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CME MONOGRAPH

# GETTING TO GOAL
## *in Glaucoma*


## Achieving Target IOP Through the Nitric Oxide Pathway



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**Original Release:** April 1, 2020
**Expiration:** April 30, 2021


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## ACTIVITY DESCRIPTION

Advances in the understanding of the pathophysiology of glaucoma and the recent US Food and Drug Administration approval of new treatment options are challenging traditional treatment paradigms, opening up new opportunities for physicians to improve visual outcomes for their patients with glaucoma. With these newer treatment options come new mechanisms of action, including nitric oxide's effect on the trabecular meshwork and the subsequent effects on the outflow of aqueous humor. More evidence-based data on the efficacy and safety of these drugs on lowering intraocular pressure are also available, and ophthalmologists who treat glaucoma must stay abreast of these developments in order to optimize patient outcomes. The desired results of this activity are to help ophthalmologists improve their practice strategies by updating them on the treatment and mechanistic effects of newer agents available to treat patients with glaucoma.

## TARGET AUDIENCE

This educational activity is intended for ophthalmologists.

## LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Describe the downstream signaling effects of nitric oxide and its relation to glaucoma
- Describe the physiologic mechanisms of action for trabecular outflow mediators
- Review recent clinical trial data for agents that mediate trabecular outflow to reduce intraocular pressure
- Design treatment plans for patients with glaucoma that maximize efficacy while minimizing the risk of adverse events that might lead to discontinuation

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# GETTING TO GOAL *in Glaucoma*

## Achieving Target IOP Through the Nitric Oxide Pathway

## INTRODUCTION: THE MODERN GLAUCOMA "PHARMAMENTARIUM"

**Donald L. Budenz, MD, MPH**

Innovation in glaucoma therapy has provided a vast array of new therapies—from drugs with novel mechanisms of action to safer and less invasive surgical procedures—all designed to lower intraocular pressure (IOP) effectively and safely for our patients with glaucoma. In 2020, we have more and better ways to lower IOP than ever before. In this activity, we will review the findings from major clinical trials of several new drugs, discuss their mechanisms of action, and, through a series of cases, demonstrate the issues to be considered when incorporating these new medications into clinical practice.

In late 2017, 2 new drugs were approved for IOP reduction: latanoprostene bunod (LBN) and netarsudil.[1,2] In 2018, a fixed combination of netarsudil and latanoprost was also approved.[3] These drugs feature novel mechanisms of action that target the trabecular meshwork (TM), the source of elevated IOP in eyes with glaucoma. Before these drugs were developed, our options for pharmacologic intervention in the TM were limited to the indirect action of miotics, such as pilocarpine,[4] and secondary effects of prostaglandin analogues.[5,6] Now we have drugs with primary activity to increase trabecular outflow, complementing our existing drug options for reducing aqueous production (beta blockers, carbonic anhydrase inhibitors, and alpha-receptor adrenergic agonists) and for increasing uveoscleral outflow (prostaglandins and alpha-receptor adrenergic agonists) **(Figure 1)**. Some of these drugs have multiple mechanisms of IOP reduction, a feature that has implications when developing multidrug treatment strategies.

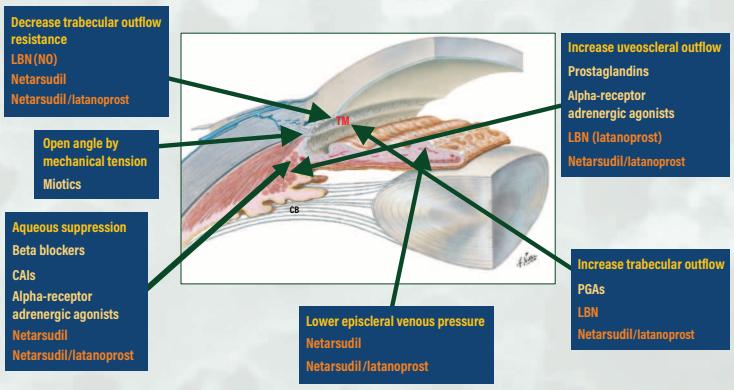


**Figure 1.** The array of intraocular pressure–lowering medications grouped by their mechanism(s) of action
Abbreviations: CAI, carbonic anhydrase inhibitor; CB, ciliary body; LBN, latanoprostene bunod; NO, nitric oxide; PGA, prostaglandin analogue; TM, trabecular meshwork.

LBN is a novel molecule consisting of the prostaglandin analogue latanoprost and a nitric oxide (NO)-donating moiety. Upon instillation onto the eye, the molecule dissociates into its 2 active components. Latanoprost, a familiar prostaglandin analogue, lowers IOP by enhancing uveoscleral outflow, whereas NO lowers IOP through direct action in the trabecular meshwork.[7] In the next section, the significance of the NO pathway in glaucoma and IOP regulation will be thoroughly reviewed. LBN's efficacy and safety have been characterized in clinical trials **(See Sidebar: Key Latanoprostene Bunod Efficacy and Safety Data)**.

Netarsudil is a novel inhibitor of the enzyme Rho kinase (ROCK). Rho kinase regulates the shape and movement of cells through action on their cytoskeletons. Inhibition of ocular ROCK leads to relaxation of cytoskeletal elements of the TM and smooth muscle relaxation of the episcleral veins. Thus, netarsudil acts to increase trabecular outflow by both increasing aqueous outflow through the TM[8,9] and also by decreasing the pressure within the episcleral venous system, thereby reducing downstream resistance to outflow.[8] Netarsudil also inhibits the action of norepinephrine transporter, which has the effect of increasing adrenergic activity within the eye, which in turn suppresses aqueous humor production.[8,9] Netarsudil's efficacy and safety have also been characterized in clinical trials **(see Sidebar: Key Netarsudil Efficacy and Safety Data)**.

## NITRIC OXIDE: A SMALL MOLECULE WITH A LARGE ROLE IN GLAUCOMA

**Louis R. Pasquale, MD, FARVO**

Nitric oxide exists as a gas at room temperature. It is relatively unstable, highly lipophilic, highly reactive, and has a molecular weight of 30 atomic mass units. The molecule was first described by Joseph Priestley in the 1770s,[10] and was considered to be a toxic gas and air pollutant found mainly in cigarette smoke and, later, automobile emissions[11] until 1977, when it was found to play a role in vasodilation.[12,13] A decade later, a fortuitous laboratory error, coupled with keen insight, led to the discovery that NO is produced by vascular endothelial cells and promotes vascular smooth muscle relaxation, resulting in vasodilation.[14] Mapping out the NO signaling pathway ultimately earned 3 researchers a Nobel prize in 1998.[15]

The NO signaling between the vascular endothelium and smooth muscle cells begins with acetylcholine (ACh) and vascular shear forces, which activate endothelial cell nitric oxide synthase 3 (NOS3, the vascular endothelial variant of the 3 nitric oxide synthase isoforms), an enzyme that converts the amino acid L-arginine to NO **(Figure 2)**. Once produced, NO—being highly lipophilic—diffuses freely from the endothelial cell into neighboring smooth muscle cells, where it binds to soluble guanylyl cyclase (sGC), an intracellular receptor in smooth muscle cells that catalyzes the reaction of guanosine triphosphate to cyclic guanosine monophosphate (cGMP). cGMP in turn stimulates a cGMP-dependent protein kinase that activates myosin light chain phosphatase, which then dephosphorylates myosin light chains, leading to smooth muscle relaxation.

Early research linking NO to the glaucoma disease process was conducted in subjects with normal-tension glaucoma (NTG). A group of patients with medically untreated NTG, as well as a group of healthy controls, were given various doses of intravenous ACh while arterial blood flow was measured in their forearms.[16] In healthy volunteers, ACh produced vasodilation presumably via the NO signaling pathway described previously, and forearm blood flow increased commensurately. In patients with NTG, however, forearm blood flow increase was far less, suggesting that these patients had impaired NO signaling.

Animal models have further enhanced our understanding of the relationship between NO and IOP regulation in glaucoma. Mean IOP was significantly

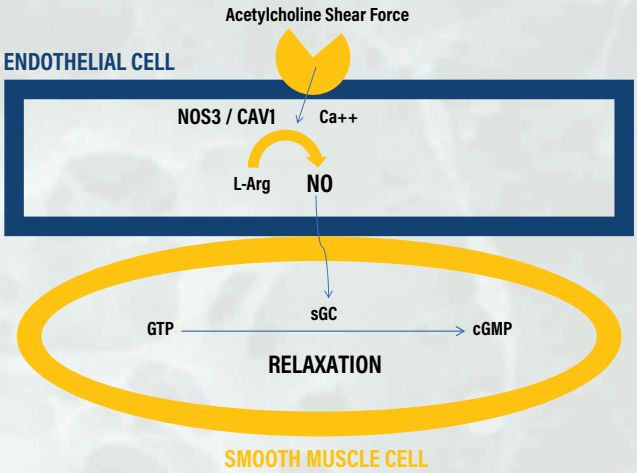


**Figure 2.** Key components of the nitric oxide signaling pathway between vascular endothelial and smooth muscle cells that leads to relaxation of smooth muscle cells

Abbreviations: CAV1, caveolin-1; cGMP, cyclic guanosine monophosphate; L-arg, L-arginine; NO, nitric oxide; NOS3, nitric oxide synthase 3; GTP, guanosine triphosphate; sGC, soluble guanylyl cyclase.

*Figure courtesy of Louis R. Pasquale, MD, FARVO*

higher in *NOS3*-knockout mice—mice that have had the *NOS3* gene inactivated so they cannot produce NOS3—than in wildtype mice with intact *NOS3* genes (18.2 mm Hg vs 13.9 mm Hg; $P < .05$).[17] The higher IOP in these knockout mice was due to significantly reduced ($P < .05$) trabecular outflow facility. These results demonstrated that functional *NOS3* is essential for IOP regulation, and loss of *NOS3* activity leads to higher IOP.

NOS3 is not the only key regulator of IOP. NOS3 exists in a complex with a second protein called caveolin-1 (CAV-1), which helps to regulate NOS3 activity.[18] CAV-1–knockout mice also develop elevated IOP,[19] demonstrating that both CAV-1 and NOS3 play key roles in IOP regulation. In fact, genetic variants in the region near the *CAV-1* and *CAV-2* genes are associated with glaucoma,[20] and have been associated specifically with early paracentral visual field defects in patients with glaucoma.[21] Furthermore, mice with knocked-out sGC develop both elevated IOP and age-related loss of retinal ganglion cells characteristic of primary open-angle glaucoma (POAG).[22]

Given endogenously, NO directly affects IOP. After both wildtype and sGC-deficient mice breathed NO-enriched oxygen, mean IOP was reduced significantly in wildtype mice (from 14.4 to 10.9 mm Hg; $P < .001$) but remained unchanged in sGC-deficient mice ($P \geq .08$).[23] In the same study, NO gas applied to the ocular surface of lambs lowered IOP ($P = .04$) and raised aqueous humor metabolites of NO ($P < .001$).

Human genetic studies continue to elucidate the role that NO plays in glaucoma. An analysis of data from the Nurses' Health Study and Health Professionals Follow-Up Study demonstrated that selected tagging variants located throughout the *NOS3* gene were related to the risk of having high-tension open-angle glaucoma in women, but not in men; this risk was modified by the use of postmenopausal hormones.[24] Further research uncovered additional associations between NOS3 variants and POAG that were modified by systemic hypertension and cigarette smoking as well as by reproductive factors.[25,26]

These direct and indirect effects of NO on IOP are mediated by NO's effect in the TM. In a study of cultured TM cells, exposure to endothelin—a potent constrictor of smooth muscle cells—produces a reduction in the intertrabecular spaces. Upon exposure to LBN, however, cytoskeletal relaxation occurs and the intertrabecular spaces increase in size. In a whole

## KEY LATANOPROSTENE BUNOD EFFICACY AND SAFETY DATA

APOLLO and LUNAR were phase 3 studies in which subjects with primary open-angle glaucoma or ocular hypertension were randomized in a 2:1 ratio to receive 3 months of treatment with either latanoprostene bunod (LBN) dosed once daily or timolol, 0.5%, dosed twice daily.[1,2] These 2 studies evaluated the noninferiority (equal to or better than) of LBN compared with timolol assessed at 8 AM, 12 PM, and 4 PM at baseline and at 2 weeks, 6 weeks, and 3 months after starting treatment as the primary end point. The **Table** summarizes the study results.[1,2] In the APOLLO study, LBN provided statistically significantly greater intraocular pressure (IOP) reductions than did timolol at all 9 time points,[2] whereas in the LUNAR study, LBN lowered IOP significantly more than did timolol at 8/9 time points.[1] Both drugs were associated with low rates of eye irritation and conjunctival hyperemia.[1,2]

**Table.** Summary of the Phase 3 APOLLO and LUNAR Studies of Latanoprostene Bunod vs Timolol[1,2]

| | APOLLO | | LUNAR | |
|---|---|---|---|---|
| | LBN (n = 284) | Timolol (n = 133) | LBN (n = 278) | Timolol (n = 136) |
| Baseline IOP, mm Hg | 26.7 | 26.5 | 26.6 | 26.4 |
| Mean IOP reductions at 3 months, mm Hg | 8-9 | 6.6-8.0 | 7.5-8.8 | 6.6-7.9 |
| Significance | LBN > timolol at all 9 time points ($P \leq .002$) | | LBN > timolol at 8/9 time points ($P \leq .025$) | |
| Common side effects | (n = 283) | (n = 135) | (n = 277) | (n = 135) |
| Eye irritation, % | 3.9 | 2.2 | 7.2 | 4.4 |
| Conjunctival hyperemia, % | 2.8 | 1.5 | 9.0 | 0.7 |

Abbreviations: IOP, intraocular pressure; LBN, latanoprostene bunod.

In a pooled analysis of the APOLLO and LUNAR data sets, 3-month mean diurnal IOP reduction was 32% and IOP was statistically lower in the LBN group than in the timolol group at all 9 time points **(Figure)**.[3] In an open-label extension study, in which crossover from timolol to LBN was permitted, mean IOP reductions through 12 months of follow-up ranged from 32% to 34%, with additional reductions in mean diurnal IOP of 6.3% to 8.3% in eyes crossing over from timolol to LBN. Adverse events were primarily mild to moderate (> 99.5%) in the 811 patients receiving LBN and included conjunctival hyperemia (5.9%), eye irritation (4.6%), and eye pain (3.5%).

VOYAGER was a phase 2 dose-finding comparison of LBN and latanoprost.[4] In this study, 4 concentrations of LBN, each dosed once daily at night, were compared with latanoprost, 0.005%, dosed once daily at night. Intraocular pressure was measured at 8 AM, 12 PM, and 4 PM at baseline and at 1, 2, and 4 weeks after starting treatment. Mean diurnal IOP reduction at week 4 (the study's primary end point) was significantly greater in the LBN, 0.024%, group (the approved dose) than in the latanoprost group (9.00 mm Hg vs 7.77 mm Hg, respectively; $P = .005$). Although the concentration of latanoprost in each of the 4 LBN groups was greater than that in the latanoprost group, evidence suggests that increasing latanoprost concentration does not increase efficacy.[5]

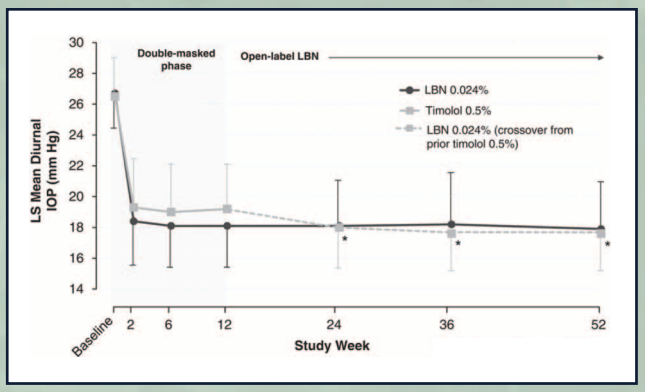


**Figure.** Mean diurnal intraocular pressure at all time points in the pooled analysis of APOLLO and LUNAR data[3]

Abbreviations: IOP, intraocular pressure; LBN, latanoprostene bunod; LS, least square.

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The JUPITER study (a single-arm, open-label study) evaluated LBN in 130 Japanese patients with ocular hypertension, primary open-angle glaucoma, and normal-tension glaucoma.[6] In Japan, most open-angle glaucoma is of the normal-tension glaucoma variety. The mean baseline IOP of this cohort was 19.6 mm Hg, well within the normal range. Following 12 months of treatment, mean IOP was reduced by 22% ($P < .001$), and the most common adverse events were conjunctival hyperemia (17.7%), eyelash growth (16.2%), and ocular irritation/pain (11.5%/10%).

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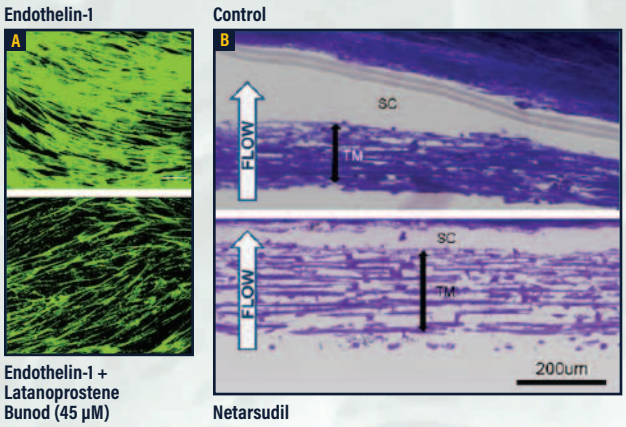


**Figure 3.** Trabecular meshwork cytoskeletal relaxation after exposure to latanoprostene bunod (A) and netarsudil (B)[27,28]

Abbreviations: SC, Schlemm canal; TM, trabecular meshwork.

Figure 3A reprinted with permission from Cavet ME, DeCory HH. The role of nitric oxide in the intraocular pressure lowering efficacy of latanoprostene bunod: review of nonclinical studies. *J Ocul Pharmacol Ther.* 2018;34(1-2):52-60. The publisher for this copyrighted material is Mary Ann Liebert, Inc, publishers.

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eye in vivo, one would expect increased trabecular outflow and IOP reduction **(Figure 3A)**.[27] A similar effect is seen with exposure of constricted TM cells to netarsudil **(Figure 3B)**,[28] although the mechanism is slightly different. Netarsudil blocks the effects of ROCK on myosin light chain phosphatase, effectively promoting smooth muscle (trabecular) relaxation, increasing trabecular outflow and lowering IOP. Netarsudil may also relax smooth muscle cells in the episcleral venous system, thus lowering episcleral venous pressure as well.[28]

In summary, NO isoforms and their associated proteins involved in the NO signaling pathway play important roles in IOP regulation. Animal models of impaired NO signaling serve to verify a role for NO signaling in POAG. Furthermore, NO lowers IOP directly by relaxing the TM cytoskeleton and increasing aqueous outflow through the trabecular outflow pathway.

## CASES

The following cases are presented to illustrate common clinical scenarios in glaucoma practice. Each case features a discussion by panelists, focusing on integrating newer medical treatment options for glaucoma into clinical practice.

### CASE 1: NEWLY DIAGNOSED GLAUCOMA

#### From the Files of Quang H. Nguyen, MD

*A 67-year-old woman was referred by her optometrist for elevated IOP and suspicious-appearing optic nerves. Her peak IOP prior to referral was 27 mm Hg OD and 25 mm Hg OS. She was a healthy woman, with only mild systemic hypertension, for which she did not require medical therapy. She reported no family history of glaucoma. On examination in the office, her visual acuity (VA) was 20/25 OD and 20/30 OS. Intraocular pressure was 26 mm Hg OD and 25 mm Hg OS, with central corneal thickness of 550 µm OD and 565 µm OS. Her corneal hysteresis was 8 mm Hg OD and 9 mm Hg OS. She had no relevant anterior segment findings suggestive of secondary glaucomas, and only mild nuclear sclerosis. Her angles were open on gonioscopy, with normal trabecular pigmentation. Upon dilation, her right optic nerve had vertical cupping and an inferior notch of the neuroretinal rim; her left optic nerve had vertical cupping as well. Both nerve heads were normal in size, and the remainder of her dilated fundus examination results were normal.* ***Figure 4*** *shows her optical coherence tomography images and visual fields.*

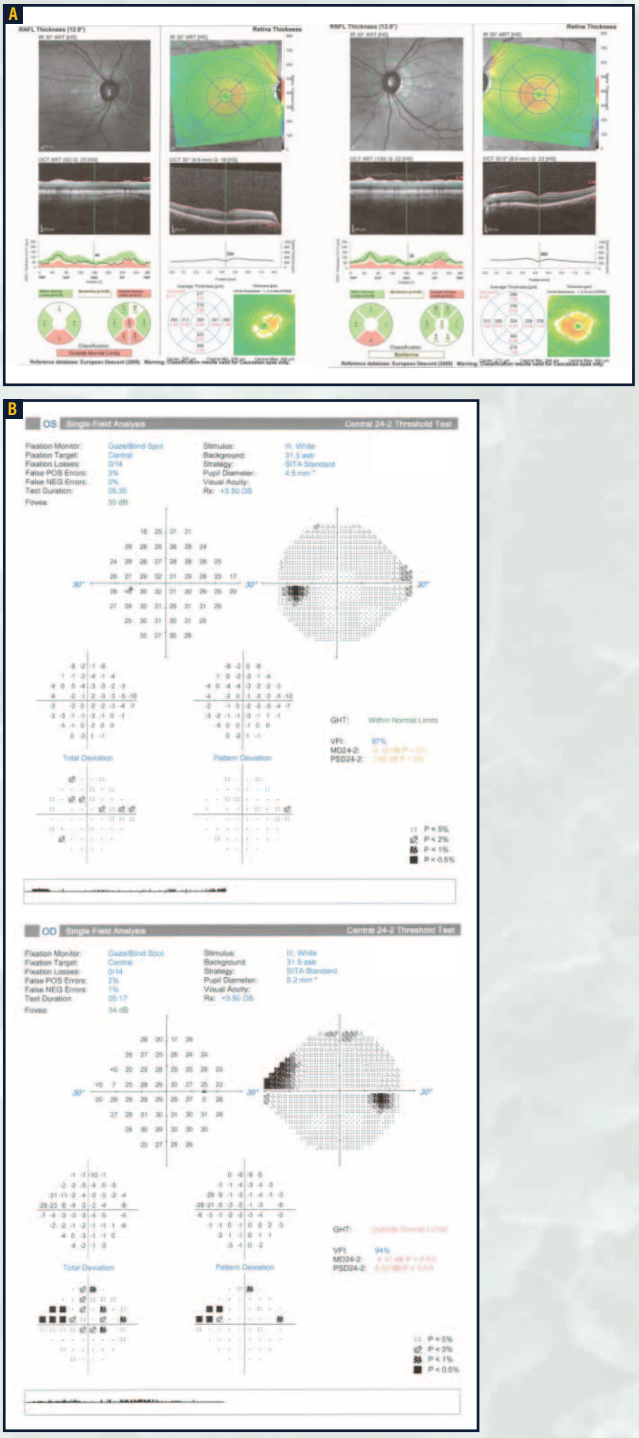


**Figure 4.** The optical coherence tomography images (A) and visual fields (B) of the patient presented in Case 1

**Dr Nguyen:** On the basis of her elevated IOP, optic nerve damage, and corresponding visual field loss, she was diagnosed with moderate POAG, worse in the right eye than in the left eye. What are her treatment goals?

**Dr Budenz:** I usually set a target IOP according to overall risk assessment. She has moderate POAG in 1 eye, and early POAG in the other. Her IOP is elevated, but not excessively so. She has no family history of glaucoma. Overall, her risk profile is moderate. The American Academy of Ophthalmology's Preferred Practice Pattern® for POAG suggests a baseline 20% to 30% IOP reduction in newly diagnosed patients, which can be adjusted upward or downward on the basis of higher or lower risk profiles.[29] I think an initial IOP reduction of 30% is reasonable for this patient.

**Dr Nguyen:** What treatment options should we consider to achieve this target IOP?

**Dr Samuelson:** The recent LiGHT (Laser in Glaucoma and Ocular Hypertension) study comparing medical therapy to initial selective laser trabeculoplasty (SLT) in newly diagnosed patients with mild-to-moderate POAG or high-risk ocular hypertension (OHT) is relevant to her case.[30] Three-year results were recently published, and an ongoing follow-up to 6 years is under way. At 3 years, 78% of eyes treated with SLT—repeated as needed—were medication free, with mean IOP levels comparable to those of medication-treated eyes. Progression rates were lower in SLT-treated eyes, and all 11 of the trabeculectomies were in eyes assigned to initial medical therapy. Overall, it appears that initial SLT is at least as good as, and perhaps better than, initial medical therapy for many of our patients with POAG and high-risk OHT. The one caveat is that patients in LiGHT had generally mild disease; approximately 32% had OHT and 50% had mild POAG, and the average visual field mean deviation was -3 dB. With these results in mind, I would have a conversation with the patient regarding the pros and cons of initial SLT vs medical therapy.

**Dr Budenz:** SLT offers another key benefit to our patients—the ability to avoid daily eye drop therapy, which may result in improved quality of life, the ultimate goal of glaucoma therapy for all our patients.[29,31] In LiGHT, there was no measurable difference in quality of life between the medication and the SLT patients,[30] but this is likely because we lack well-validated quality of life instruments that measure treatment-related effects on quality of life. As many of us have experienced, whether with SLT or surgery, patients who are able to avoid daily topical medical therapy are often very grateful. Also, in LiGHT, an included cost-effectiveness analysis demonstrated that SLT was more cost effective than medical therapy.[30] That said, some patients are still hesitant to undergo a surgical procedure as initial therapy.

**Dr Nguyen:** The patient and I had a conversation about the relative pros and cons of SLT vs medical therapy. She preferred to start with medical therapy. Because of their efficacy, safety, once-daily dosing convenience, and cost, generic prostaglandins remained our go-to first-line medical option. After 4 weeks of therapy, she reported mild redness and burning upon instillation, and her IOP was 22 mm Hg OD and 21 mm Hg OS. She said she could tolerate the side effects, but she had not attained her IOP goal, which was approximately 18 mm Hg. What should we do next?

**Dr Pasquale:** In a case such as this, I often continue therapy and recheck IOP a second time before deciding to move on. Intraocular pressure is variable over time, and we often need more than 1 measurement to better understand long-term IOP trends.[32,33] If the patient is still not at target, we have to consider switching vs adding. I add if the first medication was tolerated and effective but did not achieve target, and I switch if the medication was poorly tolerated or not effective.

**Dr Samuelson:** Adding has other limitations as well. Adjunctive therapy is often less incrementally effective than is initial therapy,[34] and adding a second medication can adversely affect adherence with the first medication.[35] Also, the side effects of each drug are cumulative, and because most drugs are preserved with benzalkonium chloride, the overall daily exposure to benzalkonium chloride rises, which can have adverse effects on the ocular surface, including symptoms of ocular surface disease and reduced success rates with subsequent glaucoma surgeries.[36] For these reasons, I try to maintain patients on monotherapy whenever possible.

**Dr Nguyen:** These are all points that I considered for this patient. We rechecked her IOP 2 weeks later, and it was still above target. Her persistent red eyes became more bothersome to her. For this reason, I suggested we switch to an alternate monotherapy. I chose LBN to preserve the once-daily dosing convenience and also because it was shown to have superior efficacy to latanoprost in the phase 2 VOYAGER study **(see Sidebar: Key Latanoprostene Bunod Efficacy and Safety Data)**.[37] This required a prior authorization from her insurer, which was quickly approved. After 3 weeks of therapy, her IOP was 17 mm Hg OD and 15 mm Hg OS, reductions of 35% to 40%, and she reported mild stinging upon instillation that was not bothersome for her.

## CASE 2: PROGRESSIVE PRIMARY OPEN-ANGLE GLAUCOMA

### From the Files of Donald L. Budenz, MD, MPH

*A 57-year-old man was referred for progressive glaucoma in the right eye. He had been diagnosed with glaucoma and treated previously by the referring physician. His IOP at the time of diagnosis was 28 mm Hg OU, and had been consistently 10 to 13 mm Hg OU on a treatment regimen consisting of travoprost, the dorzolamide/timolol fixed combination, and SLT 360° OU. He had an allergic reaction to brimonidine. On examination in the office, his VA was 20/20 OU, IOP was 10 mm Hg OD and 11 mm Hg OS, and his angles were open on gonioscopy. He had mild nuclear sclerosis and no evidence of secondary glaucomas on anterior segment examination.* ***Figure 5*** *shows his optic nerve appearance and visual field results.*

**Dr Budenz:** The diagnosis is moderate to advanced POAG, progressive in the right eye. Progression is occurring at very low IOP. What are the considerations in such eyes?

**Dr Nguyen:** This is not NTG because he started with IOP in the high 20s, but I find it helpful to consider the differential diagnosis of NTG in these eyes because many of the same issues can be present. Nonadherence can mimic this clinical scenario if patients take their drops only around the time of office visits. Thin central corneal thickness can cause us to underestimate true IOP. Large IOP fluctuations can also cause progression, and we know that IOP is typically highest at night when we cannot easily measure it.[38] Intermittent IOP elevations can occur with steroid use or during bouts of uveitis. Intermittent angle closure can also look like what is seen in this patient. Furthermore, causes of nonglaucomatous visual field loss should not be overlooked, and are more likely to be present when optic disc pallor exceeds cupping, when visual field defects are out of proportion to cupping, when defects respect the vertical meridian, if central VA or color VA is affected, or in the presence of an afferent pupillary defect without asymmetric cupping.[39]

**Dr Budenz:** We performed diurnal curve testing. The highest measured IOP was 16 mm Hg at 8 AM. The other issues Dr Nguyen raised were also considered and found not to be present, so we were left with a patient whose POAG was progressing with IOP in the low teens. What are our options for advancing therapy?

**Dr Pasquale:** The prostaglandin could be switched to a newer agent, perhaps LBN or the netarsudil/latanoprost fixed combination. Netarsudil could be added to the current regimen as a fourth drug. A minimally invasive glaucoma surgery (MIGS) procedure could be performed, either an angle-based or bleb-based option. Alternatively, a filtering procedure, such as trabeculectomy or tube-shunt implantation, could be performed. I reserve the latter surgeries for cases when all else fails or when a very low IOP is needed

## KEY NETARSUDIL EFFICACY AND SAFETY DATA

The ROCKET-1 and ROCKET-2 (Rho Kinase Elevated IOP Treatment Trials 1 and 2) studies were 3-month phase 3 comparisons of netarsudil, 0.02%, dosed once or twice daily and timolol, 0.5%, dosed twice daily,[1] whereas ROCKET-4 was a similarly designed study, in which primary efficacy was assessed after 3 months and safety assessed through 6 months.[2] All 3 of these studies were designed to establish noninferiority of netarsudil to timolol as the primary end point.[1,2] Intraocular pressure (IOP) was measured at 8 AM, 10 AM, and 4 PM at baseline and at 2 weeks, 6 weeks, and 3 months while on treatment. The **Table** shows efficacy and safety outcomes of these studies.[1,2] In ROCKET-1, mean IOP reductions in the timolol group were greater than those in the once-daily netarsudil group, and the criteria for noninferiority were not met.[1] However, a post hoc analysis of eyes with baseline IOP < 25 mm Hg revealed that once-daily netarsudil was statistically noninferior to timolol. In ROCKET-2, only eyes with baseline IOP < 25 mm Hg were included in the primary analysis. In these eyes, once-daily netarsudil was also statistically noninferior to timolol. In ROCKET-4, netarsudil met the criteria for noninferiority to timolol in the per-protocol analysis that included eyes with IOP < 25 mm Hg at baseline.[2] Across these 3 studies, netarsudil had a substantially higher rate of hyperemia than did timolol and was also associated with the development of both conjunctival hemorrhages and corneal verticillata.[1,2] In the longer ROCKET-4 safety analysis of 351 patients, the frequency of both verticillata (24.5%) and conjunctival hemorrhages (16.0%) was higher than in the 3-month ROCKET-1 and ROCKET-2 studies, whereas the rate of hyperemia (47.9%) was consistent with that in the 3-month observations.

In addition to these phase 3 studies, netarsudil was compared with latanoprost in a 4-week phase 2 study.[3] In this monotherapy study, subjects were randomly assigned to once-daily treatment with netarsudil or latanoprost. The primary end point was diurnal IOP reduction at week 4. At week 4, mean IOP reduction was 5.7 mm Hg for netarsudil and 6.8 mm Hg for latanoprost. In the statistical analysis, netarsudil was found to be inferior to latanoprost.

Netarsudil was also studied in eyes with low baseline IOP.[4] A total of 11 healthy volunteers received 7 days of once-daily netarsudil. From a mean baseline IOP of 17.4 mm Hg, mean IOP was 3.5 mm Hg lower in netarsudil-treated eyes than in vehicle-treated fellow control eyes, and episcleral venous pressure was also significantly reduced in netarsudil-treated eyes.

Netarsudil is also available in a fixed combination with latanoprost. This once-daily fixed combination has been studied in phase 2 and 3 trials. In phase 2 testing, the fixed combination lowered IOP at day 28 by a mean of 1.9 mm Hg more than did latanoprost monotherapy and 2.6 mm Hg more than did netarsudil monotherapy, with hyperemia rates of 40% in both the netarsudil and the fixed-combination groups and 14% in the latanoprost group.[5] In a pooled analysis of data from the phase 3 MERCURY-1 and MERCURY-2 trials, the fixed combination was statistically superior to either of its components.[6] From mean baseline IOP of 22.5 to 24.8 mm Hg, 22.7 to 24.7 mm Hg, and 22.5 to 24.7 mm Hg in the fixed-combination, netarsudil, and latanoprost groups, respectively, mean IOP across 9 time points through 3 months of follow-up ranged from 15.0 to 16.4 mm Hg, 17.4 to 19.4 mm Hg, and 16.9 to 18.0 mm Hg, respectively. In a pooled analysis of MERCURY-1 (12 months) and MERCURY-2 (3 months) safety data, conjunctival hyperemia, corneal verticillata, and conjunctival hemorrhages were more common in the netarsudil-containing groups than in the latanoprost group.[7]

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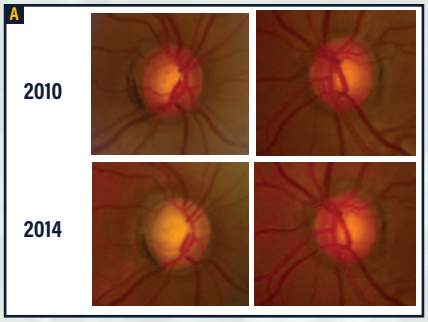
**Table.** Efficacy and Safety Outcomes of ROCKET-1, ROCKET-2, and ROCKET-4 Phase 3 Studies of Netarsudil vs Timolol[1,2]

| | ROCKET-1 (All Eyes) | | ROCKET-1 (Eyes With IOP < 25 mm Hg) | | ROCKET-2 | | ROCKET-4 | |
|---|---|---|---|---|---|---|---|---|
| | Netarsudil (n = 202) | Timolol (n = 209) | Netarsudil (n = 113) | Timolol (n = 124) | Netarsudil (n = 251) | Timolol (n = 251) | Netarsudil, 0.02% (n = 186) | Timolol (n = 186) |
| Baseline IOP, mm Hg | 21.8-23.4 | 21.5-23.4 | 20.6-22.4 | 20.5-22.5 | 20.4-22.5 | 20.6-22.5 | 20.7-22.4 | 20.7-22.4 |
| Mean IOP reductions, mm Hg | 3.3-5.0 | 3.7-5.1 | 3.7-5.1 | 3.2-4.7 | 3.3-4.6 | 3.7-5.1 | 3.9-4.7 | 3.8-5.2 |
| Significance | Netarsudil inferior to timolol | | Netarsudil noninferior to timolol | | Netarsudil noninferior to timolol | | Netarsudil noninferior to timolol | |
| Common side effects | (n = 203) | (n = 208) | — | — | (n = 251) | (n = 251) | (n = 351) | (n = 357) |
| Conjunctival hyperemia, % | 53.2 | 8.2 | — | — | 50.2 | 10.8 | 47.9 | 9.2 |
| Conjunctival hemorrhage, % | 13.3 | 0.5 | — | — | 14.7 | 0 | 16.0 | 3.1 |
| Corneal verticillata, % | 5.4 | 0 | — | — | 8.8 | 0.4 | 24.5 | 0 |

Abbreviations: IOP, intraocular pressure; ROCKET, Rho Kinase Elevated IOP Treatment Trial.



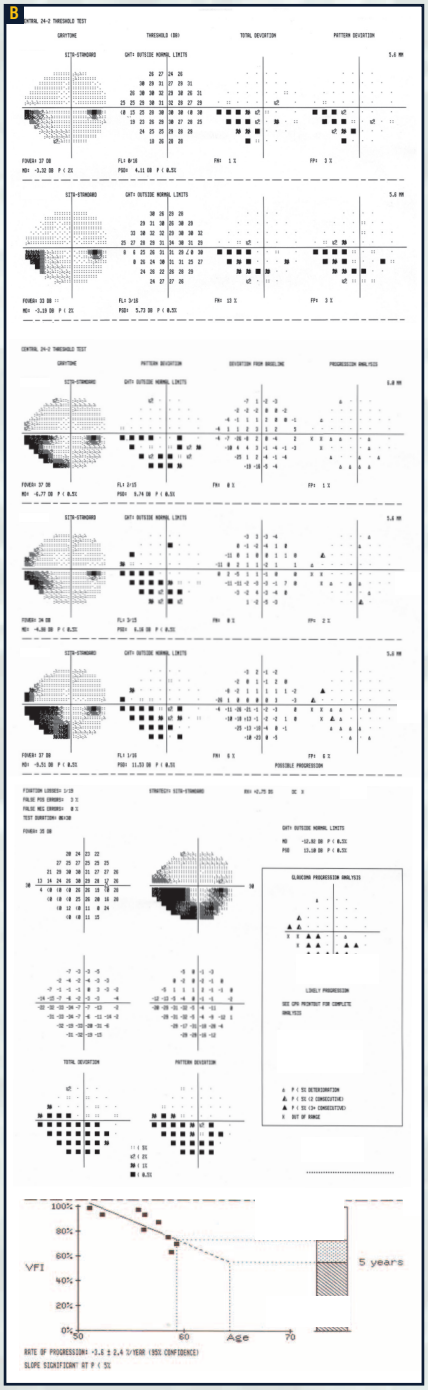




**Figure 5.** Optic nerve photographs (A) and visual fields (B) of the patient presented in Case 2

quickly. In this young patient with advanced and progressive disease despite low IOP, I think the time for surgery has come. He is losing 2 dB per year and will almost certainly become visually disabled or blind if the disease is not better controlled. I would proceed with a trabeculectomy to give the best chance of meeting the target IOP, which is now in the single digits. This approach has been shown to stabilize eyes with glaucoma progressing even at low IOP.[40,41]

**Dr Budenz:** Is there any reasonable expectation of achieving a target IOP of 10 mm Hg by adjusting medical therapy and saving surgery for later?

**Dr Samuelson:** It is always worth a try if there is time. I might try netarsudil in this case. In addition to enhancing trabecular outflow, it may lower episcleral venous pressure (EVP).[42] Ultimately, EVP is the obstacle that precludes lowering IOP below 10 to 12 mm Hg with medical therapy. If netarsudil can lower EVP, it may facilitate the achievement of lower target IOP. But, Dr Pasquale's point is well taken—time is of the essence here, so if I start by tweaking the medical regimen, I would do so quickly and have a low threshold for moving on to surgery if I cannot quickly get IOP to target with medications.

**Dr Budenz:** I told this patient that he would most likely require surgery at some point, but I wanted to exhaust nonsurgical options first. We added netarsudil for the reasons mentioned by Dr Samuelson. After 1 month, IOP in the right eye had declined from 13 mm Hg to 10 mm Hg, a 23% reduction. This was an acceptable response because prior research has demonstrated that an additional 20% IOP reduction in progressing eyes typically leads to stabilization.[43] The patient had mild hyperemia that was well tolerated, so therapy was continued. After 4 months, corneal verticillata appeared. How common are these with netarsudil therapy, and what is the consequence?

**Dr Pasquale:** Corneal verticillata are typically whorl-shaped deposits in the basal epithelium of the cornea that we have seen most frequently with amiodarone therapy **(Figure 6)**.[44] They are associated with therapy with cationic, amphiphilic drugs and represent accumulation of phospholipids within corneal epithelial cells. In the phase 3 netarsudil studies, the incidence of verticillata ranged from 5.4% to 24.5% **(see Sidebar: Key Netarsudil Efficacy and Safety Data)**.[45,46] These are typically of no visual significance and do not warrant discontinuation of therapy in most patients.

**Dr Budenz:** After discussing the deposits with the patient, he was comfortable continuing therapy, given that the alternative was most likely surgery.

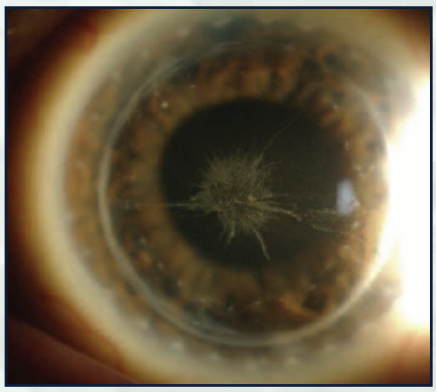


**Figure 6.** Corneal verticillata due to amiodarone therapy
*Image courtesy of Francis Mah, MD*

## CASE 3: MINIMALLY INVASIVE GLAUCOMA SURGERY AND MEDICATIONS

### From the Files of Thomas W. Samuelson, MD

*A 48-year-old woman was referred with advanced pigmentary glaucoma diagnosed at the age of 26. Her father also had pigmentary glaucoma. Her peak IOP before treatment was 26 mm Hg. Her past medical history included systemic hypertension, for which she took an oral beta blocker (atenolol) once daily in the morning. She had some associated symptoms of orthostasis, a prior blood transfusion after a gynecologic procedure, and reported cold hands, but had no formal diagnosis of Raynaud phenomenon or migraine. At the time of referral, her VA was 20/40 OD and 20/20 OS, with a high myopic correction of -7D OD and -6D OS. Her IOP was 16 mm Hg OD and 13 mm Hg OS using once-daily travoprost and twice-daily dorzolamide/timolol fixed combination in both eyes, with central corneal thickness of 550 µm OU. Anterior segment examination revealed Krukenberg spindles on the corneal endothelial surface, midperipheral slit-like iris transillumination defects, and pigment at the lens equator in both eyes consistent with pigment dispersion syndrome. She also had 2+ nuclear sclerosis in the right eye. Her angles were open, and she had a right afferent pupillary defect. Her cup-to-disc ratio was 0.95 OU.* ***Figure 7*** *shows her visual fields.*

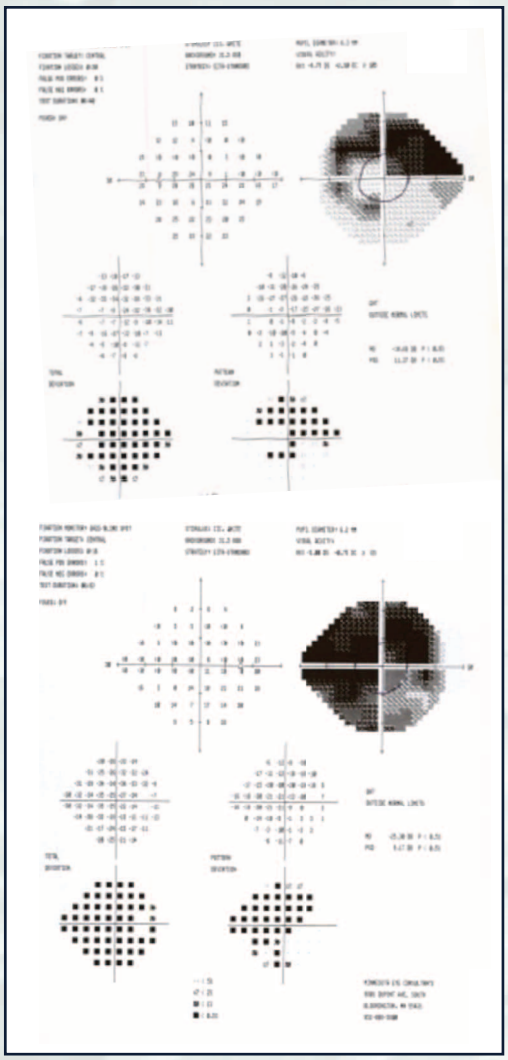


**Figure 7.** Visual fields of the patient presented in Case 3

**Dr Samuelson:** How would you manage this patient?

**Dr Nguyen:** She is a young patient with advanced disease. In the absence of progression in the midteens, her IOP may be acceptable in the right eye. But she has a visually significant cataract in that eye, and there is the opportunity to address her glaucoma surgically at the same time. She might be a good candidate for a combined phacoemulsification and MIGS procedure, or a phacotrabeculectomy.

**Dr Samuelson:** Given her young age and severe disease, I opted for combined phacoemulsification and trabeculectomy, which lowered her IOP into the low teens over the next several years. Considering her advanced visual field loss, how would you follow this patient in the future? How do you modify the test format when the baseline visual field is so advanced? What other tests are of value?

**Dr Budenz:** The optical coherence tomography is of less value in advanced glaucoma because of its floor effect, so visual fields remain the most important test for advanced glaucoma. Given the extensive loss in her right eye, a 24-2 test strategy may not be the best choice. A 10-2 field may give you more information in the central region, where she still has function. Alternatively, continuing the 24-2 approach but using a size V stimulus can be helpful.

**Dr Samuelson:** We switched to 10-2 fields in both eyes, and she remained stable in both eyes over the next 4 years until she began to develop a cataract in the left eye. At that time, her IOP was 12 mm Hg using 4 medications—travoprost and the dorzolamide/timolol fixed combination OU, with brimonidine added OD—and her glaucoma was well controlled and stable. Once it became available, LBN replaced travoprost in her regimen. I feel that there might be some benefits of NO on the TM and optic nerve in addition to the benefits of latanoprost. Plus, in advanced cases like this, it is reassuring to know that you are using the most potent prostaglandin formulation. What else would you do for the left eye?

**Dr Pasquale:** Given that she is well controlled, you might just address the cataract. Cataract surgery alone can significantly lower IOP and the need for IOP-lowering medications in eyes with glaucoma.[47]

**Dr Samuelson:** We discussed a phacotrabeculectomy because it worked so well in the right eye, but that eye was in worse condition at the time of surgery, and the added risks of trabeculectomy were justified. We also discussed MIGS procedures, including the gel stent, gonioscopy-assisted transluminal trabeculotomy, and trabecular microbypass shunts. She elected to undergo phacoemulsification with placement of 2 first-generation microbypass shunts, with the acknowledgement that she could undergo more aggressive surgery later, if necessary. At the patient's last follow-up, IOP was in the low teens in both eyes on 4 medications in the right eye and 3 medications in the left eye, and her visual fields had stabilized in both eyes. Although a reduction in medication in her left eye was discussed, she elected to continue treatment because she was adherent and still had to administer a similar regimen in her right eye.

## TAKE-HOME POINTS

- NOS3 and CAV-1 in the NO signaling pathway play important roles in IOP regulation and optic nerve homeostasis
- Nitric oxide lowers IOP by relaxing the TM and increasing trabecular outflow
- LBN lowers IOP by increasing both uveoscleral outflow (by latanoprost) and trabecular outflow (by NO)
- Netarsudil lowers IOP by increasing trabecular outflow, reducing aqueous production, and reducing episcleral venous pressure
- Both LBN and netarsudil lower IOP safely and effectively according to clinical trial data
- New drugs with novel mechanisms of action expand the ability to develop individualized treatment plans for patients with glaucoma

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1. Which of the following is true regarding NO?
   a. It is produced by CAV-1
   b. It is highly hydrophilic and diffuses poorly from cell to cell
   c. It binds to sGC
   d. It stimulates contraction of trabecular cells

2. The relationship between NOS3 and IOP is characterized by all the following, EXCEPT:
   a. NOS3 produces NO, which lowers IOP
   b. Mice without the *NOS3* gene have lower IOP than mice with intact *NOS3* genes
   c. NOS3 is regulated in part by CAV-1
   d. CAV-1–knockout mice have higher IOP than healthy mice

3. In studies of cultured TM cells, cytoskeletal relaxation and increase in intertrabecular spaces were observed upon the application of _____.
   a. LBN and latanoprost
   b. Latanoprost and timolol
   c. LBN and netarsudil
   d. Netarsudil and timolol

4. With which type of visual field defect are variants of the *CAV-1* gene associated?
   a. Nasal step
   b. Superior arcuate scotoma
   c. Rim artifact
   d. Paracentral defect

5. Latanoprost bunod lowers IOP by:
   a. Increasing uveoscleral outflow and decreasing aqueous humor production
   b. Increasing trabecular outflow and increasing uveoscleral outflow
   c. Decreasing trabecular outflow and decreasing uveoscleral outflow
   d. Increasing aqueous humor production and increasing trabecular outflow

6. Netarsudil lowers IOP by:
   a. Increasing trabecular outflow, increasing uveoscleral outflow, and decreasing aqueous production
   b. Increasing trabecular outflow, decreasing aqueous humor production, and increasing EVP
   c. Increasing trabecular outflow, decreasing uveoscleral outflow, and increasing aqueous production
   d. Increasing trabecular outflow, decreasing aqueous humor production, and decreasing EVP

7. In phase 3 clinical trials, LBN lowered IOP by _____ mm Hg.
   a. 4.5 to 6.0
   b. 5.0 to 7.5
   c. 7.5 to 9.0
   d. 8.5 to 10.0

8. In phase 3 clinical trials, netarsudil lowered IOP by _____ mm Hg.
   a. 2.5 to 3.3
   b. 3.3 to 5.1
   c. 4.5 to 5.3
   d. 5.5 to 7.3

9. A patient with moderate POAG was inadequately controlled with once-daily prostaglandin therapy. She lived alone, had early dementia, and had a caregiver who visited once daily to help administer her drops, which she otherwise often forgot to take. Which is the most reasonable next treatment step?
   a. Switch to twice-daily dorzolamide/timolol fixed combination
   b. Add twice-daily timolol to her prostagandin
   c. Switch to once-daily LBN
   d. Add twice-daily dorzolamide/timolol fixed combination

10. A female patient whose IOP is being managed on netarsudil develops mild corneal verticillata after 6 months of therapy. Which is the next best step for this patient?
    a. Netarsudil should be stopped immediately before her cornea decompensates and she requires a corneal transplant
    b. Netarsudil should be continued until her VA begins to decline, after which it can be discontinued and the verticillata will dissipate
    c. Netarsudil should be stopped because the corneal changes indicate that the drug will soon lose its IOP-lowering effect
    d. Netarsudil should be continued because it is working well and the verticillata are clinically insignificant