

NEW THERAPIES IN GLAUCOMA

ALEX CHERRY, PGY-5
JUNE 5, 2020

1

FINANCIAL DISCLOSURES

- None

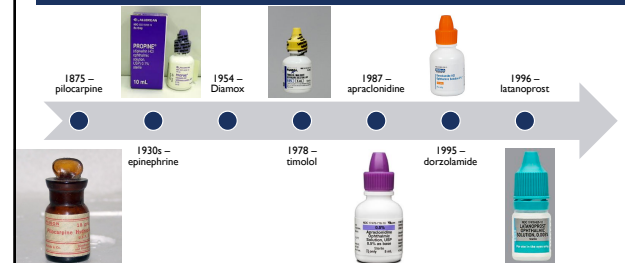
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LEARNING OBJECTIVES

1. Review of new topical treatments for intraocular pressure lowering
2. Compare available and future microinvasive glaucoma surgeries
3. Discuss potential complications with new therapies for glaucoma

3

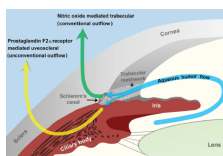
BRIEF HISTORY



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LATANOPROSTENE BUNOD -- VYZULTA

- Nitric Oxide Mechanism of Action
 - NO signaling is endogenously involved in TM contraction and relaxation
 - Activates trabecular cell relaxation and vasodilation, which increases outflow
 - Aqueous levels of NO are reduced in glaucoma patients



Mehran NA, Sishu S, Razaehisaid B. New glaucoma medications: latanoprostene bimat, netarsodil and fixed combination netarsodil-latanoprost. *Eye (Lond)*. 2020;34(1):72-83.

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LATANOPROSTENE BUNOD -- VYZULTA

- Latanoprostene Bunod 0.024%
 - Only current nitric oxide product for glaucoma
 - Broken down by corneal esterases into latanoprost, nitric oxide, and butanediol
 - Dual mechanism of action to lower IOP
- Clinical Pearls
 - Dosed once daily before bed
 - IOP reduction after 1-3 hours with maximum effect at 11-13 hours
 - Preserved with BAK



Mehran NA, Sisha S, Bazzeghinad B. New glaucoma medications: latanoprostene bimat, netarsudil, and fixed combination netarsudil/latanoprost. *Eye (Lond)*. 2020;24(1):72-81.

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LATANOPROSTENE BUNOD -- VYZULTA

- Voyager
 - Dose response study with comparison to latanoprost
- Apollo and Lunar
 - Phase III RCT vs timolol
 - Overall ~32% reduction in IOP
 - LBN sustained IOP reduction to 12 months
 - Crossover participants reduced IOP an additional 6-8%

Figure 1 Mean diurnal intraocular pressure (IOP) in the study eye at baseline and on Day 28 (intent-to-treat population). *p<0.005 versus latanoprost

Worster RN, Ong T, Savatelli Stracchi R, et al. A randomized, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open-angle glaucoma. The VOYAGER Study. *Am J Ophthalmol*. 2011;151(5):738-746.

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LATANOPROSTENE BUNOD -- VYZULTA

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 - Dose response study with comparison to latanoprost
- Apollo and Lunar
 - Phase III RCT vs timolol
 - Overall ~32% reduction in IOP
 - LBN sustained IOP reduction to 12 months
 - Crossover participants reduced IOP an additional 6-8%
 - Overall, on average, LBN offers an additional 1-3 mmHg of IOP lowering vs latanoprost or timolol

Figure 1 Mean reduction in IOP from baseline (mmHg) in the study eye at baseline and on Day 28 (intent-to-treat population). *p<0.005 versus latanoprost

Worster RN, Ong T, Savatelli Stracchi R, et al. A randomized, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open-angle glaucoma. The VOYAGER Study. *Am J Ophthalmol*. 2011;151(5):738-746.

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LATANOPROSTENE BUNOD -- VYZULTA

- Side Effects
 - Hyperemia (7%)
 - Stinging on instillation (8%)
 - Punctate Keratitis (3%)
 - Eye irritation, pain, or dryness (5-10%)
 - 22% experience at least one side effect
 - 1.4% discontinued due to side effects
 - Overall very similar profile to latanoprost
- Financial side effects
 - ~\$220 through GoodRx
 - Industry coupon for \$35.60 but excludes Medicare and Medicaid. Good for 6 refills.

Number subjects receiving LBN in safety population*	Pooled total 637
Ocular TEAEs, N (%)	
Instillation site pain	53 (8.3%)
Conjunctival hyperemia	31 (4.9%)
Punctate keratitis	19 (3.0%)
Ocular hyperemia	12 (1.9%)
Eye irritation	11 (1.7%)
Eye pain	7 (1.1%)
Dry eye	6 (0.9%)
Abnormal or foreign-body sensation	5 (0.8%)
Instillation site pruritus	2 (0.3%)
Photophobia	2 (0.3%)
Conjunctival disorder, unspecified	1 (0.2%)
Reduced visual acuity	1 (0.2%)
Total subjects with ≥1 ocular TEAE	140 (22.0%)
Nonocular TEAEs, N (%)	
Headache	3 (0.5%)
Fatigue	1 (0.2%)
Hair color changes	1 (0.2%)
Hair disorder, unspecified	1 (0.2%)
Sinus congestion	1 (0.2%)
Total subjects with ≥1 nonocular TEAE	6 (0.9%)
TEAEs leading to discontinuation of therapy	7 (1.1%)

Source: GA, Ngai P, Measek S, Liu KY. Critical evaluation of latanoprostene bunod in the treatment of glaucoma. *Clin Ophthalmol*. 2014;7:2055-2065.

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NETARSUDIL -- RHOPRESSA

- Rho kinase inhibitor mechanism
 - Increase trabecular outflow through cellular contraction
 - Decrease extracellular matrix protein production
 - Potential reduction in episcleral venous pressure
- Norepinephrine transporter inhibitor mechanism
 - Reduction in aqueous production
- Bonus effects?
 - Neuroprotection
 - Blood flow!
 - Scarring!

Figure 1 Rho kinase inhibitor mechanism. Netarsudil increases trabecular outflow through cellular contraction, decreases extracellular matrix protein production, and potentially reduces episcleral venous pressure. Rhopressa inhibits the norepinephrine transporter, leading to reduced aqueous production.

Malhotra NA, Sethi S, Kanchanapong R. New glaucoma medications: latanoprostene bunod, netarsudil, and fixed combination netarsudil-latanoprost. *Eye (Lond)*. 2020;24(1):75-88.

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NETARSUDIL -- RHOPRESSA

- Netarsudil 0.02%
 - Only current rho kinase inhibitor for glaucoma in USA
 - Long half life
 - 16h in aqueous, ~70+ hours in iris and ciliary body
- Clinical Pearls
 - Dosed once daily before bed
 - Preserved with BAK
 - pH of ~5
 - White cap

Figure 1 Netarsudil 0.02% mechanism. Netarsudil inhibits Rho kinase, leading to increased trabecular outflow and reduced aqueous production.

Malhotra NA, Sethi S, Kanchanapong R. New glaucoma medications: latanoprostene bunod, netarsudil, and fixed combination netarsudil-latanoprost. *Eye (Lond)*. 2020;24(1):75-88.

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NETARSUDIL -- RHOPRESSA

- ROCKET I and 2

Clinical Trial	Sample	Baseline IOP	3 month IOP	Noninferior
Rocket I <27	182	23.42	19.81	No
Rocket I <25	113	22.39	18.22	Yes
Rocket 2 <25	129	22.54	18.24	Yes

- Netarsudil QD equivalent to BID with more side effects
- Inferior to latanoprost by ~1mm Hg in separate study except for those with IOP <26

Figure 1 ROCKET-2: Ocular hypotensive effect of netarsudil once daily (qd) and twice daily (bid) compared with timolol 0.5% in the primary efficacy population (subset with baseline IOP < 26 mm Hg).

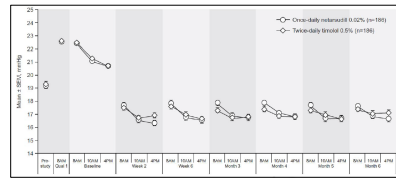
Seiler JF, et al. Two phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure. *Netarsudil Versus Timolol (NETAR) Study*. *Am J Ophthalmol*. 2018;181:14-27.

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NETARSUDIL -- RHOPRESSA

ROCKET 4

- Enrolled patients with OAG or OHTN and IOP 17-30
- High dropout rate
- Noninferior to timolol in all groups
- IOP reduction of ~20%
- Sustained effect
- Overall, netarsudil provides a 4-5 mm Hg effect and may be more effective than other medications at low pressures



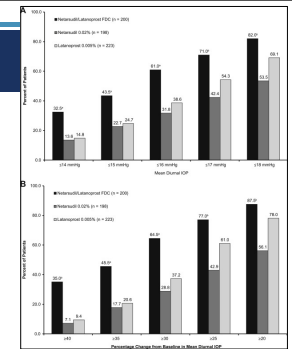
Khanolkar AS, Seraj B, Barkun J, et al. Once-Daily Netarsudil Versus Twice-Daily Timolol in Patients With Elevated Intraocular Pressure: The Randomized Phase 3 ROCKET-4 Study. *Am J Ophthalmol*. 2019;204:97-104.

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NETARSUDIL -- ROCKLATAN

MERCURY

- Phase III trial for combination netarsudil + latanoprost
- Enrolled OAG or OHTN with IOP 20-36
- Similar side effect profile to netarsudil
- Additional 1.3-2.5 mm-Hg vs latanoprost
- 64.5% of patients had 30% or more reduction in IOP
- 82% of patients had mean IOP of <18

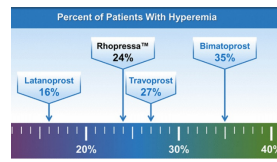


Khanolkar AS, Seraj B, Barkun J, et al. Netarsudil/Latanoprost Fixed-Dose Combination for Elevated Intraocular Pressure: Three-Phase Study from a Randomized Phase 3 Trial. *Am J Ophthalmol*. 2019;207:448-457.

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NETARSUDIL -- RHOPRESSA

- Side Effects
 - Hyperemia 25-50%
 - Corneal Verticillata ~25%
 - Subconjunctival Hemorrhage ~15-20%
 - Tearing, itching, or blurred vision 4-8%
 - ~80% experience at least 1 side effect
 - ~25% discontinued due to side effects
- Financial Side Effects
 - Rhopressa: \$290; Rocklatan: \$310
 - Coupon for \$25-50 with commercial insurance



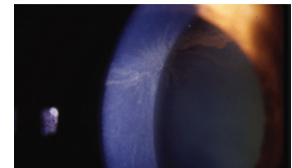
Khanolkar MY, Seraj B, Pak FS, et al. Long-term Safety and Ocular Hypertensive Efficacy Evaluation of Netarsudil Ophthalmic Solution: The Krasovskiy IOP Treatment Trial (ROCKET-2). *Am J Ophthalmol*. 2019;200:110-117.

Khanolkar AS, Seraj B, Barkun J, et al. Once-Daily Netarsudil Versus Twice-Daily Timolol in Patients With Elevated Intraocular Pressure: The Randomized Phase 3 ROCKET-4 Study. *Am J Ophthalmol*. 2019;204:97-104.

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NETARSUDIL -- RHOPRESSA

- Corneal Verticillata
 - Mean time to onset 172 days (40-396)
- Observational study of 45 patients enrolled
 - Medication discontinued
 - 26 resolved before study began
 - 3 patients did not resolve
 - Median resolution time 314 days
 - No meaningful change in visual function observed



Khanolkar MY, Seraj B, Pak FS, et al. Long-term Safety and Ocular Hypertensive Efficacy Evaluation of Netarsudil Ophthalmic Solution: The Krasovskiy IOP Treatment Trial (ROCKET-2). *Am J Ophthalmol*. 2019;200:110-117.

Khanolkar AS, Seraj B, Barkun J, et al. Once-Daily Netarsudil Versus Twice-Daily Timolol in Patients With Elevated Intraocular Pressure: The Randomized Phase 3 ROCKET-4 Study. *Am J Ophthalmol*. 2019;204:97-104.

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MAXIMUM MEDICAL THERAPY

- Conventional:
 - Prostaglandin analogue, beta blocker, alpha agonist, and carbonic anhydrase inhibitor
 - Latanoprost, Cosopt, and Brimonidine
- Theoretical:
 - Vyzulta, Rhopressa, Cosopt, and Brimonidine
 - 6 medications
 - Price tag: \$590-630 for 30 days

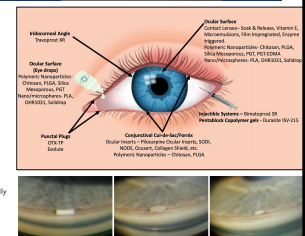


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FUTURE THERAPIES

- New Medications
 - Onidapnep
 - Prostanoid analogue without the classic side effects
 - Phase III trial underway; approved in Japan
- Depot Drugs
 - Injection of biodegradable implant into anterior chamber angle
 - Bimatoprost SR
 - Sustained IOP lowering for 12 weeks with less hyperemia
 - Travoprost XR
 - Sustained IOP lowering for 11 months
 - Glaukos (Dose - implanted reservoir with membrane eluting stent into TM
 - Sustained IOP lowering for 9 months
 - Graybug - drug encapsulated microparticle formulation injected subconjunctivally
 - Punctal Plugs
 - OTX-TP - 3 month eluting travoprost punctal plug



Smith RB, et al. Promising therapeutic drug delivery systems for glaucoma: a comprehensive review. *Trans Am Ophthalmol Soc*. 2018;116:1041-1050.

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HYDRUS MICROSTENT

- COMPARE Study
 - Prospective RCT
 - 152 eyes randomized to Hydrus vs iStent x2
 - Followup 1 year
 - Complete success: IOP 18 or less off all meds
 - Preop: IOP 19 on 2.5 meds; MD -6 (both groups); ~2/3 phakic
 - Hydrus had greater success rate and patients were on fewer meds
 - Complete success rate: 30% Hydrus vs 9% iStent

A IOP at 12 Months

Difference in Change
at 12 months, 2009 CI: -0.9 to 0.7, p=0.03

Change from Preop, 0 to 4 weeks, p=0.001

Change from Preop, 12 to 16 weeks, p=0.004

B Medications at 12 Months

Difference in Change
at 12 months, 2009 CI: -0.9 to 0.7, p=0.004

Change from Preop, 0 to 4 weeks, p=0.001

Change from Preop, 12 to 16 weeks, p=0.001

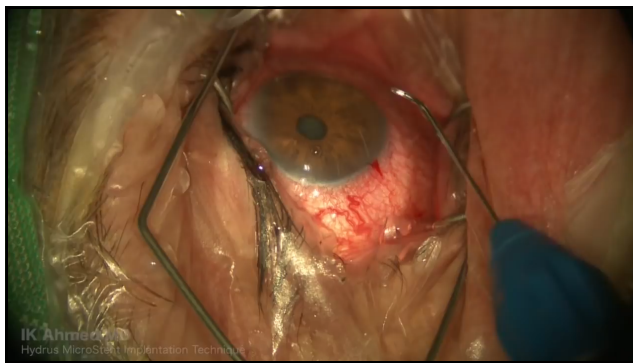
Alsaad HM, Foa A, Au L, et al. A Prospective Randomized Trial Comparing Hydrus and iStent Microstents Glaucoma Surgery Implants for Long-term Treatment of Open-Angle Glaucoma: The COMPARE Study. Ophthalmology. 2010;117(11):2141.

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HYDRUS MICROSTENT

- Operative Complications
 - Hard stop: pushing too hard into eye wall with injector (rarely anatomical obstruction)
 - Posterior dive: stent dives supraciliary from posterior or partial incision
 - Proper coverage of inlet
- Postop
 - Hyphema is expected and a good sign of proper location
 - Day 1 hyphema is the norm
 - Stop the glaucoma drops
 - Monitor for steroid response

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MIGS DEVICE OVERVIEW

Implant

- Trabecular Outflow
 - iStent
 - Hydrus Microstent
- Suprachoroidal Space
 - CyPass
 - Stent SUPRA
 - MINIject
- Subconjunctiva Filtration
 - XEN 45 Gel Stent
 - Preserflo Microport

Nonimplant

- Trabecular Outflow
 - Trabectome
 - Kahook Dual Blade
 - Gonioscopy-assisted transilluminal trabeculotomy
 - Ab interno canaloplasty
 - OMNI Surgical System
- Decrease Aqueous Production
 - Endoscopic cyclophotocoagulation

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CYPASS

The Cypass is clearly in contact with endothelium, though the central endothelial cell count is still > 2000

Karls-Born and Pius-Born Eye Hospital 2014

MIGS.ORG

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ISTENT SUPRA

ISTAR MINIJECT

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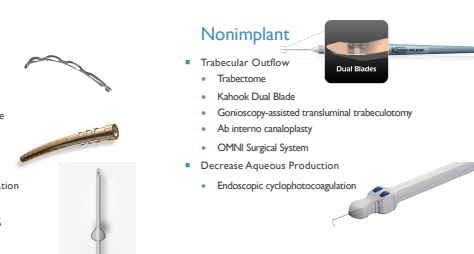
MIGS DEVICE OVERVIEW

Implant

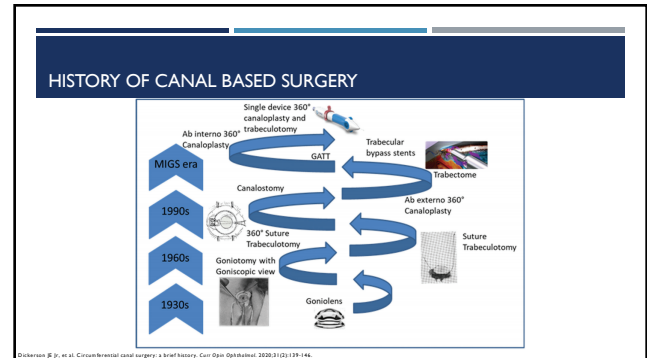
- Trabecular Outflow
 - iStent
 - Hydus Microstent
- Suprachoroidal Space
 - Cypass
 - iStent SUPRA
 - Minilens
- Subconjunctiva Filtration
 - XEN 45 Gel Stent
 - Preserflo Microshunt

Nonimplant

- Trabecular Outflow
 - Trabectome
 - Kahook Dual Blade
 - Gonioscopy-assisted transilluminal trabectotomy
 - Ab interno canaloplasty
 - OMNI Surgical System
- Decrease Aqueous Production
 - Endoscopic cyclophotocoagulation



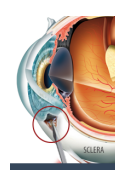
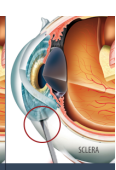
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AB INTERNO CANALOPLASTY (ABIC)

- Internal approach
 - Conjunctiva sparing
- iTrack illuminated catheter
 - Can also use prolene suture
- Viscodilation of Schlemm's canal and collector channels
- No suture or hardware
- Can combine with trabectulotomy
- Approved as standalone procedure

AB-EXTERNO Canaloplasty
Micro-catheter is inserted via Superficial and Deep cuts on the Sclera into Schlemm's canal

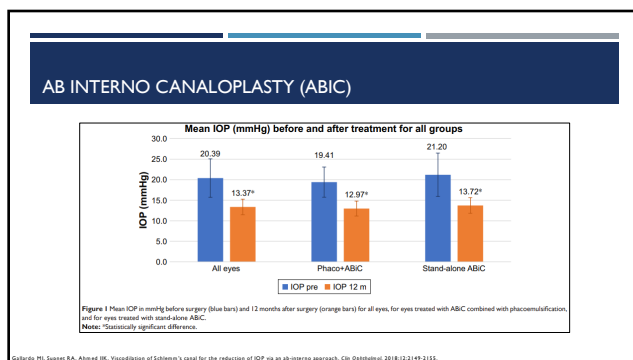
AB-INTERNO Canaloplasty
Micro-catheter is inserted through either a corneal or limbal micro-incision into the Schlemm's Canal

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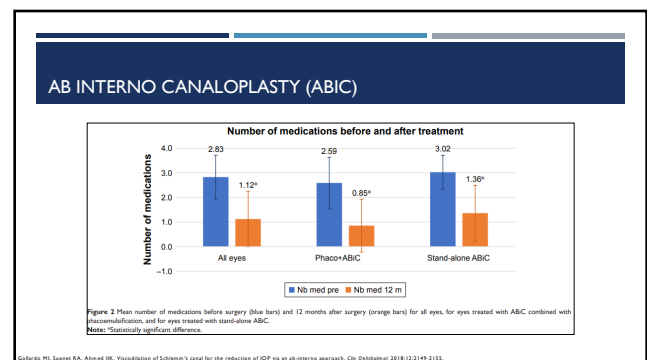
ABiC / IOS / GATT: In Vivo Aqueous Venography for Glaucoma

M Schlenker, B Ford, A Crichton, P Gooi
2019

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AB INTERNO CANALOPLASTY (ABIC)

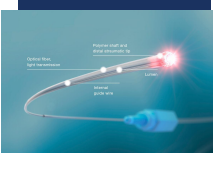


Table 3. Intraocular pressure reductions (mmHg $\pm$ SD) in published canaloplasty studies

Reference	Procedure	Diagnosis	N	Baseline IOP	IOP at last follow-up (length of follow-up)	Percentage change
Carmona et al. [28]	Ab externo 360° POAG	POAG	56	25.1 $\pm$ 8.7	16.7 $\pm$ 4.4 (8 month)	-33.5
Grosholz et al. [27]	Ab externo 360° POAG in Black patients	POAG	90	42.7 $\pm$ 12.3 (8-10 years)	19.2 $\pm$ 4.4 (15 month)	-55.0
Yonker et al. [31]	Ab externo 360° w/ future	OAG	18	45.0 $\pm$ 12.1	16.4 $\pm$ 5.9 (15 month)	-63.6
Ueno et al. [30]	Ab externo 360° w/ future	OAG	127	23.6 $\pm$ 4.8	14.0 $\pm$ 4.3 (24 month)	-32.2
Kilmer [32]	Ab externo 360° POAG	POAG	28 ^a	18.5 $\pm$ 3.4	15.5 $\pm$ 2.8 (8 month)	-16.2
Vastav et al. [34**]	Ab externo 360° w/ future	Stable			(12 month)	
		Advanced	172	19.2 $\pm$ 6.4	13.3 $\pm$ 4.5	-27.9
		Moderate	51	20.7 $\pm$ 5.0	15.2 $\pm$ 4.0	-
		Early	39	21.3 $\pm$ 5.7	18.1 $\pm$ 3.8	-
		With phaco				
		Advanced	212	19.4 $\pm$ 7.5	14.5 $\pm$ 4.7	-16.5
		Moderate	51	19.5 $\pm$ 5.9	14.2 ^b	-
		Early	30	19.4 $\pm$ 7.3	14.5 ^b	-
Onofre and Kolker [34**]	Ab interno 360° POAG	POAG	72	24.6 $\pm$ 7.1	14.6 $\pm$ 2.8 (12 month)	-41%
		ICP > 18 mmHg	34	16.2 $\pm$ 3.8	13.6 $\pm$ 2.9	-
		ICP < 18 mmHg	38	16.2 $\pm$ 3.8	13.6 $\pm$ 2.9	-
Brar et al. [33*]	Ab externo 360° Steroid OHT	Steroid OHT	9	30.4 $\pm$ 6.8	13.7 $\pm$ 1.9 (12 month)	-54.9

ICP, intraocular pressure; OAG, open-angle glaucoma; POAG, primary open-angle glaucoma; POAG, secondary open-angle glaucoma.
^an = 4 at 6 months.
^bdata not published; IOP estimated from published figures.

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GONIOSCOPY-ASSISTED TRANSLUMINAL TRABECULOTOMY (GATT)

Table 1. Intraocular pressure reductions (mmHg $\pm$ SD) in circumferential trabeculotomy studies

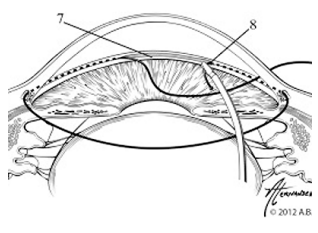
Reference	Procedure	Diagnosis	N	Baseline IOP	IOP at last follow-up (length of follow-up)	Percentage change
Chin et al. [21]	Ab externo 360° POAG/SOAG	POAG/SOAG	43	27.8 $\pm$ 12.2	12.9 $\pm$ 2.5 (18 months)	-53.6
Grover et al. [23**]	Ab interno 360° POAG	POAG				
		Phakic	46	26.0 $\pm$ 6.9	15.6 $\pm$ 5.7	-40.0
		w/Phaco	36	22.5 $\pm$ 5.4	14.1 $\pm$ 3.2	-37.3
		Pseudo	37	24.7 $\pm$ 6.2	15.8 $\pm$ 7.4	-36.0
		Other ^a				
		Phakic	30	30.9 $\pm$ 10.0	13.8 $\pm$ 4.5	-55.3
		w/Phaco	25	25.7 $\pm$ 6.3	14.5 $\pm$ 4.4	-43.6
		Pseudo	24	26.8 $\pm$ 7.9	13.4 $\pm$ 4.7 (24 month)	-50.0
Sarkisian et al. [25**]	Ab interno 360° POAG (83%)	POAG (83%)	81	23.7 $\pm$ 6.3 ^b	15.7 $\pm$ 5.5 ^b (12 month)	-33.8

ICP, intraocular pressure; POAG, primary open-angle glaucoma; SOAG, secondary open-angle glaucoma.
^aOther included chronic angle closure, pseudoexfoliation, pigment dispersion, uveitic, mixed mechanism. Other OAG, trauma, steroid.
^bSD estimated from error bars in published figures.

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GONIOSCOPY-ASSISTED TRANSLUMINAL TRABECULOTOMY (GATT)

- Same internal approach
 - Conjunctiva sparing
- Long history in congenital and pediatric glaucoma
- Preferred choice in JOAG
- Postoperative Considerations
 - High rate of hyphema
 - Stop the glaucoma drops
 - Monitor for steroid response



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MIGS DEVICE OVERVIEW

Implant

- Trabecular Outflow
 - Stent
 - Hydus Microstent
- Suprachoroidal Space
 - Cypass
 - Stent SUPRA
 - MiMax
- Subconjunctival Filtration
 - XEN 45 Gel Stent
 - Preserflo Microstent

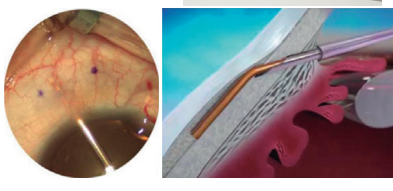
Nonimplant

- Trabecular Outflow
 - Trabectome
 - Kahook Dual Blade
 - Gonioscopy-assisted transluminal trabeculotomy
 - Ab interno canaloplasty
 - OMNI Surgical System
- Decrease Aqueous Production
 - Endoscopic cyclophotocoagulation



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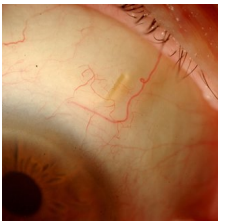
XEN GEL STENT



- Subconjunctival bleb-forming device designed to limit postoperative hypotony
- Biocompatible material designed to be less inflammatory to reduce encapsulation (porcine gelatin cross-linked with glutaraldehyde)
- Implanted using various techniques
 - Ab-interno vs externo, with and without peritomy
 - Subconj vs sub-tenon
- Still use MMC

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XEN GEL STENT

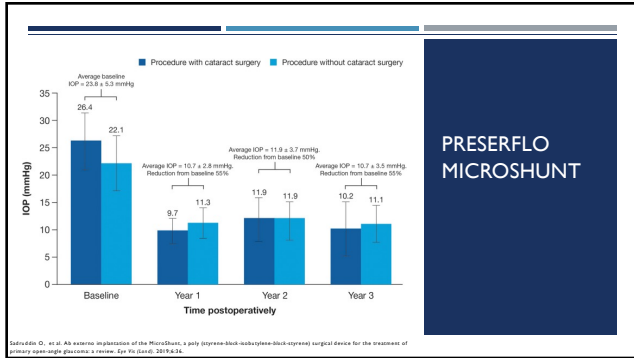


- No prospective comparative study
- Similar rates of success vs trabeculectomy in retrospective studies
 - Less hypotony and bleb leaks / resuturing
 - Higher rates of needling (30-40%)
 - Re-operation rate ~10%
 - Can achieve lower IOP with trabeculectomy
- Ideal POD#1 IOP between 3-10 mmHg
- Posterior, diffuse, low lying blebs with mild vascularity and multiple microcysts
- Revisions can restore flow

Dr. A.T. Parks, M. Pava, J.B. Subconjunctival microinvasive glaucoma surgery: an update on the Xen gel stent and the Preserflo Microstent. Curr Opin Ophthalmol. 2020;31(2):132-138.

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SUBCONJUNCTIVAL DEVICES

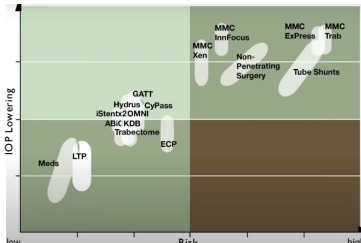
- Still using MMC
- Frequently still cutting conjunctiva
- Postoperative Management
 - Antibiotic drops for 1 week
 - Frequent steroids with long taper (6-10 weeks)
 - May require needling with additional antifibrotics
- Lower risk of hypotony and leaks
- Upcoming prospective studies and long term data needed



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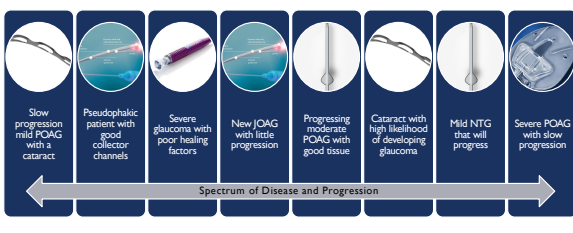
CURRENT PRACTICE

- Hydrus or Canaloplasty
- Kahook or GATT
- Microshunt or Xen
- Tube or Trab



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FUTURE DIRECTIONS



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