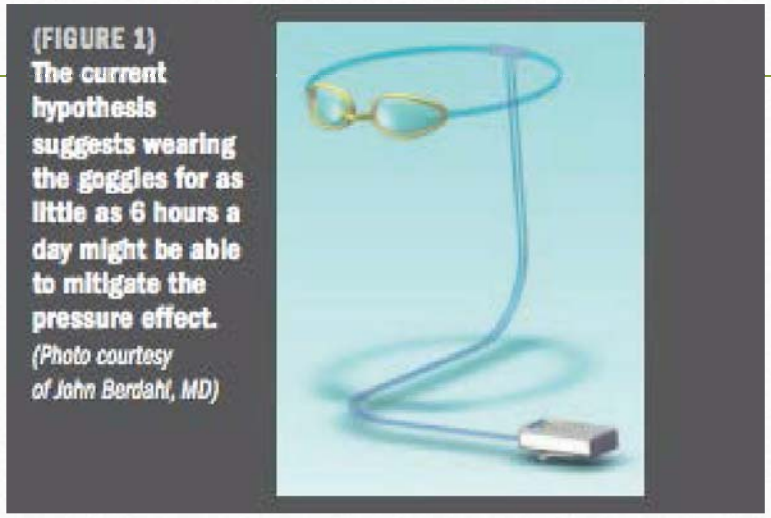
CSF pressure



Translaminar pressure difference



IOP Control Device

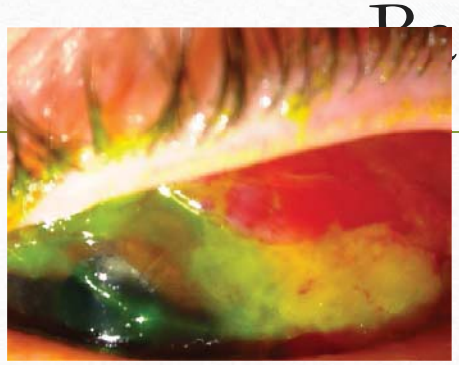


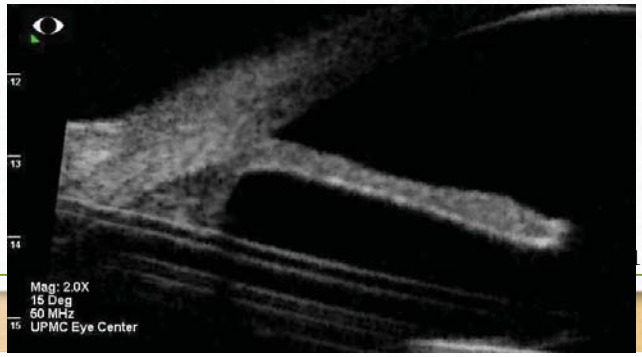
(FIGURE 1)
The current hypothesis suggests wearing the goggles for as little as 6 hours a day might be able to mitigate the pressure effect.
(Photo courtesy of John Berdahl, MD)

6. Trab's vs Tubes: A New Paradigm

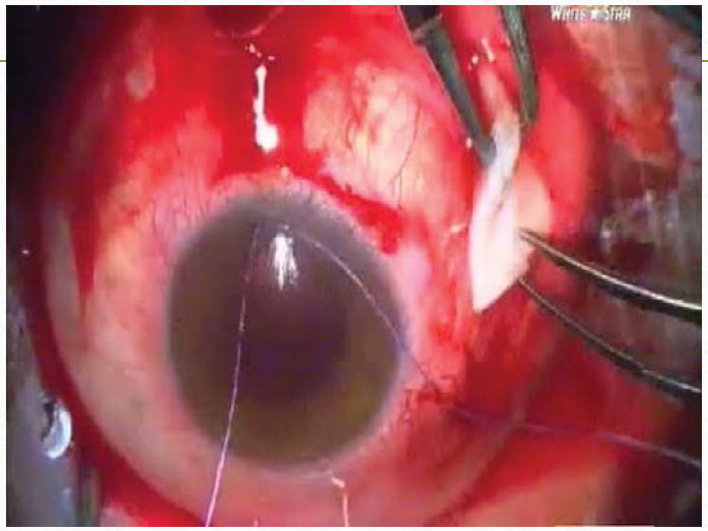
Opp's Move Over for the New Kid in Town!

Baerveldt





Baerveldt Patch Graft Placement

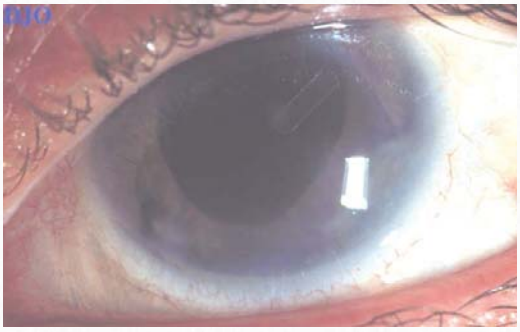


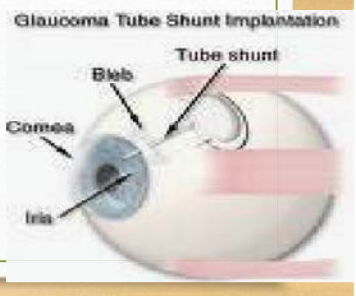
Baerveldt Advantages

- Effective for almost all types of glaucoma
- Able to do when other procedures are not possible
- Not dependent on patient healing
- Can implant multiple devices

TUBE SHUNT SURGERY

- Tube in anterior chamber connects to a reservoir sutured to posterior globe
  - reservoir (plate) prevents scar from blocking tube opening
  - scar around reservoir will limit IOP



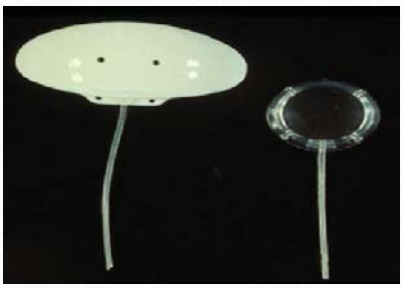


TUBE PROBLEMS

- Gradual failure due to scarring around reservoir
- Erosion of tube through conjunctiva
  - Consequent serious risk of infection
- Decompensation of corneal endothelium
  - can occur even without contact of tube and endothelium
  - corneal transplants usually fail over several years if tube is in anterior chamber
  - tube can be moved to posterior chamber after vitrectomy

Common tube types

- Ahmed has a valve to limit early hypotony
- Baerveldt has larger surface area
  - 1-2 points lower than Ahmed
  - but greater risk of suprachoroidal hemorrhage



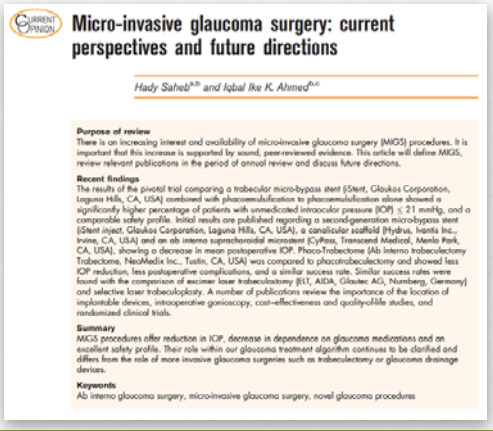
Physiologic outflow

- Two subsections:
  - Trabecular meshwork
  - Schlemm's canal and episcleral veins
- Conventional fistulization surgery bypasses both
- Non-penetrating may bypass just TM or both sections

7. MIGS: The Future of Glaucoma Therapy

MIGS – Micro-Invasive Glaucoma Surgery

- Ab-interno approach
  - Clear corneal micro-incision (<2.0mm)
  - Conjunctival sparing
- Minimally traumatic
  - Negligible disruption of normal anatomy/physiology
  - Excellent biocompatibility
- Efficacious
- Extremely high safety profile
- Rapid recovery



Micro-invasive glaucoma surgery: current perspectives and future directions

Hady Saheb[a,b] and Iqbal Ike K. Ahmed[b,c]

Purpose of review
There is an increasing interest and availability of micro-invasive glaucoma surgery (MIGS) procedures. It is important that this increase is supported by sound, peer-reviewed evidence. This article will define MIGS, review relevant publications in the period of annual review and discuss future directions.

Recent findings
The results of the pivotal trial comparing a trabecular micro-bypass stent (iStent, Glaukos Corporation, Laguna Hills, CA, USA) combined with phacoemulsification to phacoemulsification alone showed a significantly higher percentage of patients with unmedicated intraocular pressure (IOP) ≤ 21 mmHg, and a comparable safety profile. Initial results are published regarding a second-generation micro-bypass stent (iStent inject, Glaukos Corporation, Laguna Hills, CA, USA), a canalicular scaffold (Hydrus, Irantis Inc., Irvine, CA, USA) and an ab interno suprachoroidal microstent (CyPass, Transcend Medical, Menlo Park, CA, USA), showing a decrease in mean postoperative IOP. Phaco-Trabectome (Ab Interno trabeculectomy Trabectome, NeoMedix Inc., Tustin, CA, USA) was compared to phacotrabeculectomy and showed less IOP reduction, less postoperative complications, and a similar success rate. Similar success rates were found with the comparison of excimer laser trabeculostomy (ELT, AIDA, Glaukos AG, Nurnberg, Germany) and selective laser trabeculoplasty. A number of publications review the importance of the location of implantable devices, intraoperative gonioscopy, cost-effectiveness and quality-of-life studies, and randomized clinical trials.

Summary
MIGS procedures offer reduction in IOP, decrease in dependence on glaucoma medications and an excellent safety profile. Their role within our glaucoma treatment algorithm continues to be clarified and differs from the role of more invasive glaucoma surgeries such as trabeculectomy or glaucoma drainage devices.

Keywords
Ab interno glaucoma surgery, micro-invasive glaucoma surgery, novel glaucoma procedures

Curr Opin Ophthalmol 2012, 23:96 - 104

Current OAG Treatment Algorithm[1]

Newly Diagnosed POAG Patient

Prescription Therapy (30 – 90 Days)

Laser Trabeculoplasty

Switch or Add Rx Therapy

Add More Rx Therapy

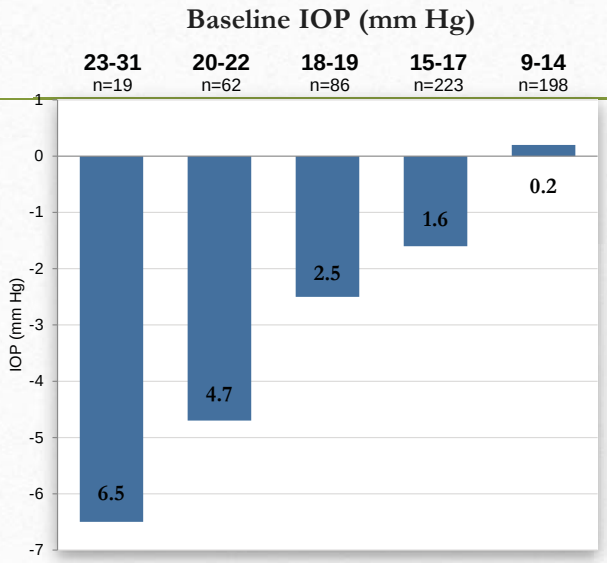
Invasive Surgery Trabeculectomy

Drug therapy has been the standard of care in glaucoma for over 30 years.

Approximately 50% of patients are taking 2 or more medications increasing the disease management challenges of glaucoma and financial burden to patients and the healthcare system.[2,3]

[1]AAO Preferred Practice Pattern, Primary Open Angle Glaucoma. AAO committee 2003.
[2]Stein J., Newman-Casey P., Niziol L., et. al. Association between the use of glaucoma medications and mortality. *Arch Ophthalmol. 2010*;128(2):235-245.
[3]Market Scope Quarterly Glaucoma Report, 4th quarter 2013.

Effect of Cataract Surgery on IOP Reduction



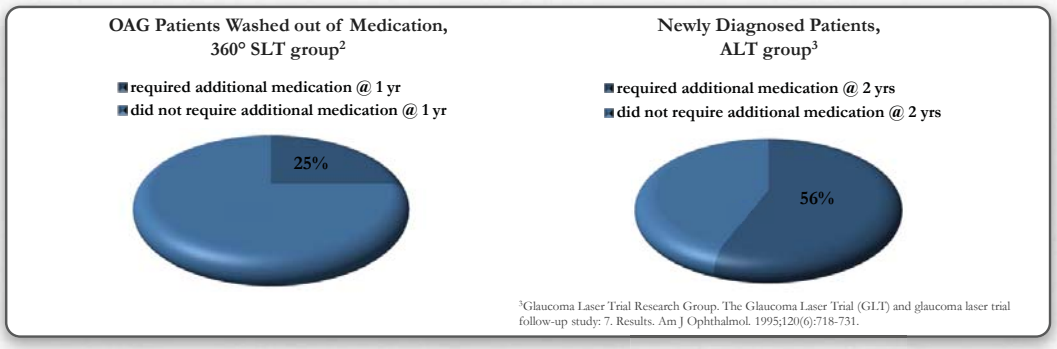
According to Preferred Practice Patterns, cataract surgery with IOL implantation alone results in a modest reduction in IOP of less than 2mm Hg on average.[1]

- Chart review of 588 normotensive and OHT subjects[2]
- 53% had a mean reduction of 1.6 to 2.5 mm Hg[2]

[1]American Academy of Ophthalmology, Preferred Practice Patterns, 2010.
[2]Poley BJ, Lindstrom RL, et al. Long-term effects of phacoemulsification with intraocular lens implantation in normotensive and ocular hypertensive eyes. J *Cataract Refract Surg* .2008;34(5):735-42.

Selective and Argon Laser Trabeculoplasty

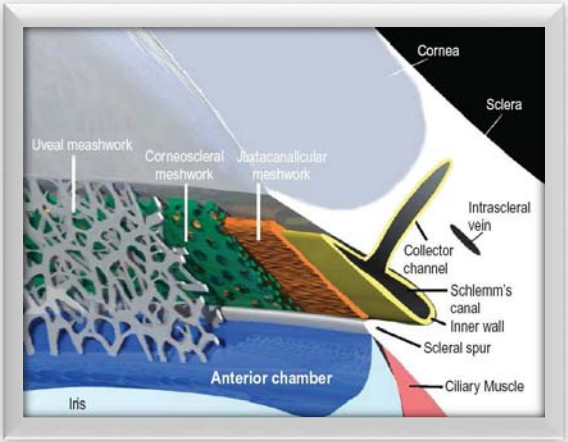
- Compared to medications, SLT demonstrates similar IOP reductions (6-8mm Hg from baseline), safety, and tolerability, and no issues with compliance/adherence[1]
- Following laser trabeculoplasty, many patients require the addition of medication to maintain target IOP



[3]Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT) and glaucoma laser trial follow-up study: 7. Results. Am J Ophthalmol. 1995;120(6):718-731.

[1]Katz LJ, Steinmann WC, Kabir A, Molineaux J, Wizov SS, Marcellino G. Selective laser trabeculoplasty versus medical therapy asinitial treatment of glaucoma: a prospective, randomized trial [published online ahead of print May 3, 2011]. J Glaucoma.
[2]Nagar M, Ogunyomade A, O'Brart DP, Howes F, Marshall J. A randomised, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma. Br J Ophthalmol. 2005;89(11):1413-1417.

Primary Source of Resistance: Diseased Trabecular Meshwork



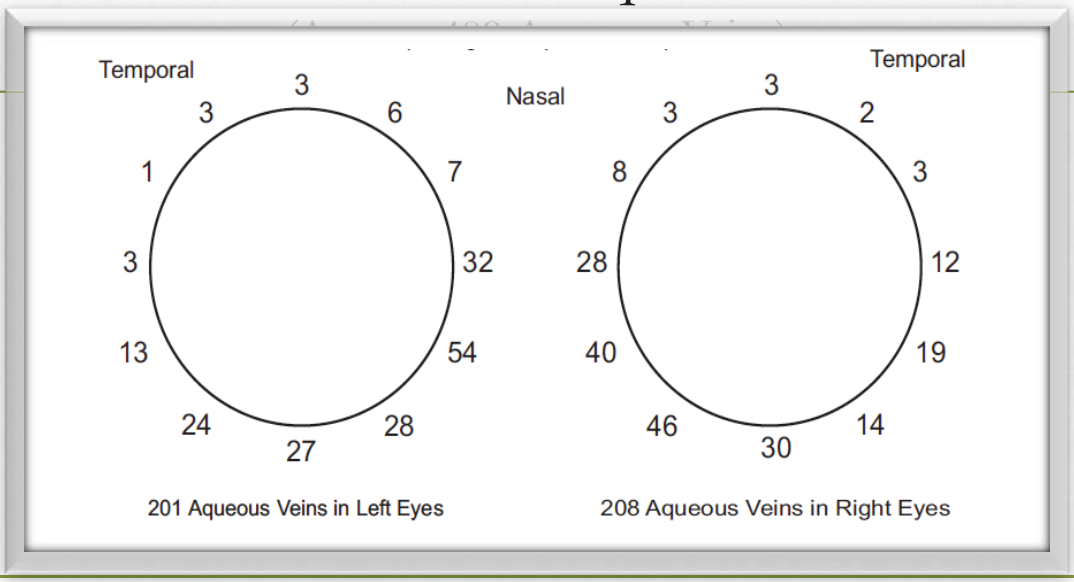
- Abnormality of the trabecular meshwork (TM) is the primary source of elevated intraocular pressure (IOP) in open-angle glaucoma[1]
- 50-75% of total resistance to aqueous humor outflow is found in the juxtacanalicular tissue of the TM[2,3]
- Bypassing the TM allows access to Schlemm's canal and the distal system in order to improve aqueous outflow through the conventional outflow pathways

[1]Grant WM. Further studies on facility of flow through the trabecular meshwork. *Arch Ophthalmol.*1958;60(4)1:523-33.
[2]Rosenquist R, Epstein D, Melamed S, Johnson M, Grant WM. Outflow resistance of enucleated human eyes at two different perfusion pressures and different extents of trabeculotomy. *Curr Eye Res.* 1989;(12):1233-40.
[3]Johnson DH, Johnson M. How does non-penetrating glaucoma surgery work? Aqueous outflow resistance and glaucoma surgery. J *Glaucoma*.2001;10:55-67.

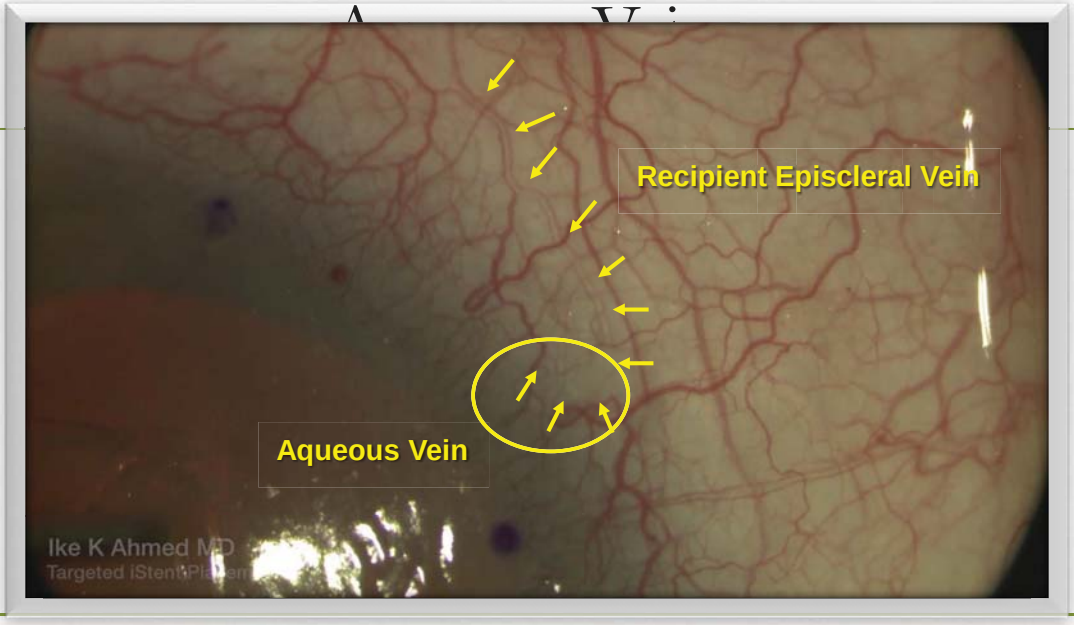
iStent® Indication for Use (US Label)

The iStent Trabecular Micro-Bypass Stent is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication

Distribution of Aqueous Veins

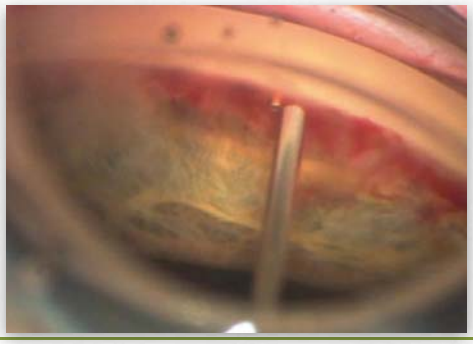


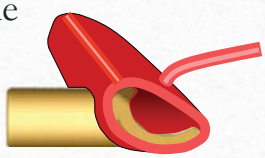
De Vries 1947



iStent® Surgical Procedure

- iStent® rails are seated against scleral wall of Schlemm's canal
- iStent® Snorkel sits parallel to the iris plane





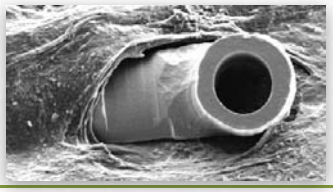


Photo courtesy of Ike Ahmed, MD

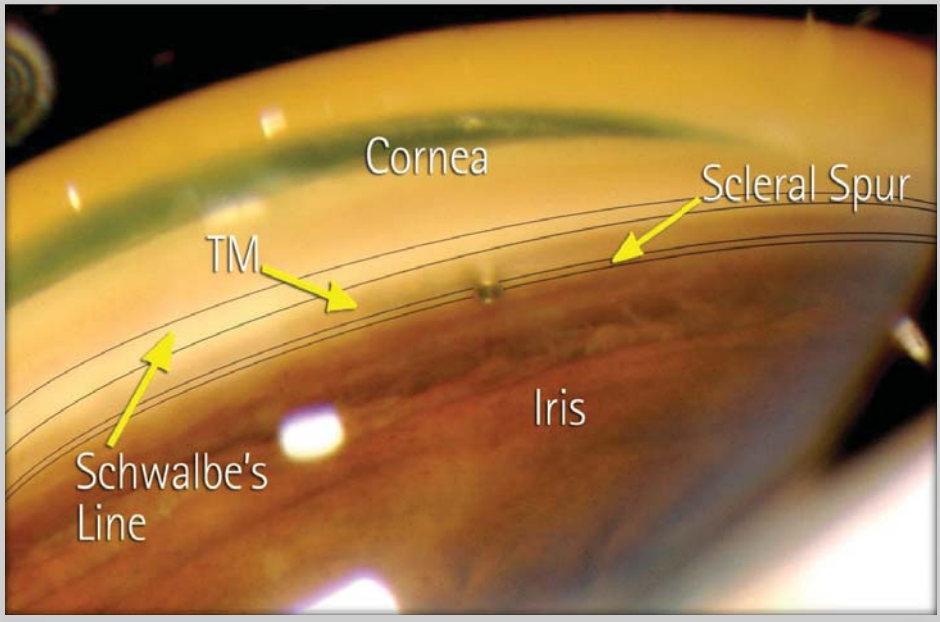
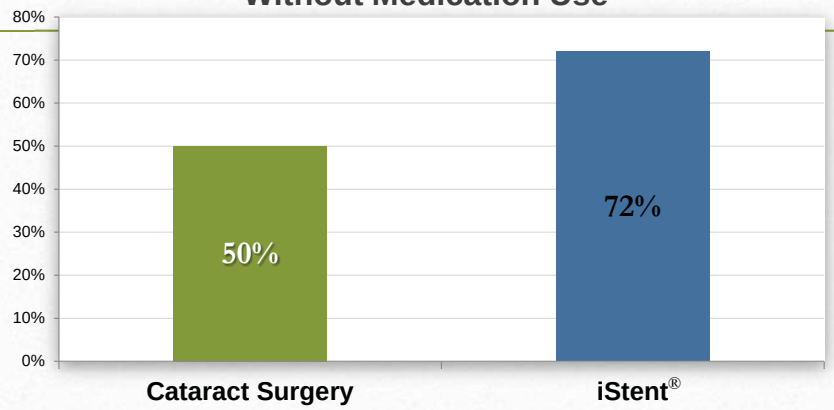


Photo courtesy of Tom Samuelson, MD

US IDE Trial – Primary Endpoint

Percent of Patients with IOP ≤21 mm Hg Without Medication Use

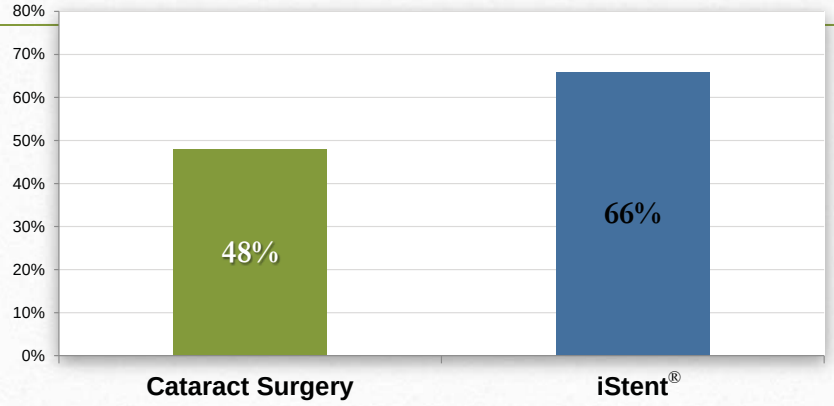


- **At 12 months, 72% of iStent® subjects with IOP ≤ 21 mm Hg without medication vs. 50% with cataract surgery alone (*P*<0.001)**

Samuelson TW, Katz LJ, Wells JM, Duh Y-J, Giamporcaro JE, for the US iStent Study Group. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology 2011; 118:459–467.

US IDE Trial – Secondary Endpoint

Percent of Patients with IOP ≤20% Reduction in IOP Without Medication Use



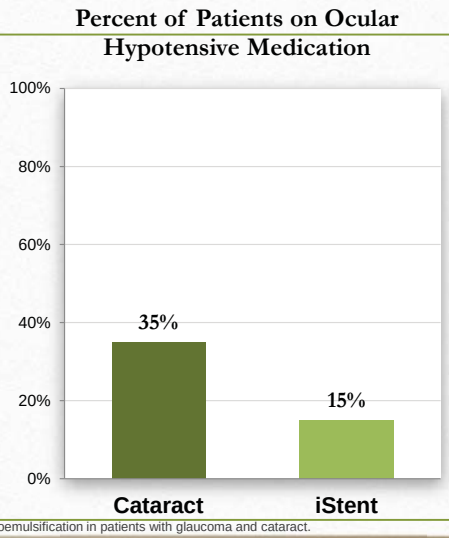
- **At 12 months, 66% of iStent® subjects with ≥ 20% IOP reduction without medication vs. 48% with cataract surgery alone (P=0.003)**

Samuelson TW, Katz LJ, Wells JM, Duh Y-J, Giamporcaro JE, for the US iStent Study Group. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology 2011; 118:459–467.

iStent® Pivotal US IDE Trial
Significant IOP and Medication Reductions

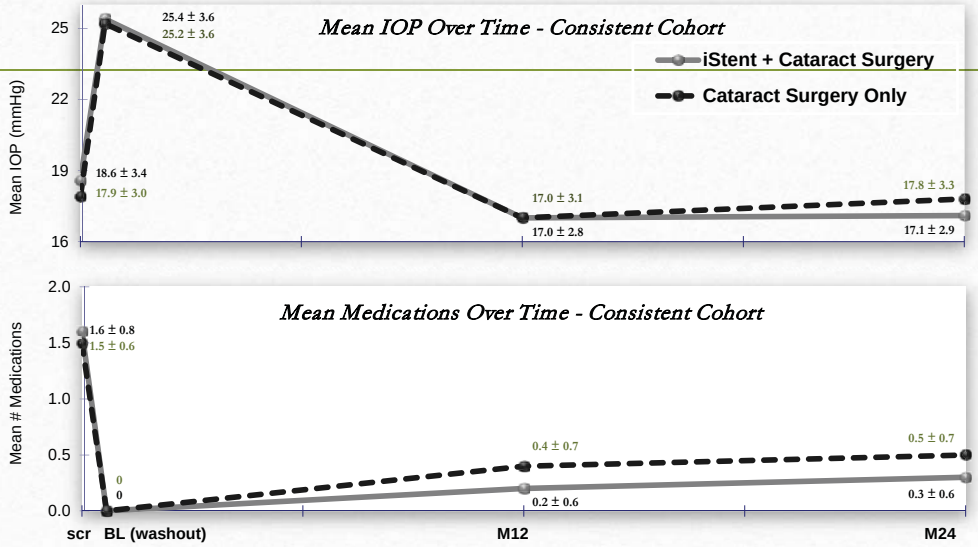
At 12 months:

- **>30% reduction from baseline IOP**
  - Similar outcome validated adherence to study design *(manage to threshold IOP)*
- **For iStent subjects, IOP reduction with significantly less medication (P=0.001)**
  - 15% of iStent vs. 35% cataract group on medication



Samuelson TW, Katz LJ, Wells JM, et al. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. *Ophthalmology*. 2011;118:459-467 .

iStent® US IDE Trial - 2-year Follow-up on IOP and Medications



Craven ER, Katz LJ, Wells JM, Giamporcaro JE, for the iStent Study Group. Cataract surgery with trabecular micro-bypass stent implantation in patients with mild-to-moderate open-angle glaucoma and cataract: Two-year follow-up. J Cataract Refract Surg 2012; 38:1339–1345.

XEN Glaucoma Implant™ Materials and Methods

Materials

- Permanent, collagen derived, gelatin implant, 6 mm long
- Implant is soft, compressible, and flexible when hydrated
- Material and design mitigate traditional implant issues
  - Absence of Migration
  - Tissue-conforming
  - Non-inflammatory

Methods

- Pre-loaded, disposable Inserter
- Handles like IOL inserter
- Straightforward procedure
- With or without cataract surgery
- Removable and/or repeatable
- Mild, Moderate & Refractory Glaucoma

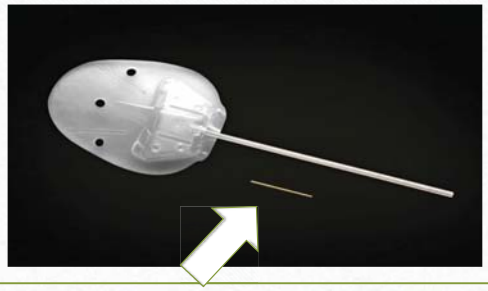
XEN GLAUCOMA IMPLANT

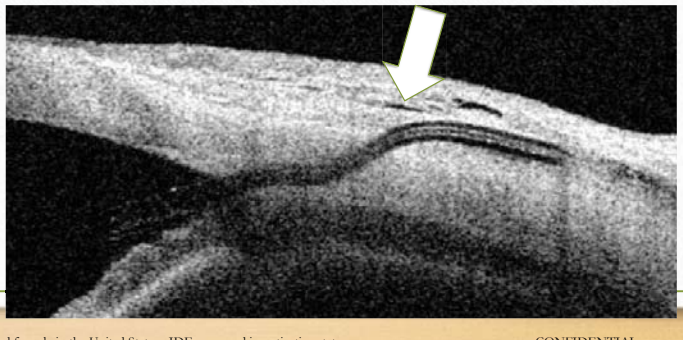
XEN Glaucoma Implant™ Mechanism of Action

Ab Interno Sub-Conjunctival Drainage

- Surgical "Gold Standard" IOP reduction in minimally invasively procedure
- Clinically proven outflow pathway
- Bypasses all potential outflow obstructions
- Conjunctiva sparing: alternative surgical options remain
- Single implant delivers desired effectiveness

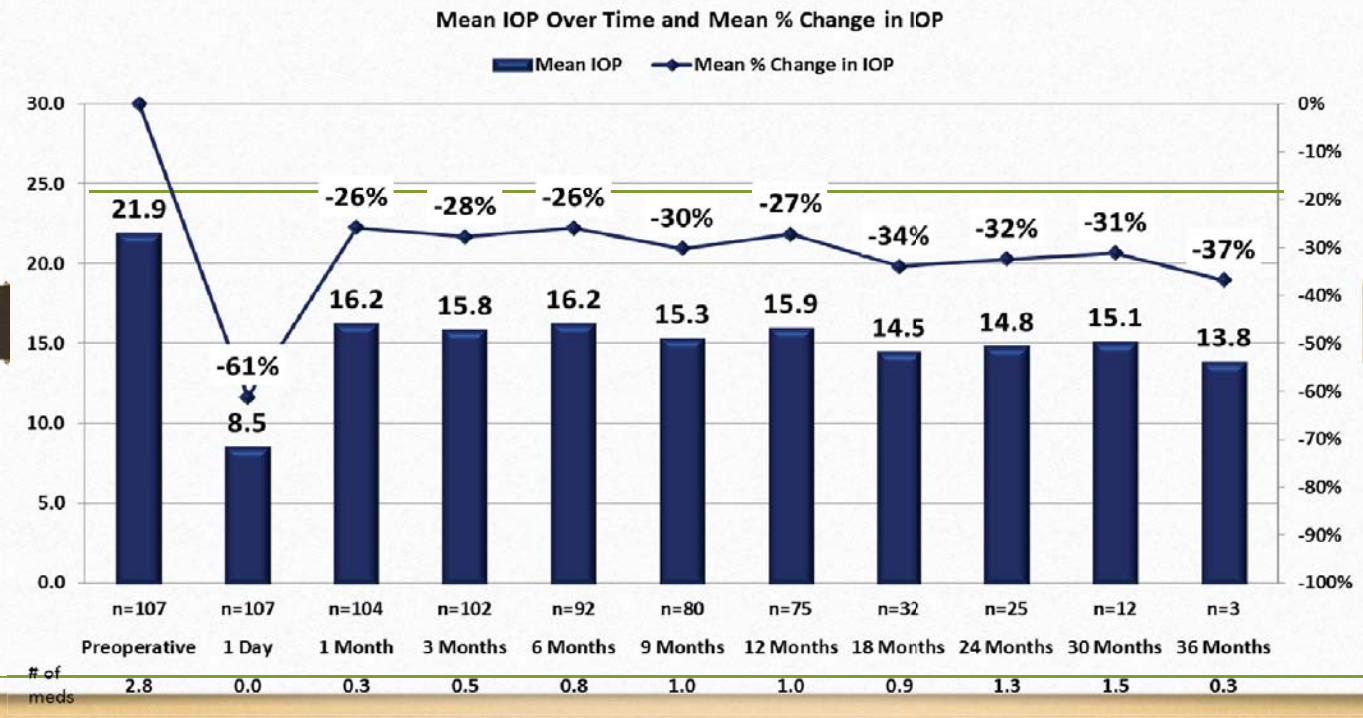
Gelatin Material is Tissue Conforming





Summed patients: primary, combined and refractory

POAG Only



**Mean preoperative IOP is best medicated. Patients were not washed out prior to surgery.*

InnFocus, Inc.

- Based in Miami, Florida
- Founded in 2004
- Biomaterials-based company
- Have worked closely with Bascom Palmer Eye Institute
- Two of the three inventors of the InnFocus MicroShunt are from BPEI
  - Francisco Fantes, M.D.
  - Jean Marie Parel, Ph.D.
- The third inventor is Leonard Pinchuk, Ph.D, D.Sc., who is the President and CEO of InnFocus.

The Device: The InnFocus MicroShunt™

(previously known as the *MIDI A*

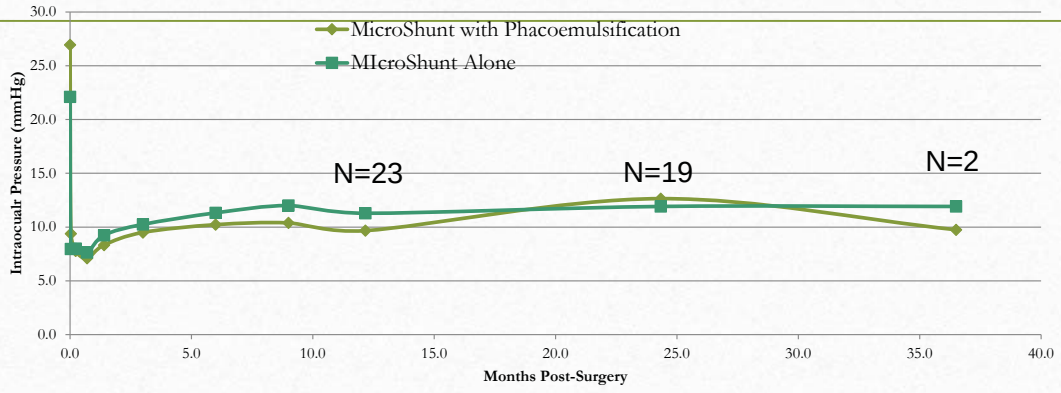
100% SIBS

- Outer diameter is 350 µm
- Lumen diameter is 70 µm
- 8.5 mm long
- Matches the compliance of ocular tissue
- Conforms to the curvature of the eye
- Does not require a cadaver patch
  - Soft, flexible, rubbery, no erosion
- Atraumatic fins prevent
  - Migration
  - Peri-tubular leakage
- No MRI interference

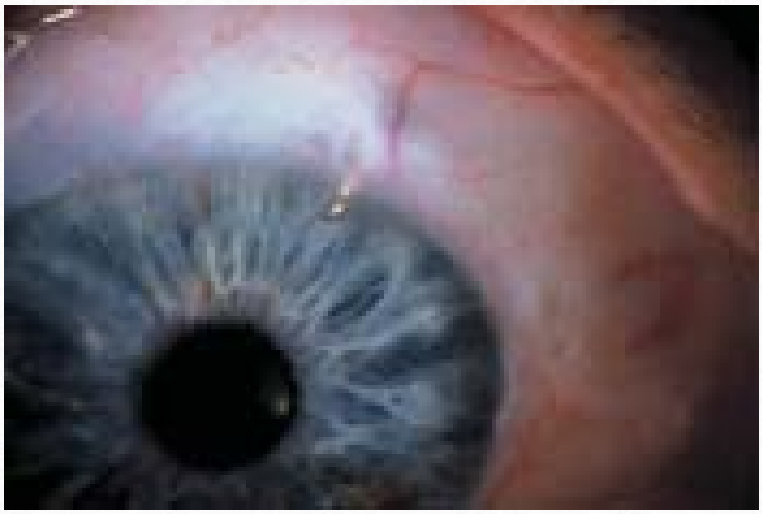
Hagen-Poiseuille Equation

$$D = \sqrt[4]{2.547 \times 10^{-6} \frac{QL}{P_0 - P_L}}$$

Dominican Republic: Average Change in Intraocular Pressure with Time: Alone and Implanted in Combination with Phacoemulsification



Trabeculectomy with Express Minishunt



Express Minishunt Advantages

- Reduces operating time
- Eyes appear to be quieter earlier in post-op course
- No iridectomy
- Uniform opening
- If hypotony occurs, tends to be less severe

Resident Surgery with Ex-PRESS

- No difference
  - postoperative IOP
  - proportional decrease in IOP
- Ex-PRESS group
  - Significantly less medication to control IOP at 3 months
  - No difference at 6 months or 1 year (P≥0.28)
  - More Ex-PRESS patients had good IOP control without meds at 3 (P=0.057) and 6 months (P=0.076)
  - No difference was found in the rates of sight-threatening complications (P≥0.22)

Seider MI. Resident-performed Ex-PRESS Shunt Implantation Versus Trabeculectomy J Glaucoma. 2011 Apr 25. [Epub ahead of print]

Retrospective Case Series

- Moorefields Bleb Grading System
  - Less vascularity and height but more diffuse area associated with the Ex-PRESS blebs
- Fewer cases of early postoperative hypotony and hyphema
- Final percent IOP lowering was similar
- Quicker visual recovery
  - The Ex-PRESS group required fewer postoperative visits compared with the trabeculectomy group (P < .000).

Good TJ. Assessment of bleb morphologic features and postoperative outcomes after Ex-PRESSdrainage device implantation versus trabeculectomy. Am J Ophthalmol. 2011 Mar;151(3):507-13.e1. Epub 2011 Jan 13.

Ex-PRESS in prior operated eyes

- Success complete in 60(60%) and qualified in 24 (24%) eyes
- Mean IOP
  - ~~27.7 ± 9.2 mm Hg with 2.73 ± 1.1~~
  - 14.02 ± 5.1 mm Hg with 0.72 ± 1.06 drugs ($p < 0.0001$)
- Failure
  - Uncontrolled IOP (11%)
  - bleb needling (4%)
  - persistent hypotony (1%)

Lankaranian D. Intermediate-term results of the Ex-PRESS(TM) miniature glaucoma implant under a scleral flap in previously operated eyes. Clin Experiment Ophthalmol. 2010 Dec 22.

5 year study Ex-press vs Trabeculoectomy

- EX-PRESS more effective without medication
  - At year 1 12.8% of patients required IOP meds after EX-PRESS implantation vs 35.9% after trabeculectomy
  - At year 5 (41% versus 53.9%)
- Responder rate was higher with EX-PRESS
- Time to failure was longer
- Surgical interventions for complications were fewer after EX-PRESS implantation

deJong et al. Five-year extension of a clinical trial comparing the EX-PRESS glaucomafiltration device and trabeculectomy in primary open-angle glaucoma. Clin Ophthalmol. 2011;5:527-33. Epub 2011 Apr 29.