MODULE 3:
Medical treatment

EAGLE ALLIANCE

Acknowledgement

Our sincere thanks to the **EAGLE Faculty** for developing the modules, and to the **APGS Review Experts** for their contributions throughout the review and approval process. Their guidance and dedication have been essential in ensuring the accuracy, clarity, and relevance of these educational resources.

EAGLE Alliance Faculty – Module 3

- **Chair:** Prof. Tina Wong (Singapore)
- Assoc Prof. Megumi Honjo (Japan)
- Assoc Prof. Poeman Chan (Hong Kong SAR)
- Assoc Prof. Victor Koh (Singapore)

APGS Expert Review – Module 3

- Prof. Kazuhiko Mori (Japan)
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Introduction to the **EAGLE Alliance Initiative**

Welcome to the EAGLE Alliance initiative:

The EAGLE Alliance has been developed to strengthen clinical capacity in glaucoma management among general ophthalmologists across Asia. Through expert-led modules aligned with the APGG (4th edition), we aim to provide practical, guideline-based learning that supports everyday clinical practice.

How to use each module:

Each module follows the flow of one section of the APGG, concluding with a summary to reinforce key learning points

Look out for:

Expert tips and tricks – practical insights from the faculty

Tips and tricks from the experts

FAQs from the APGG – answers to common clinical questions

FAQs from the APGG

APGG: Asia-Pacific Glaucoma Guidelines.

Asia–Pacific Glaucoma Society (APGS). Asia–Pacific Glaucoma Guidelines. 4th ed. May 2024.

Introduction to **Module 3: Medical treatment**

Module 3 focuses on the medical treatment of glaucoma. It addresses fixed-dose combinations, emerging treatment options, ocular surface considerations, and strategies to improve treatment adherence:

- Topical medical treatment
- Principles of medical treatment
- Fixed-dose combinations
- Side effects of medical treatments
- EP2 receptor agonists
- ROCK inhibitors
- Treatment adherence

Meet the expert faculty:

The diagnostic workup module was developed with guidance and insights from the following faculty members from the EAGLE Alliance, whose expertise helped shape the content for use in daily practice:

Assoc. Prof. Victor Koh | **Assoc. Prof. Poemen Chan** | **Prof. Megumi Honjo**

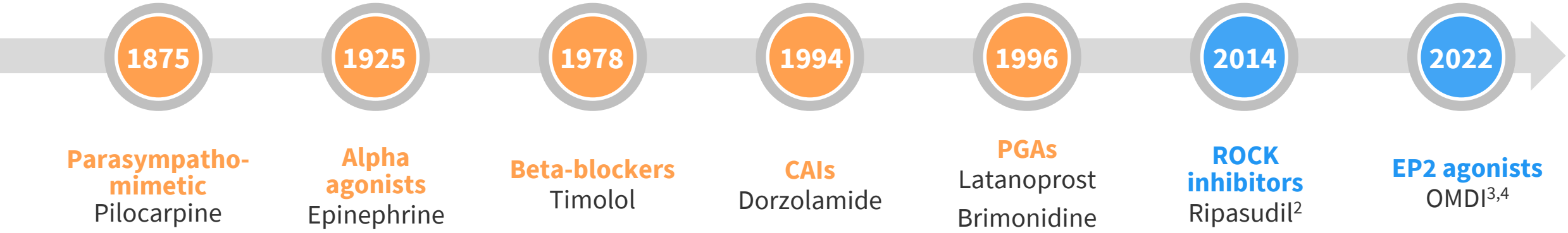
ROCK: Rho-kinase.

Asia–Pacific Glaucoma Society (APGS). Asia–Pacific Glaucoma Guidelines. 4th ed. May 2024.

The evolution of medical glaucoma management

EP2 agonists and ROCK inhibitors brings the **first new MoAs** for the medical management of glaucoma in almost 20 years[1,2]

IOP-lowering molecules and year of first clinical use (globally)[1]



CAI: carbonic anhydrase inhibitor; IOP: intraocular pressure; MoA: mechanism of action; PGA: prostaglandin analogue; ROCK: Rho-kinase.

1. European Glaucoma Society (EGS). Terminology and guidelines for glaucoma. 5th ed. Br J Ophthalmol 2021;105(Suppl 1):1–169. Available at: https://www.eugs.org/eng/guidelines.asp. Last accessed October 2025; **2.** GLANATEC® (ripasudil) Prescribing information (PMDA). Available at: https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/270072_1319763Q1022_1_08. Last accessed October 2025; **3.** Eybelis® (Omidenepag Isopropyl). Prescribing Information (PMDA). Available at: https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/300237_1319764Q1027_1_08. Last accessed October 2025; **4.** Omlonti® (Omidenepag Isopropyl). Prescribing Information (FDA). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215092s000lbl.pdf. Last accessed October 2025.

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Mechanism of action of topical glaucoma medications[1–13]

Drug class and target site of action	Preparations	Mechanism of action
Prostaglandin analogues; uveoscleral outflow	Latanoprost; travoprost; bimatoprost; tafluprost	Increase in aqueous outflow
Prostanoid EP2 receptor agonist; uveoscleral and trabecular outflow	Omidenepag isopropyl	
α1 blockers; uveoscleral outflow	Bunazosin	
α2 agonists	Brimonidine; apraclonidine	
α1-β-blockers; uveoscleral outflow	Nipradilol	
Cholinergics; trabecular outflow	Pilocarpine; carbachol	
ROCK inhibitors; trabecular outflow and episcleral venous pressure (for netarsudil)	Ripasudil; netarsudil	
β-blockers	β1-nonselective antagonist; timolol; levobunolol; carteolol; β-1-selective antagonist; betaxolol	Decrease in aqueous production
α2 agonists	Brimonidine; apraclonidine	
α1-β-blockers	Nipradilol	
Carbonic anhydrase inhibitors	Acetazolamide; methazolamide; dichlorphenamide; dorzolamide; brinzolamide	

ROCK: Rho kinase.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** European Glaucoma Society. *Terminology and Guidelines for Glaucoma*. 4th ed. Savona, Italy: PubliComm; 2014; **3.** Hoyng PF, van Beek LM. *Drugs* 2000;59:411–34; **4.** Soltau JB, Zimmerman TJ. *Surv Ophthalmol* 2002;47(Suppl 1):S2–5; **5.** Frishman WH, et al. *Heart Dis* 2001;3:386–97; **6.** Susanna R, Medeiros FA. *Curr Opin Ophthalmol* 2001;12:149–56; **7.** Herkel U, Pfeiffer N. *Curr Opin Ophthalmol* 2001;12:88–93; **8.** Goldberg I. *Aust Prescr* 2002;25:142–6; **9.** Mauger TF, Craig EL. *Havener's Ocular Pharmacology*. 6th ed. St Louis, Mosby; 1994; **10.** Fuwa M, et al. *J Ocul Pharmacol Ther* 2018;34:531–7; **11.** Honjo M, et al. *Invest Ophthalmol Vis Sci* 2001;42:137–44; **12.** Rao PV, et al. *Invest Ophthalmol Vis Sci* 2001;42:1029–37; **13.** Inoue T, Tanihara H. *Expert Opin Pharmacother* 2017;18:1669–73; **14.** European Glaucoma Society. *Br J Ophthalmol* 2021;105(Suppl 1):1–169.

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Efficacy and dosing of topical glaucoma medications[1–17]

Drug class	Daily dosage	Preparations (%)
FP receptor agonist or PGAs	OD	25–35
Prostanoid EP2 receptor agonist	OD	15–35
β-blockers*	OD to BD	20–25
α1 blockers	BD	15–20
α2 agonists†	BD to TDS	18–25
α1-β-blockers	BD	20
ROCK inhibitors	OD to BD	20–25
Cholinergics	TDS to QDS	20–25
Hyperosmotic agents	Stat dose(s)	15–30
CAIs		
Topical	BD to TDS	20
Systemic	BD to QDS	30–40

Drug class	Daily dosage	Efficacy (%)
Proprietary FDCs		
β-blocker + CAI	BD	25–30
β-blocker + PGA	OD	25–35
β-blocker + α2 agonist*†	BD	25–35
CAI + α2 agonist	BD to TDS	25–35
ROCK inhibitor + α2 agonist	BD	25–35
ROCK inhibitor + PGA	OD	25–35

*In patients taking systemic beta-blockers, the IOP-lowering efficacy of topical beta blockers is likely reduced and the potential for systemic side effects increased: consider other drug classes first. †Alpha-2 agonists are absolutely contraindicated for patients taking monoamine oxidase inhibitors and children <2 years.

BD: twice daily; CAI: carbonic anhydrase inhibitor; EP2: prostaglandin E2; FDC: fixed-dose combination; FP: prostaglandin F; IOP: intraocular pressure; OD: once daily; PGA: prostaglandin analogue; QDS: four times daily; ROCK: Rho kinase; TDS: three times daily.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** European Glaucoma Society. *Terminology and Guidelines for Glaucoma*. 4th ed. Savona, Italy: PubliComm; 2014; **3.** Hoyng PF, van Beek LM. *Drugs* 2000;59:411–34; **4.** Soltau JB, Zimmerman TJ. *Surv Ophthalmol* 2002;47(Suppl 1):S2–5; **5.** Frishman WH, et al. *Heart Dis* 2001;3:386–97; **6.** Susanna R, Medeiros FA. *Curr Opin Ophthalmol* 2001;12:149–56; **7.** Herkel U, Pfeiffer N. *Curr Opin Ophthalmol* 2001;12:88–93; **8.** Goldberg I. *Aust Prescr* 2002;25:142–6; **9.** Mauger TF, Craig EL. *Havener's Ocular Pharmacology*. 6th ed. St Louis, Mosby; 1994; **10.** Goldberg I. In: Ritch R, et al (eds.). *The Glaucomas*. St Louis, Mosby; 1996; **11.** Aihara M, et al. *Am J Ophthalmol* 2020;220:53–63; **12.** Aihara M, et al. *Jpn J Ophthalmol* 2020;64:398–406; **13.** Wu JH, et al. *Graefes Arch Clin Exp Ophthalmol* 2022;260:937–48; **14.** EYBELIS® (omidenepag isopropyl 0.002% ophthalmic solution) [package insert]; **15.** RHOPRESSA® (netarsudil 0.02% ophthalmic solution) [package insert]; **16.** ROCKLATAN® (netarsudil 0.02% and latanoprost 0.005% ophthalmic solution) [prescribing information]; **17.** Stalmans I, et al. *Graefes Arch Clin Exp Ophthalmol* 2024;262:179–90.

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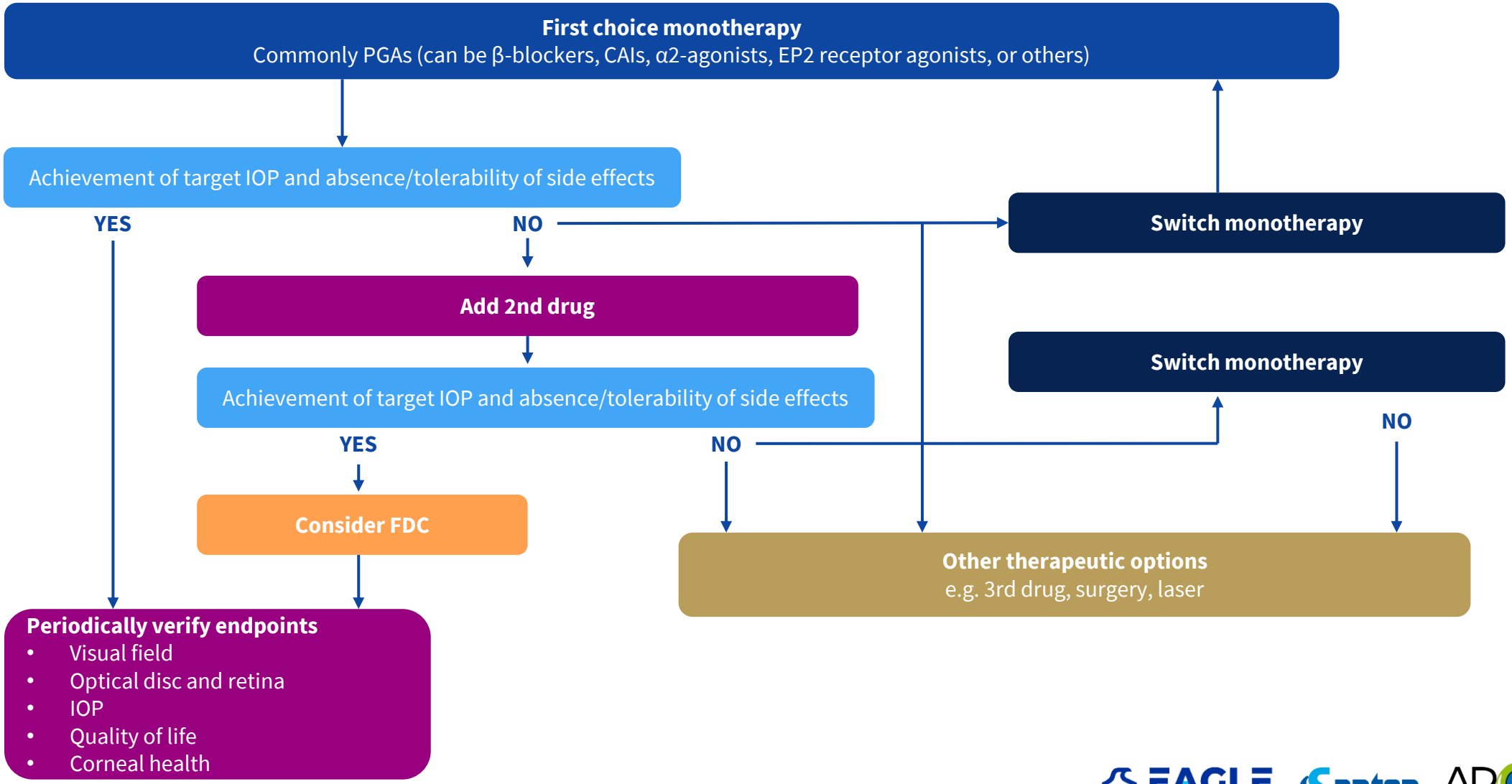
Medical treatment algorithm



CAI: carbonic anhydrase inhibitor; IOP: intraocular pressure; PGA: prostaglandin analogue.

Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024.

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Special considerations when initiating glaucoma medications

RESPIRATORY	Consider whether β-blockers should be avoided
CARDIOVASCULAR	Consider whether β-blockers and α-agonists should be avoided
ENDOCRINE	β-blockers may mask some symptoms
CNS	Affects drug adherence; Consider whether β-blockers should be avoided; α-agonists contraindicated with MAOIs
MUSCULOSKELETAL	Affects drop use; RA-related dry eyes may worsen
UROGENITAL	Avoid systemic CAIs
DRUG ALLERGY	Avoid systemic and topical CAIs
SYSTEMIC MEDICATIONS	Various risks (POAG, OHT, angle closure, drug interactions)
PREGNANCY AND LACTATION	Avoid PGAs, β-blockers, and α-agonists

CAI: carbonic anhydrase inhibitor; CNS: central nervous system; MAOI: monoamine oxidase inhibitors; OHT: ocular hypertension; PGA: prostaglandin analogue; POAG: primary open-angle glaucoma; RA: rheumatoid arthritis.

Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024.

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Key principles of medical therapy

Choose most appropriate medication[1]

- Greatest chance of reaching target IOP
- Best safety and tolerability profiles
- Minimal inconvenience using FDCs
- Affordable
- Maximal likelihood of adherence
- Consider using PF medications

Maximize likelihood of adherence[2]

- Build a strong doctor–patient/ family alliance
- Discuss side effects upfront
- Educate patients and families
- Keep regimen simple and minimally disruptive
- Encourage reminder systems

Inadequate initial response to treatment[1]

- Start by confirming correct instillation technique and consistent use
- Switch before adding, preferably to a different class
- Only combine agents with complementary efficacy
- Avoid overlapping mechanisms/duplicate FDCs
- Consider starting with >1 agent if large IOP reduction is needed

FDC: fixed-dose combination; IOP: intraocular pressure; PGA: prostaglandin analogue.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Goldberg I. In: Ritch R, et al (eds.). *The Glaucomas*. St Louis, Mosby; 1996.

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Overview of FDCs

PGAs with β-blockers[1]

Most common FDC; combines increased AH outflow and reduced production for additive IOP lowering, typically once daily

β-blockers with CAIs[2,3]

Reduces AH production via dual mechanisms; used twice daily, often alongside PGAs

α2-adrenergic agonists with CAIs[4]

β-blocker–free option combines increased AH outflow and reduced production; twice daily, but less effective than monotherapy

β-blockers with α2-adrenergic agonists[5]

Combines reduced AH production and increased drainage; fast-acting and applied twice daily

ROCK inhibitor-based FDCs[6]

A novel, β-blocker–free class targeting trabecular outflow, with partner-dependent effects on uveosclearal outflow or aqueous humor production (PGAs or α2-adrenergic agonists)

AH: aqueous humor; CAI: carbonic anhydrase inhibitor; FDC: fixed-dose combination; IOP: intraocular pressure; PGA: prostaglandin analogue; ROCK: Rho kinase.

1. Konstas AG, et al. *Expert Opin Pharmacother* 2018;19:1981–8; **2.** Wayman L, et al. *Arch Ophthalmol* 1997;115:1368–71; **3.** Hatanaka M, et al. *J Glaucoma* 2010;19:331–5; **4.** Aung T, et al. *Ophthalmology* 2014;121:2348–55; **5.** Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **6.** ROCKLATAN® (netarsudil 0.02% and latanoprost 0.005% ophthalmic solution) [prescribing information].

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Advantages and disadvantages of FDCs

Advantages[1]

1. Simplified regimen
2. Enhanced convenience
3. Cost-effectiveness
4. Improved tolerability
5. Prevents washout

Disadvantages[1]

1. Limited dose flexibility
2. Challenges in identifying the causative agent in adverse reactions
3. Restricted availability

FDC: fixed-dose combination.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Bangalore S, et al. *Am J Med* 2007;120:713–9; **3.** Barnebey HS, Robin AL. *Am J Ophthalmol* 2017;176:61–9.

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Commercially available FDCs

Product name	Company	Components	Mechanism of IOP reduction
Xalacom	Pfizer	Latanoprost (PGA) + timolol (β-blocker)	↑ **AH outflow** (PGA and α2-agonist) ↓ **AH production** (β-blocker and CAI)
Ganfort/Ganfort PF*	Allergan	Bimatoprost (PGA) + timolol (β-blocker)	
DuoTrav	Novartis	Travoprost (PGA) + timolol (β-blocker)	
Tapcom/Tapcom-S*	Santen	Tafluprost (PGA) + timolol (β-blocker)	
Simbrinza	Alcon	Brinzolamide (CAI) + brimonidine (α2-agonist)	
Combigan	Allergan	Brimonidine (α2-agonist) + timolol (β-blocker)	
Cosopt/Cosopt-S*	Santen	Dorzolamide (CAI) + timolol (β-blocker)	↓ **AH production** (β-blocker and CAI)
Azarga	Novartis	Brinzolamide (CAI) + timolol (β-blocker)	
Gla-Alpha	Kowa	Ripasudil (ROCK inhibitor) + brimonidine (α2-agonist)	↑ **TM outflow** + ↓ **AH production** (ROCK inhibitor and α2-agonist)
Rocklatan	Santen	Netarsudil (ROCK inhibitor) + latanoprost (PGA)	↑ **TM outflow** + ↓ **EVP** (ROCK inhibitor) ↑ **AH outflow** (PGA)

*Preservative-free option.
AH: aqueous humor; CAI: carbonic anhydrase inhibitor; EVP: episcleral venous pressure; FDC: fixed-dose combination; IOP: intraocular pressure; PF: preservative-free; PGA: prostaglandin analogue; ROCK: Rho-kinase; TM: trabecular meshwork.
Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024.

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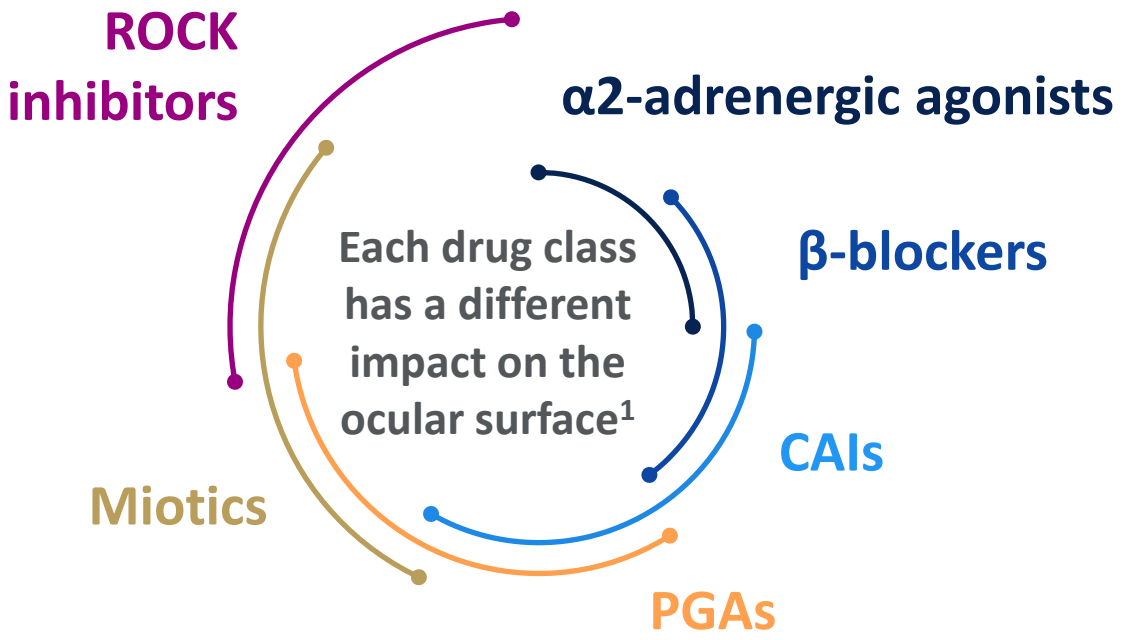
What is OSD?

OSD is a multifactorial disorder of the conjunctival epithelium, corneal epithelium, lacrimal glands, and meibomian glands that results in either deficient or inappropriate tear production, and leads to decreased visual clarity and ocular discomfort through various inflammatory pathways[1,2]

Preservatives and OSD:[3,4]

BAK is the most commonly used preservative in antiglaucoma drops. However, **it can cause ocular surface damage**, including epithelial cell toxicity, goblet cell loss, delayed healing, and inflammation



BAK: benzalkonium chloride; CAI: carbonic anhydrase inhibitor; OSD: ocular surface disease; PGA: prostaglandin analogue; ROCK: Rho-kinase.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Pflugfelder SC, de Paiva CS. *Ophthalmology* 2017;124:S4–13; **3.** Caraccio TR, McGuigan MA. In: Dart RC (ed). *Medical Toxicology*. 3rd ed. New York, NY: Lippincott Williams & Wilkins; 2004:1255–7; **4.** Goldstein MH, et al. *Eye (Lond)* 2022;36:361–8.

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The impact of OSD

Patient impact: poor adherence & quality of life

OSD symptoms such as stinging and burning are a major driver of poor patient adherence and are associated with a significantly reduced, disease-specific quality of life[1]

Clinical impact: treatment failure

Poor adherence can lead to IOP and treatment failure. Chronic conjunctival inflammation can be a risk factor for the long-term failure of surgeries like trabeculectomy[2]

Escalating the Problem

Treatment failure can lead to addition of more medications, escalating cumulative daily exposure to preservatives, worsening underlying OSD.[3]

IOP: intraocular pressure; OSD: ocular surface disease; QoL: quality of life.

1. Skalicky SE, et al. *Am J Ophthalmol* 2012;153:1–9; **2.** Lee S, et al. *Sci Rep* 2024;14:28341; **3.** Kahook MY, et al. *Ocul Surf* 2024;34:213–24.

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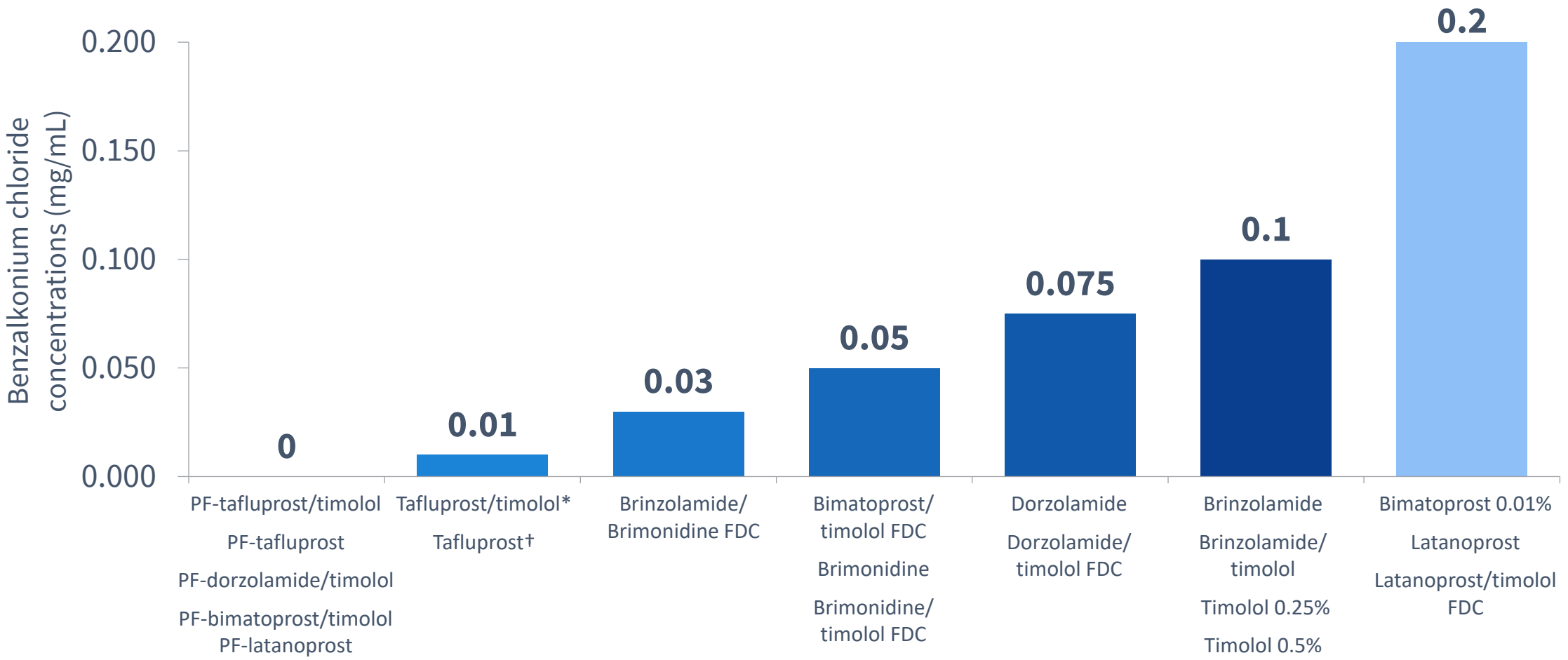
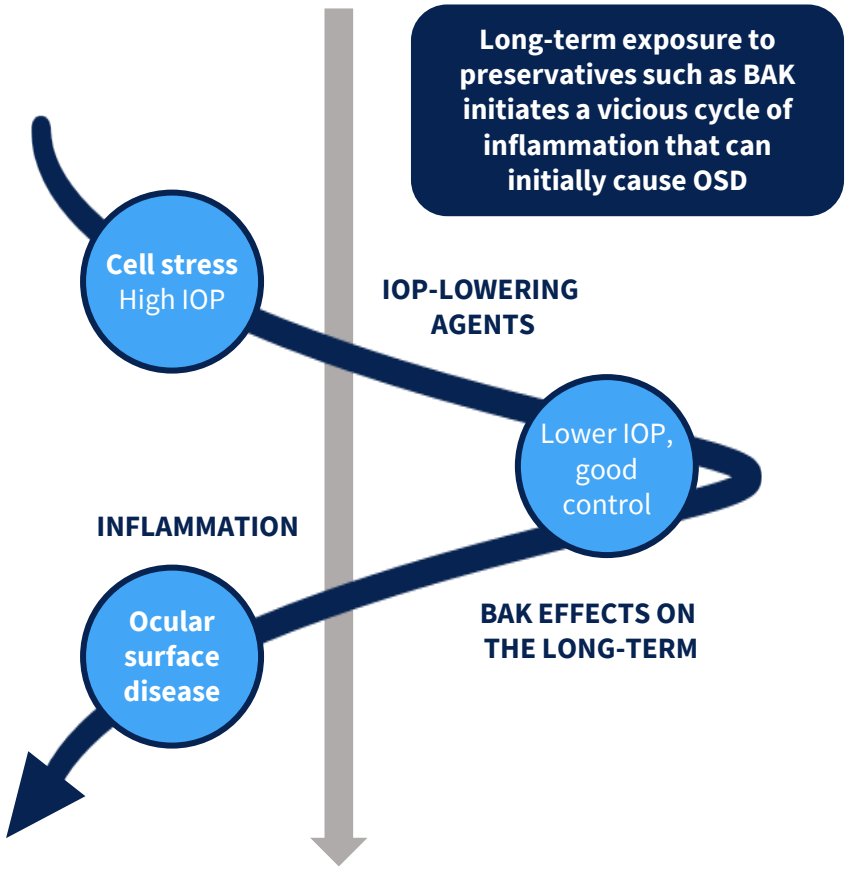
Concentrations of BAK across different topical anti-glaucomatous medications



Data as reported from their respective Summary of Product Characteristics. *Data from Fuwa M et al. 2016. †Data from Keating GM. 2016

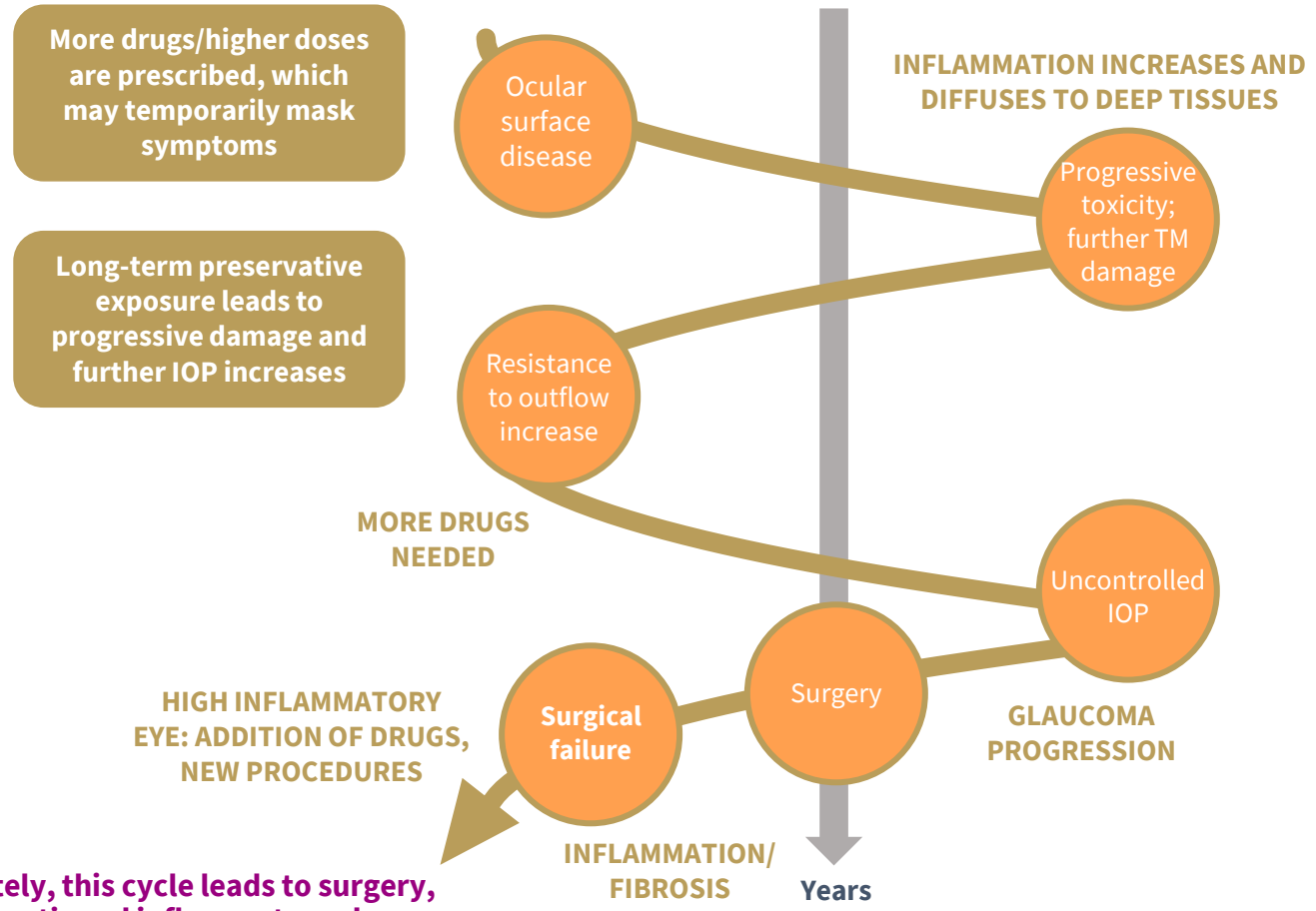
The vicious cycle of preservative damage

THE VICIOUS CYCLE BEGINS WITH OSD SYMPTOMS[1,2]



Progressive inflammation and damage to the TM may clinically appear as an initial loss of efficacy of topical IOP-lowering drugs

THE VICIOUS CYCLE CONTINUES WITH FURTHER DAMAGE TO THE TM[1,2]



Ultimately, this cycle leads to surgery, but the continued inflammatory changes in the anterior segment of the eye will negatively affect surgical outcomes

IOP: intraocular pressure; OSD: ocular surface disease; TM: trabecular meshwork.

1. Kahook M, et al. *Ocul Surf* 2024:34:213–24; 2. Zhou X, et al. *Ophthalmol Ther* 2022;11:1681–704.

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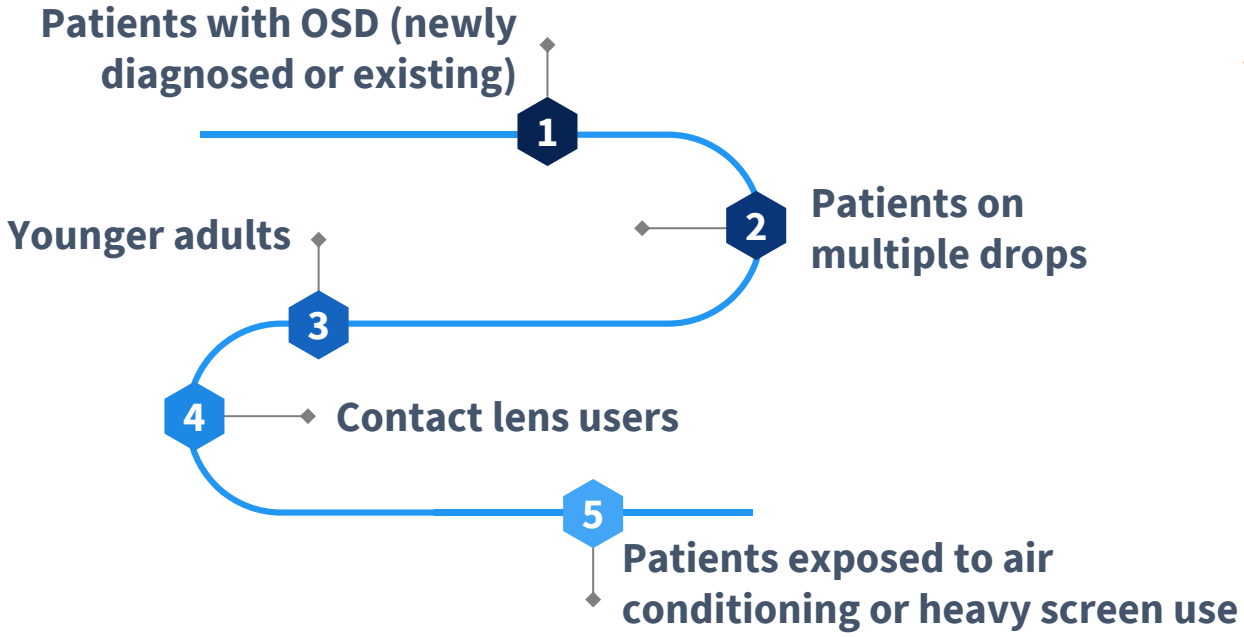
PF medications should be considered for the management of OSD

PF medications are the logical choice for most patients. However, if cost is a concern, it is appropriate to consider PF therapy for the subsets of glaucoma patients who would benefit most[1,2]

PF medical treatment may be most valuable for:[1]



Considerations for surgery to reduce drop burden

Surgical options include punctal occlusion, early SLT, MIGS, and filtration surgery to reduce drop burden[1]

Prof. Megumi Honjo

PF medications can benefit patients of all ages, as older patients often have severe OSD. However, patients under 50 may be particularly suitable for PF therapy due to contact lens use and the likelihood of needing long-term glaucoma treatment.

OSD: ocular surface disease; MIGS: minimally invasive surgery; PF: preservative-free; SLT: selective laser trabeculoplasty.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Thygesen J. *Clin Ophthalmol* 2018;12:707–17; **3.** Jones L, et al. *Ocul Surf* 2017;15:575–628.

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What is PAPS?

PAPS is the constellation of eyelid and orbital changes that result from the topical administration of PGAs

PAPS clinical findings:[1,2]

- Upper lid ptosis
- DUES
- Involution of dermatochalasis
- Periorbital fat atrophy
- Mild enophthalmos
- Inferior scleral show
- Increased prominence of lid vessels
- Tight eyelids

Shimane University PAPS grading system:[1,3]

No PAPS (no cosmetic change)

Superficial cosmetic PAPS (cosmetic changes, including eyelid pigmentation, and/or eyelash growth)

Deep cosmetic PAPS (cosmetic changes with at least one sign of PAPS, including DUES, blepharochalasis involution, periorbital fat loss, or enophthalmos)

Tonometric PAPS (**difficulty in performing GAT and/or reduced reliability of GAT-measured IOP due to PAPS-related DUES**, hardening of eyelids, ptosis, or enophthalmos)

DUES: deepening of the upper eyelid sulcus; GAT: Goldmann applanation tonometry; IOP: intraocular pressure; PAPS: prostaglandin-associated periorbitopathy syndrome; PGA: prostaglandin analogue.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Sakata R, et al. *Eye (Lond)* 2014;28:1446–51; **3.** Tanito M, et al. *Medicine (Baltimore)* 2021;100:e26874.

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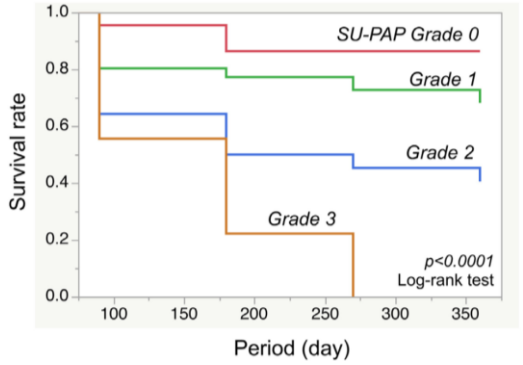
Impact and management of PAPS

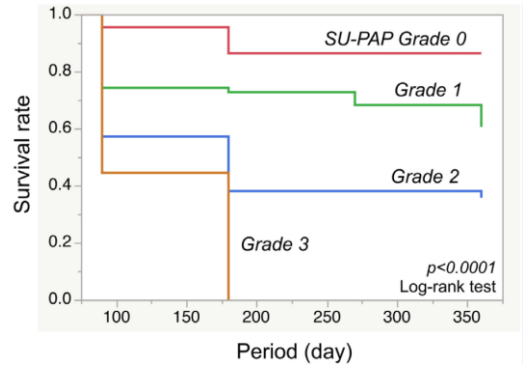
PAPS is not just cosmetic

1. It can directly impact glaucoma assessment and surgical outcomes[1]
2. It can complicate accurate GAT IOP measurement[2]
3. It may contribute to IOP overestimation with GAT[3]
4. Patients with PAPS undergoing trabeculectomy require closer postoperative monitoring[4]

Postoperative IOP >15 mmHg[3]



Postoperative IOP >12 mmHg[3]



Success rates of trabeculectomy in patients with POAG were worse in eyes with higher SU-PAP grades than in eyes with lower grades[5]

PAPS can compromise glaucoma assessment and surgical outcomes post-trabeculectomy – affecting bleb evaluation and IOP measurement – so patients require careful postoperative monitoring[1–5]

DUES: deep upper eyelid sulcus; GAT: Goldmann applanation tonometry; IOP: intraocular pressure; PAPS: periocular and periorbital side effects; PGA: prostaglandin analogue; POAG: primary open-angle glaucoma; SU-PAP: Shimane University prostaglandin-associated periorbitopathy.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Sobel RK, Tienor BJ. *Curr Opin Ophthalmol* 2013;24:500–5; **3.** Tanito M, et al. *Medicine (Baltimore)* 2021;100:e26874; **4.** Miki T, et al. *PLoS One* 2017;12:e0181550; **5.** Ishida A, et al. *Ophthamology* 2023;130:297–30.

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Impact and management of PAPS

Consider PAPS when initiating glaucoma therapy in **treatment-naïve patients**, as well as **existing PGA users**[1], and avoid unilateral PGA use where possible due to increased cosmetic asymmetry

In **existing PGA users**, **PAPS is often reversible upon discontinuation**. Alternatives to PGAs (other drug classes such as EP2 receptor agonists, laser, or surgery) can be equally effective at lowering IOP[1]

If PGAs are necessary, **switching to latanoprost or tafluprost** (lower PAPS risk) may reverse DUES[2–4]

Patient education is key to reducing PAPS risk[1]

DUES: deep upper eyelid sulcus; GAT: Goldmann applanation tonometry; IOP: intraocular pressure; PAPS: periocular and periorbital side effects; PGA: prostaglandin analogue; POAG: primary open-angle glaucoma; SU-PAP: Shimane University prostaglandin-associated periorbitopathy.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Sakata R, et al. *Jpn J Ophthalmol* 2013;57:179–84; **3.** Sakata R, et al. *Jpn J Ophthalmol* 2014;58:212–7; **4.** Inoue K, et al. *J Glaucoma* 2013;22:626–31.

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PAPS summary

1. PAPS impact should be considered when selecting medical treatment – both for naïve glaucoma patients and existing PGA patients[1]

2. PAPS can have more than just cosmetic impacts – causing inaccurate IOP measurements and poor trabeculectomy outcomes, negatively impacting long-term glaucoma management[2,3]

3. Using PGA alternatives (such as EP2 receptor agonists), or PGAs with lower PAPS risk (such as latanoprost or tafluprost) can help lower risk of PAPS or reverse symptoms[1]

IOP: intraocular pressure; PAPS: periocular and periorbital side effects; PGA: prostaglandin analogue.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Sobel RK, Tienor BJ. *Curr Opin Ophthalmol* 2013;24:500–5; **3.** Ishida A, et al. *Ophthamology* 2023;130:297–30.

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Why is 24-hour control important?

Management of glaucoma has been largely based on single IOP measurements during check-ups, but **IOP is a dynamic entity** that changes throughout the 24 hours of a day.[1]

Fluctuations can occur as a result of many factors[2–4] including:

- **Physiologic positions**
- **Eye movements**
- **Circadian patterns**

IOP fluctuations can occur[3,4]

- **In the short-term (over days to weeks)**
- **In the long-term (over months to years)**

IOP: intraocular pressure.

1. Agnifili L et al. *Acta Ophthalmol* 2015;93:e14–e21; **2.** Nuyen B et al. *Open Ophthalmol* J 2016;10(Suppl 1):44–55; **3.** Kim JHK et al. *J Ophthalmic Vis Res* 2018;13:170–74.
4. Sit AJ. *Can J Ophthalmol* 2014;49:484–8.

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24-hour fluctuations should be considered

Irregularities in 24-hour IOP fluctuations are correlated with progression

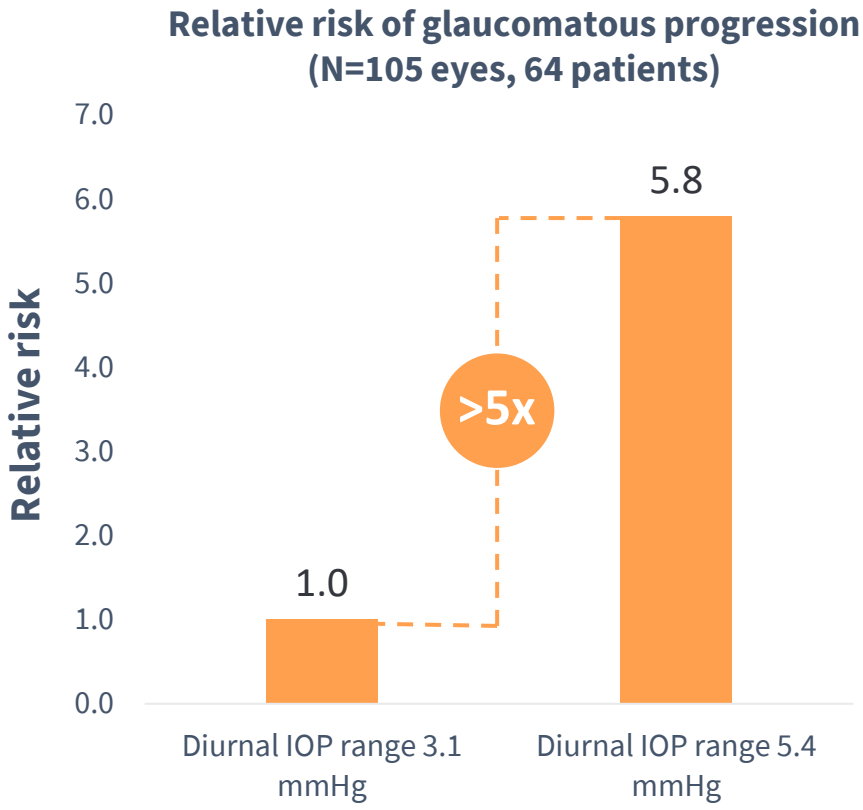
>5x

Relative risk of disease progression was **5.76 times greater** (95% CI: 2.21, 14.98) in eyes in the **highest quartile of range of diurnal IOP** versus eyes in the lowest quartile

*

This was statistically significant after adjusting for variations in **office IOP, age, race, and baseline visual field status**.

In patients with glaucoma with office IOP in the normal range, **large fluctuations** in diurnal IOP are a **significant risk factor**, independent of parameters obtained in the office.



A prospective cohort study (N=64) carried out in patients with open angle glaucoma; IOP measurements was obtained through self tonometry five times daily for five days. The mean follow-up period was five years.
CI: confidence interval; IOP: intraocular pressure.

1. Asrani S et al. *J Glaucoma* 2000;9:134–42.

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Practical tips for simplifying a complex regimen

Better IOP control starts with better measurement

Single IOP measurement is **insufficient** to make clear IOP diagnosis

Use **in-office-hour day phasing** as an alternative to 24 hour IOP measurement

Possible high-risk patients suitable for 24 h IOP measurement

- Normal tension glaucoma
- Advanced-staged glaucoma
- One functional eye
- Complex underlying disease
- Adherence challenges

IOP: intraocular pressure.

Selecting EP2 receptor agonists

EP2 receptor agonists lower IOP by enhancing AH outflow via both the uveoscleral and trabecular pathways

Commercially available EP2 receptor agonist for glaucoma:

- **Omidenepag isopropyl (OMDI)**

OMDI provides PAPS-free IOP control

When to select OMDI:

Patients who are treatment-naïve: OMDI is appropriate for a wide range of patients, from young to old, who wish to avoid PAPS. This is particularly true for naïve patients who use single eye drops or are concerned about cosmetic appearance

Switching from PGAs: OMDI is an appropriate choice for existing PGA patients who have experienced local ocular side effects from FP receptor agonists

IOP: intraocular pressure; OMDI: omidenepag isopropyl; PGA: prostaglandin analogue; PAPS: prostaglandin-associated periorbitopathy syndrome.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Fuwa M, et al. *J Ocul Pharmacol Ther* 2018;34:531–7; **3.** Aihara M, et al. *Am J Ophthalmol* 2020;220:53–63; **4.** Aihara M, et al. *Jpn J Ophthalmol* 2021;65:810–9; **5.** Aihara M, et al. *Jpn J Ophthalmol* 2020;64:398–406; **6.** EYBELIS® (omidenepag isopropyl 0.002% ophthalmic solution) [package insert].

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Efficacy and safety of EP2 receptor agonists

OMDI is as effective as FP receptor agonists but without the side effect of PAPS, representing an optimal balance between efficacy and safety[1,2]

Efficacy of OMDI:

1. **AYAME:** OMDI was **non-inferior to latanoprost** in terms of the mean daily change in IOP, with both groups experiencing significant reductions in IOP from their respective baselines[3]
2. **RENGE:** OMDI, alone or administered **concomitantly with timolol** 0.5%, resulted in significant and sustained IOP reduction over 52 weeks in patients with OAG or OHT[4]
3. **FUJI:** OMDI demonstrated a clinically significant reduction in IOP and was well tolerated in patients with primary open-angle glaucoma and OHT who were **non-/low responders to latanoprost[5]**

Side effects of OMDI:[4,6]

It is important to note that the administration of OMDI is contraindicated in cases with IOL insertion or aphakia

The main side effects were:

- Conjunctival hyperemia
- Corneal thickening (within physiological range)
- Iritis
- Macular edema
  (in patients who are pseudophakic/aphakic)

IOL: intraocular lens; IOP: intraocular pressure; OAH: ocular arterial hypertension; OHT: ocular hypertension; OMDI: omidenepag isopropyl; PAPS: prostaglandin-associated periorbitopathy syndrome.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Fuwa M, et al. *J Ocul Pharmacol Ther* 2018;34:531–7; **3.** Aihara M, et al. *Am J Ophthalmol* 2020;220:53–63; **4.** Aihara M, et al. *Jpn J Ophthalmol* 2021;65:810–9; **5.** Aihara M, et al. *Jpn J Ophthalmol* 2020;64:398–406; **6.** EYBELIS® (omidenepag isopropyl 0.002% ophthalmic solution) [package insert].

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EP2 receptor agonists for the management of normal-tension glaucoma

The only known modifiable risk factor that can alter the progression of NTG is IOP reduction.[4]

Eybelis®, an EP2 receptor agonist, consistently demonstrates IOP lowering in patients with NTG:[1–3]

	Inoue K, et al. *Clin Ophthalmol* 2020[1]	Lee S, et al. *J Glaucoma* 2023[2]	Inoue K, et al. *Jpn J Ophthalmol* 2024[3]
Study description	Retrospective evaluation of the **short-term** efficacy of Eybelis in patients with NTG	Retrospective analysis of medical records of patients with NTG treated with Eybelis for **≥6 months**	Retrospective evaluation of the **3-year** efficacy of Eybelis in patients with NTG
Treatment regimen	**Eybelis ophthalmic solution (0.002%)**	**Eybelis ophthalmic solution (0.002%)**	**Eybelis ophthalmic solution (0.002%)**
Participants	54 eyes	62 eyes	100 eyes
Outcomes	IOP at baseline, 1–2 months after, and 3–4 months after Eybelis	IOP, refraction, keratometry, CCT, endothelial cell count, CV, corneal erosion, and central retinal thickness at 1, 3, and 6 months after Eybelis	IOP at baseline and 6, 9, 12, 18, 24, 30, and 36 months after Eybelis
Duration of follow-up	4 months	6 months	36 months
Key efficacy results	**There was a significant decrease in IOP at 4 months following treatment with Eybelis in patients with NTG (P<0.0001)**	**Treatment with Eybelis elicited significant and stable IOP reductions after 6 months in patients with NTG with low IOP (P<0.001). Patients who switched to Eybelis showed reductions in PAPS symptoms**	**Within 3 years of treatment with Eybelis, IOP significantly decreased (P<0.0001) from baseline, and visual fields were maintained in patients with NTG**
Key safety results	AEs occurred in four patients (7.4%), including conjunctival hyperemia in three patients and eye pain in one patient	Transient myopic and corneal endothelial cell changes, development of corneal thickening, and corneal erosion should be considered when using Eybelis	AEs occurred in 11 patients (11.0%), including conjunctival hyperemia in six patients
Conclusion	After administration of Eybelis, IOP in patients with NTG was significantly decreased.	Eybelis elicited significant and stable IOP reductions in patients with NTG and low IOP.	Eybelis can be used as the first-line treatment for patients with NTG.

AE: adverse event; CCT: central corneal thickness; CV: coefficient of variation of endothelial cell area; IOP: intraocular pressure; NTG: normal-tension glaucoma; PAPS: prostaglandin-associated periorbitopathy syndrome.

1. Inoue K, et al. *Clin Ophthalmol* 2020;14:2943–9; **2.** Lee S, et al. *J Glaucoma* 2023;32:245–51; **3.** Inoue K, et al. *Jpn J Ophthalmol* 2024;68:206–10; **4.** Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024.

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Selecting ROCK inhibitors

ROCK inhibitors lower IOP by increasing outflow facility through the conventional pathway (modification of the TM and Schlemm's canal cytoskeleton and cellular function) and reducing EVP, as well as possible neuroprotection[1–4]

Commercially available ROCK inhibitors for glaucoma:[1]
- **Netarsudil**
- **Ripasudil**

Monotherapy

ROCK inhibitors are effective alone

Combination therapy

ROCK inhibitors are effective when combined with other known ocular hypotensive medications

EVP: episcleral vein pressure; IOP: intraocular pressure; PGA: prostaglandin analogue; ROCK: Rho-kinase; TM: trabecular meshwork.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Honjo M, et al. *Invest Ophthalmol Vis Sci* 2001;42:137–44; **3.** Rao PV, et al. *Invest Ophthalmol Vis Sci* 2001;42:1029–37; 4. Inoue T, et al. *Expert Opin Pharmacother* 2017;18:1669–73; **5.** Esaki Y, et al. *J Ocul Pharmacol Ther* 2020;36:529–33.

Efficacy and safety of netarsudil

Netarsudil significantly reduces IOP both as a monotherapy or an add-on therapy in patients with glaucoma and OHT, with efficacy comparable to PGAs[1–6]

Efficacy of netarsudil:

1. **Phase II study:** Netarsudil acts on the conventional outflow pathway, both proximal and distal, to significantly reduce IOP by improving trabecular outflow and decreasing EVP[2]
2. **Phase IV study:** Netarsudil consistently maintained IOP control when it replaced previous therapies and provided additional IOP-lowering efficacy when added to treatments[3]
3. **ROCKET-1 to 4:** Once-daily netarsudil resulted in IOP lowering that was non-inferior to twice-daily timolol[5]
4. **J-ROCKET:** Once-daily netarsudil was more effective in reducing IOP than twice-daily ripasudil in patients with POAG and OHT[6]

Safety of netarsudil:

1. All patients reporting an AE reported conjunctival hyperemia of mild or moderate severity[2]
2. AEs were reported in 40.4% of patients; ocular hyperemia was the most common AE, and is a known vasodilatory side effect of ROCK inhibitors[3,4]
3. The most common ocular AE, conjunctival hyperemia (netarsudil, 54.4%; timolol, 10.4%), was graded as mild in 77.6% of affected patients treated with netarsudil[5]
4. Netarsudil was well tolerated with no eye-related SAEs reported; the most frequently reported AE was conjunctival hyperemia (netarsudil, 54.9%; ripasudil, 62.6%)[6]

AE: adverse event; EVP: episcleral vein pressure; IOP: intraocular pressure; OHT: ocular hypertension; PGA: prostaglandin analog; POAG: primary open-angle glaucoma; ROCK: Rho-kinase; SAE: serious adverse event.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Sit AJ, et al. *Am J Ophthalmol* 2021;226:262–9; **3.** Zaman F, et al. *Curr Med Res Opin* 2021;37:1011–20; **4.** Lin CW, et al. *J Ocul Pharmacol Ther* 2018;34:40–51; **5.** Singh IP, et al. *J Glaucoma* 2020;29:878–84; **6.** Araie M, et al. *Adv Ther* 2023;40:4639–56.

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Efficacy and safety of ripasudil

Ripasudil significantly lowers IOP across glaucoma types and OHT, with efficacy comparable to timolol and sustained reductions over the long term[1–4]

Efficacy of ripasudil:

Safety of ripasudil:

1. **ROCK-J:** Ripasudil demonstrated significant reductions in IOP maintained over 24 months of treatment with no new safety signals in patients naïve to ripasudil with glaucoma or OHT[2]
   → 25.3% of patients experienced ADRs; the most common were blepharitis (8.6%), conjunctival hyperemia (8.5%), and conjunctivitis (6.3%)[2]

2. **Meta-analysis:** With a treatment duration of 1–3 months, ROCK inhibitors showed effective IOP reduction that was non-inferior to timolol as both monotherapy and adjunctive therapy[3]
   → The most common ocular AEs of ROCK inhibitors were conjunctival hyperemia (19–65%), conjunctival hemorrhage (6–20%), and cornea verticillata (13–26%)[3]

3. **ROCK-S:** In patients with secondary glaucoma who needed further IOP reduction, the addition of ripasudil led to significant IOP reduction from baseline at 1, 3, and 6 months[4]
   → 37.7% of patients experienced ADRs; the most common were blurred vision (7.5%), conjunctival hyperemia (6.4%), blepharitis (2.8%), and eye pruritus (2.8%)[4]

ADR: adverse drug reaction; AE: adverse events; IOP: intraocular pressure; OHT: ocular hypertension; ROCK: Rho-kinase.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Tanihara H, et al. *Adv Ther* 2022;39:1659–77; **3.** Wu JH, et al. *Graefes Arch Clin Exp Ophthalmol* 2022;260:937–48; **4.** Futakuchi A, et al. *Sci Rep* 2020;10:10308.

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ROCK inhibitors for the management of normal-tension glaucoma

The only known modifiable risk factor that can alter the progression of NTG is IOP reduction.[4]

ROCK inhibitors have demonstrated IOP-lowering in patients with NTG:[1–3]

	Tanihara H, et al. *BMC Ophthalmol* 2020[2]	Tanihara H, et al. *Adv Ther* 2022[3]	Effect of netarsudil vs brimonidine in NTG patients on latanoprost (NCT06449352)
Study description	Prospective, open-label, observational study of patients with glaucoma or OHT who started ripasudil during routine care	**ROCK-J:** Prospective, open-label, observational study of patients who were naïve to ripasudil with glaucoma or OHT who initiated ripasudil in Japan	Phase IV, randomized, multicenter, investigator-masked prospective study of the addition of netarsudil vs brimonidine in patients with NTG currently on latanoprost
Treatment regimen	**Ripasudil ophthalmic solution (0.4%)**	**Ripasudil ophthalmic solution (0.4%)**	**Netarsudil 0.02% vs brimonidine 0.1%**
Participants	Total study population: 3359 patients **Subset of patients with NTG: 1229 patients**	Total study population: 3374 patients **Subset of patients with NTG: 1237 patients**	Estimated enrollment: 100 patients
Outcomes	IOP at baseline, 3 months, and 6 months after ripasudil	Least-squares mean change in IOP from baseline to 24 months after ripasudil	Visual acuity and IOP
Duration of follow-up	12 months	24 months	*Currently recruiting*
Key efficacy results	**There was a significant reduction in IOP at 12 months after treatment with ripasudil in patients with NTG (P<0.001)**	**There was a significant reduction in IOP at 24 months after treatment with ripasudil in patients with NTG (P<0.001)**	*Currently recruiting*
Key safety results	ADRs occurred in 626 patients (18.6%); the most common were conjunctival hyperemia and blepharitis*	ADRs occurred in 853 (25.3%) of patients; the most common were blepharitis (8.6%), conjunctival hyperemia (8.5%), and conjunctivitis (6.3%)†	*Currently recruiting*
Conclusion	Ripasudil was safe and effective in patients with glaucoma or OHT during routine care.	Ripasudil was safe and effective, with no new safety signals identified and significant IOP reductions at 24 months.	*Currently recruiting*

*Safety results are reported for the total study population; 3323 patients were included in the safety analysis set.[2] †Safety results are reported for the total study population.[3]
ADR: adverse drug reaction; IOP: intraocular pressure; NTG: normal-tension glaucoma; OHT: ocular hypertension; ROCK: Rho-kinase.

1. Tanihara H, et al. *BMC Ophthalmol* 2020;20:275; **2.** Tanihara H, et al. *Adv Ther* 2022;39:1659–77; **3.** ClinicalTrials.gov. NCT06449352. Available at: https://clinicaltrials.gov/study/NCT06449352. Last accessed August 2025; **4.** Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024.

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Netarsudil and ripasudil: Head-to-head

Feature	Netarsudil		Ripasudil	
Dose	1x per day (QD) in the evening.		2x per day (BID).	
Formulation	Pro-drug. It is metabolized in the eye into its active form.		Active drug. Administered in its active form.	
Mechanism of action	**Dual-action:** 1. Increases trabecular outflow (ROCK inhibitor) 2. Decreases episcleral venous pressure		**Primary-action:** Increases trabecular outflow (ROCK inhibitor)	
Concentration	0.02%		0.40%	
Efficacy (J-ROCKET)[1]*	Demonstrated superiority in a 4-week trial, with a **1.74 mmHg** greater IOP reduction than ripasudil. • Mean IOP reduction from baseline: **4.65 mmHg (22.6%)**		Showed a lower IOP reduction compared to netarsudil. • Mean IOP reduction from baseline: **2.98 mmHg (14.3%)**	
Key AEs (J-ROCKET)[1]*	**Overall incidence**	59.8%	**Overall incidence**	69.1%
	Most common AE (conjunctival hyperemia)	54.9%	**Most common AE (conjunctival hyperemia)**	62.6%
	Conjunctival hemorrhage	4.9%	**Conjunctival hemorrhage**	0%
	Cornea verticillata	1.6%	**Cornea verticillata**	0%

*Efficacy and adverse event data are from the J-ROCKET study, a 4-week, head-to-head Phase 3 trial conducted in 245 Japanese patients with POAG or OHT. This is the only direct head-to-head trial comparing these two agents; for further data from non-comparative trials, please refer to other publications.
AE: adverse event; IOP: intraocular pressure.
Araie M, et al. *Adv Ther.* 2023;40:4639–56.

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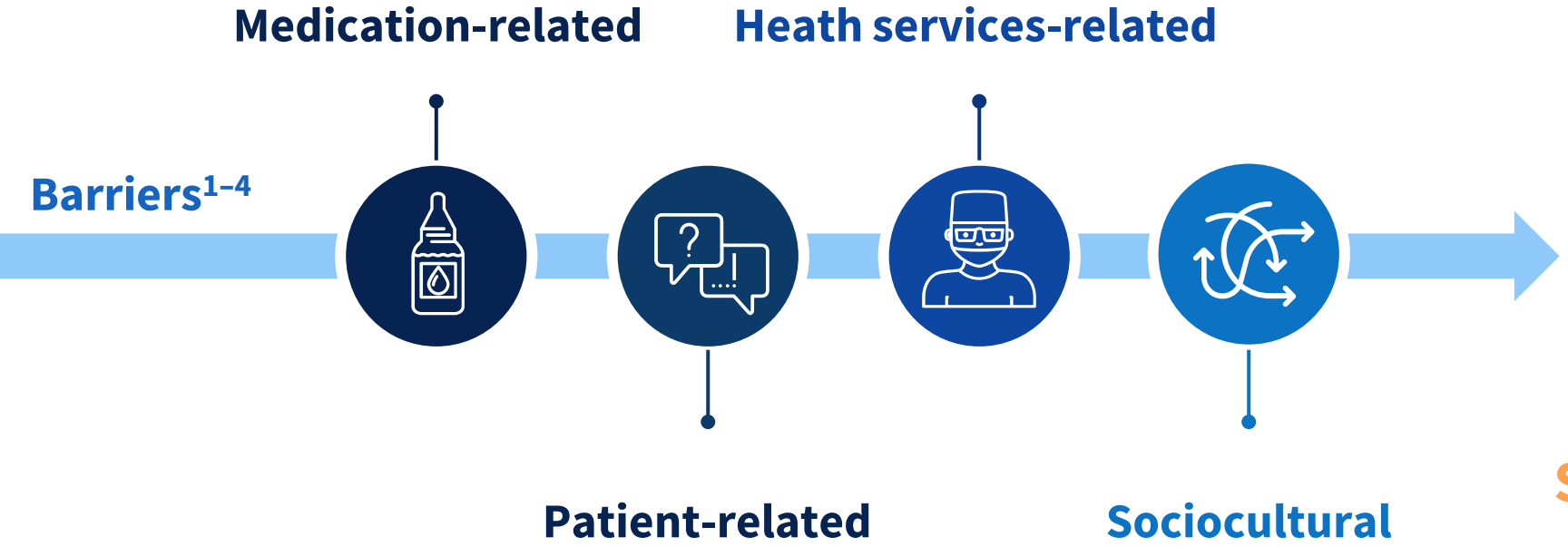
Barriers to adherence

Assoc. Prof. Poemen Chan, Prof. Megumi Honjo, and Assoc. Prof. Victor Koh

Common patient misconceptions include:

- If I don't feel any difference, it's okay to stop using my eye drops
- Using eye drops long term will make me dependent on them
- Preservatives in drops are harmful, so it's better to avoid them
- The discomfort from applying eye drops causes long-term damage
- In NTG, eye pressure is already low, so further lowering with drops is not helpful



Support in early stages is crucial, as the first year predicts 3-year adherence[5–9]

NTG: normal-tension glaucoma.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Newman-Casey PA, et al. *Ophthalmology* 2015;122:1308–16; **3.** Tsai JC. *Ophthalmology* 2009;116:S30–6; **4.** Friedman DS, et al. *Ophthalmology* 2008;115:1320–7; **5.** Tielsch JM, et al. *Am J Epidemiol* 1991;134:1102–10; **6.** Gurwitz JH, et al. *Am J Public Health* 1993;83:711–6; **7.** Patel SC, et al. *Ophthalmic Surg* 1995;26:233–6; **8.** Friedman DS, et al. *Ophthalmology* 2009;116:1097–105; **9.** Newman-Casey P, et al. *Ophthalmology* 2015;122:2010–21.

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Adherence to medication is poor, but ophthalmologists and patients can overestimate[1]

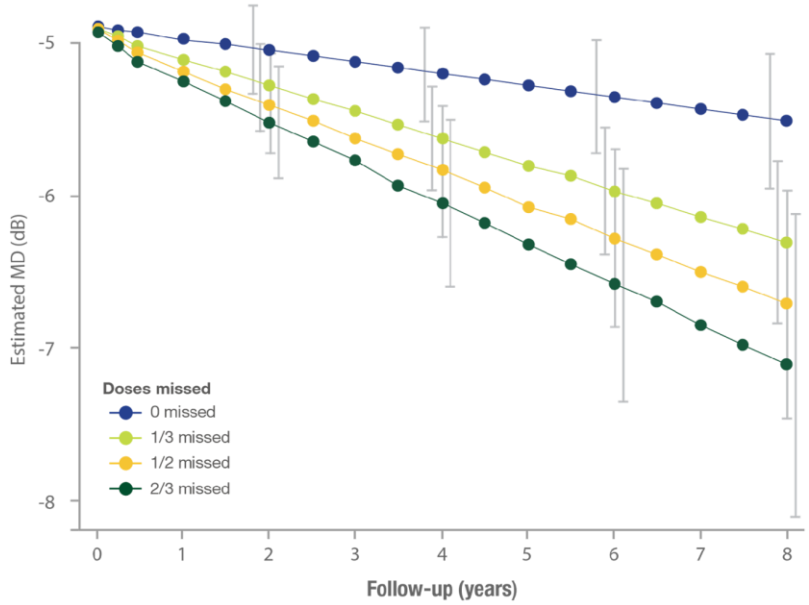
Missing just 1/3 of their doses caused the rate of VF loss to be more than double the standard age-related loss[2]

CIGTS randomised clinical trial medication arm (n=307)[2]

Never missed a dose	Missed 1/3 doses	Missed 2/3 doses
-0.62 dB over 8 years	**-1.42 dB over 8 years**	**-2.23 dB over 8 years**
Consistent with age-related loss (95% confidence interval, CI=0.17−1.06; p=0.007)	(CI=0.86−1.98; p<0.0001)	(CI=1.19−3.26; p<0.0001)

Participants (n=307) randomised to the medication arm of the Collaborative Initial Glaucoma Treatment Study (CIGTS) were followed at 6-month intervals for up to 10 years. Self-reported medication adherence and visual fields were measured.

Linear mixed regression model of visual field progression



Early adherence is critical: missed doses linked to long-term visual field deterioration[1,2]

dB: decibel; CIGTS: Collaborative Initial Glaucoma Treatment Study; VF: visual field.

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Newman-Casey PA, et al. *Ophthalmology* 2020;127:477–83.

Improving adherence

1. Education and patient communication[3]

2. Simplify the medication schedule[4]

3. Set a reminder schedule[5,6]

4. Provide personalized counselling and care plans based on individual needs[2,7]

1. Asia-Pacific Glaucoma Society (APGS). Asia-Pacific Glaucoma Guidelines. 4th ed. May 2024; **2.** Ha A, et al. *Ophthalmology* 2022;129:1294–304; **3.** Djafari F, et al. *Ophthalmic Epidemiol* 2015;22:380–6; **4.** Zimmerman TJ, Zalta AH. *Surv Ophthalmol* 1983;28:252–7; **5.** Boland MV, et al. *JAMA Ophthalmol* 2014;132:845–50; **6.** Lai Y, et al. *Ophthalmol Glaucoma* 2020;3:369–76; **7.** Gray T, et al. *Eye (Lond)* 2012;26:407–17.

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Summary

1. Choose treatments that are effective, safe, and practical while fostering strong patient engagement to support adherence
2. PAPS and OSD are conditions affecting the eyelids and ocular surface; both prevention and management of these unnecessary side effects are recommended
3. A single IOP measurement is insufficient to make clear IOP diagnosis and fluctuations need to be accounted for. If 24-hour IOP measurement is not practical, then use in-office-hour day phasing as an alternative
4. EP2 receptor agonists should be considered in patients who are treatment-naïve who use single eye drops or are concerned about cosmetic appearance, as well as existing PGA patients who have experienced PAPS
5. ROCK inhibitors are effective both as a monotherapy and when combined with other known ocular hypotensive medications
6. High medication adherence is critical to prevent disease progression, and patterns in the first year predict future adherence

IOP: intraocular pressure; OMDI: omidenepag isopropyl; OSD: ocular surface disease; PAPS: prostaglandin-associated periorbitopathy syndrome; PGA: prostaglandin analog; ROCK: Rho-kinase.

Asia–Pacific Glaucoma Society (APGS). Asia–Pacific Glaucoma Guidelines. 4th ed. May 2024.

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