CME Monograph

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Real-World Management of Glaucoma

THE AGE OF OUTFLOW

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FACULTY

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This continuing medical education activity is jointly sponsored by **New York Eye and Ear Infirmary of Mount Sinai** and **MedEdicus LLC**.

This continuing medical education activity is supported through an unrestricted educational grant from Bausch & Lomb Incorporated.

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Activity Description
To address the educational needs of ophthalmologists, this case-based program will focus on elucidating the role of nitric oxide in glaucomatous eyes, providing strategies to achieve target intraocular pressure levels with newer topical agents that home in on the trabecular meshwork, and interpreting clinically relevant data supporting the efficacy and safety of these new agents. The desired results of this activity are for ophthalmologists to improve their understanding of the pathophysiology of glaucoma and the mechanisms of action of newly approved agents to better treat their patients.

Target Audience
This activity intends to educate ophthalmologists caring for patients with glaucoma.

Learning Objectives
Upon completion of this activity, ophthalmologists will be better able to:
- Discuss the effects of nitric oxide on the trabecular meshwork
- Recognize the role of novel pharmacologic mechanisms on aqueous humor dynamics
- Identify clinically relevant data supporting the role of new topical therapies for patients with glaucoma
- Apply evidence-based treatment strategies for achieving target intraocular pressure levels in patients with glaucoma

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Real-World Management of Glaucoma

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Introduction

Primary open-angle glaucoma (POAG) affects 2 to 3 million adults in the United States.[1] In eyes with POAG, progressive damage of the trabecular meshwork (TM) and the trabecular outflow system results in elevated intraocular pressure (IOP) that leads to optic nerve deterioration and visual field (VF) loss. All the proven and approved therapies for POAG work by lowering IOP to prevent further optic nerve damage and VF loss. In the past 2 years, 3 new drugs—latanoprostene bunod (LBN), netarsudil, and the fixed combination of netarsudil and latanoprost—with novel mechanisms of action lower IOP by direct activity in the TM, where the root of the IOP problem lies. This educational activity presents a series of common clinical scenarios that review relevant topics to guide management decisions and demonstrate evidence-based approaches to incorporate these new IOP-lowering agents into routine real-world practice.

Case 1: To Treat or Not To Treat

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

A 48-year-old white woman was referred for a glaucoma evaluation because of elevated IOP (24 mm Hg in both eyes) at a routine vision evaluation with her primary eye care provider. She had no ocular complaints beyond reduced visual acuity (VA), which was corrected with new spectacles. She was healthy and used no systemic medications. Her father had glaucoma. On examination, her VA was 20/20 OU, with a small myopic correction. Her pupils were normally reactive, with no afferent defect. Her IOP was 23 mm Hg OD and 24 mm Hg OS. Her angles were open, with no peripheral anterior synechiae. Her central corneal thickness (CCT) was 494 µm OD and 500 µm OS. **Figure 1** shows her optic nerves and VFs.

The differential diagnosis for this patient included ocular hypertension (OHT), POAG suspect, and POAG. OHT is characterized by elevated IOP in the absence of optic nerve damage and VF loss. Her VFs were essentially normal in both eyes, aside from a few stray spots likely associated with her inexperience with the test (this was her first attempt). The optic nerves had large cups, with mild asymmetry (approximately 0.7-0.75 OD and 0.6 OS), but the neuroretinal rims were intact 360°, with no focal thinning, hemorrhages, or obvious retinal nerve fiber layer (RNFL) defects in either eye. In the absence of frank glaucomatous optic neuropathy, her disease was labeled as POAG suspect, with the caveat that it might be early, preperimetric glaucoma.

The patient elected to receive treatment. This set her target IOP in the range of 18 to 20 mm Hg. After a discussion of treatment options that included the benefits and risks of medical vs laser treatment, she elected medical therapy and was started on once-daily generic latanoprost in both eyes. Six months later, her IOP was meeting target at 17 mm Hg OD and 18 mm Hg OS. A repeat VF test at this visit, however, revealed new bilateral paracentral defects. The Ocular Hypertension Treatment Study demonstrated

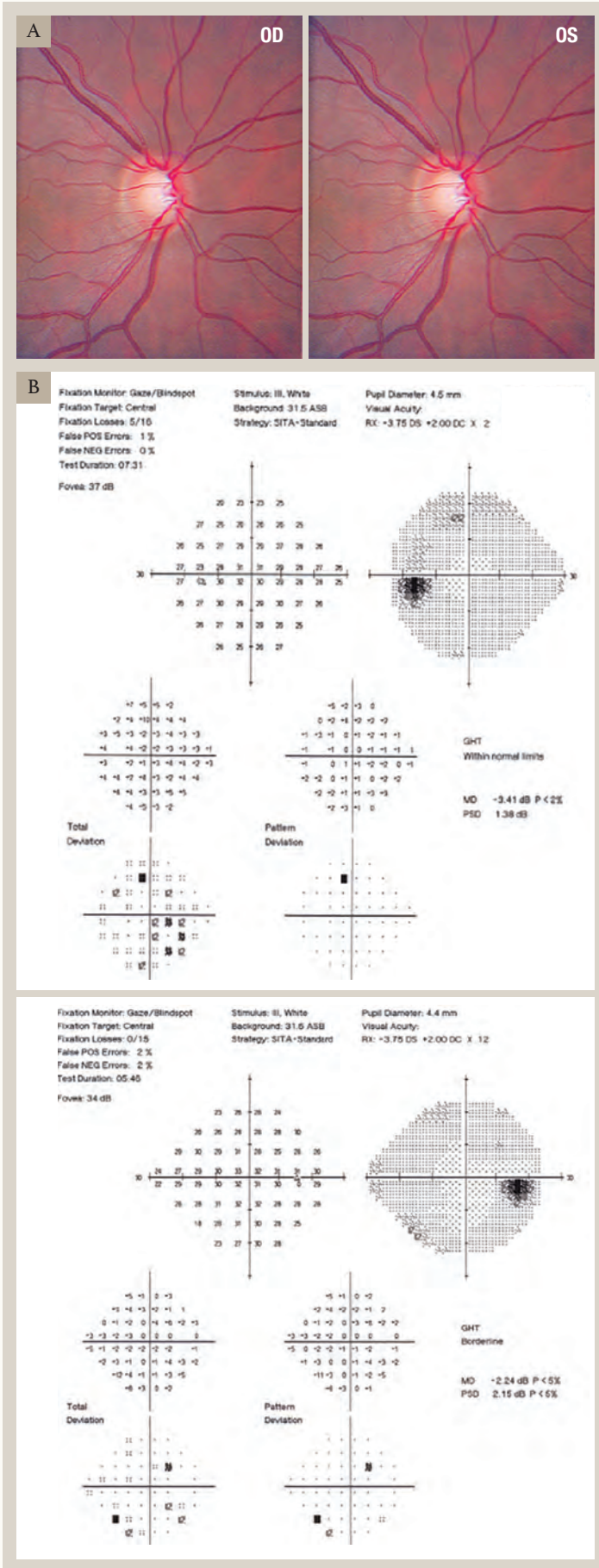

Figure 1. Optic nerves (A) and visual fields (B) of the patient presented in Case 1

that in eyes with OHT and full fields at baseline, new defects are nearly always artifactual, and 86% resolve with retesting.[2] Her VFs were normalized on retesting.

Over the next 3 years, her IOP remained at target and her VFs and nerves remained stable. In the fourth year of follow-up, however, her IOP rose consistently to the low 20-mm Hg range. After a 2-week drug holiday prompted by her running out of medication, her IOP was 29 mm Hg in both eyes, and she had new field defects in both eyes that were confirmed on retesting. Her elevated IOP was also confirmed at a subsequent visit to be 30 mm Hg in both eyes.

Her IOP was now significantly higher than at the time of her initial diagnosis 4 years ago. Why had it risen, and how did this affect her diagnosis and management? Intraocular pressure is determined by the balance of aqueous humor production by the processes of the ciliary body and aqueous outflow through both the trabecular and uveoscleral outflow pathways. In POAG, the TM is altered and aqueous outflow through the trabecular pathway is reduced.[3] Specifically, the TM in eyes with POAG becomes stiffer than normal. Stiffness is a biomechanics term that describes a tissue's tendency to resist deformation when a force is applied to it. In POAG, the tissue is the TM and the force is the IOP. The TM in eyes with POAG is 20 times stiffer than that in healthy eyes. This stiffness arises because of both the contractile tone of the trabecular endothelial cells and to changes within the makeup of the extracellular matrix (ECM). Increased TM cell contraction leads to ECM changes, and ECM changes can increase TM cell tone. This stiffness can impede aqueous egress through the trabecular outflow tract, thus raising IOP. It stands to reason then that relaxing TM contractile tone, altering the makeup of the ECM, or both, could increase trabecular outflow and lower IOP.

In 2017, 2 new drugs were approved for IOP reduction in the United States—LBN and netarsudil—both of which have their direct IOP-lowering effects in the TM **(Figure 2)**, and one of which, LBN, incorporates the activity of nitric oxide (NO) **(see Sidebar: Nitric Oxide in The Eye, p 5)** into its mechanism of action in the TM.

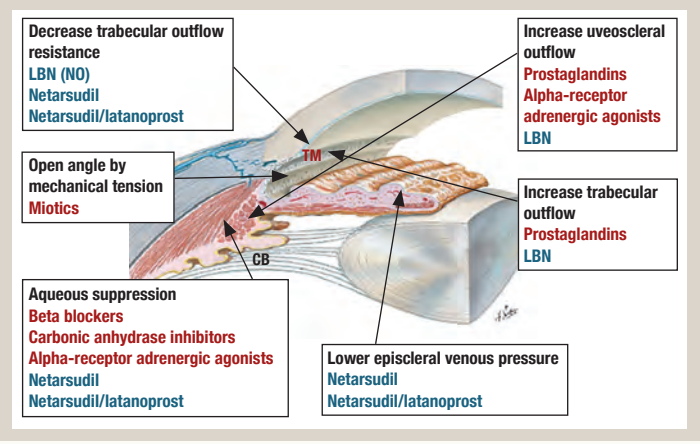

Figure 2. Sites of action of intraocular pressure–lowering drugs

Abbreviations: CB, ciliary body; LBN, latanoprostene bunod; NO, nitric oxide; TM, trabecular meshwork.

LBN is a novel molecule consisting of the prostaglandin analogue latanoprost and an 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 TM.[4] LBN's effect on IOP has been evaluated in several clinical studies **(see Sidebar: Latanoprostene Bunod Clinical Studies, p 6)**.

Netarsudil is a novel Rho kinase inhibitor. Rho kinase is an enzyme that regulates the shape and movement of cells through action on the cytoskeleton. Inhibition of ocular Rho kinase leads to smooth muscle relaxation of both the TM and episcleral veins. Thus, netarsudil acts to increase trabecular outflow both by increasing aqueous outflow through the TM[5,6] and by decreasing the pressure within the episcleral venous system, therefore reducing downstream resistance to outflow.[5] 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.[5,6] Netarsudil's effect on IOP has also been studied in a series of glaucoma clinical trials **(see Sidebar: Netarsudil Clinical Studies, p 8)**.

As evidenced by her elevated IOP and progressive VF loss, this patient now has POAG. The recommended initial IOP reduction for early POAG is 30%.[1] Options include restarting prostaglandin monotherapy, adding a second medication, switching to an alternate monotherapy, or performing selective laser trabeculoplasty (SLT). The patient was highly motivated to remain on a single drop per day and was not enthusiastic about laser therapy. Her therapy was switched to once-daily LBN, 0.024%, which she tolerated well, with IOP in the range of 17 to 19 mm Hg (> 30% reduction from her new washed-out baseline) and stabilization of her VF over the next several visits.

Nitric Oxide in the Eye

Nitric oxide (NO) plays an important role in achieving trabecular meshwork (TM) relaxation. Nitric oxide is an endogenous signaling molecule generated naturally by the enzyme NO synthase, which regulates many functions throughout the body.[1,2] One key action of NO is the relaxation of smooth muscle to regulate blood flow.[1,3,4] Another is to relax the smooth muscle in the TM to lower intraocular pressure (IOP).[5]

In healthy eyes, NO is synthesized in the endothelium of uveal vasculature, Schlemm canal, and the ciliary body.[6,7] Nitric oxide is known to increase trabecular outflow facility in the human anterior segment,[8] and NO donors lower IOP in animal models.[1] The mechanism by which NO lowers IOP is relaxation of cells in the TM and Schlemm canal via activation of the cyclic guanosine monophosphate signaling pathway[9] and subsequent inhibition of actin-myosin interactions, which leads to increased aqueous outflow and IOP reduction **(Figure)**.[6,10]

In glaucoma, NO metabolism is altered. Nitric oxide levels in the anterior chamber are lower in eyes with glaucoma than in those of healthy controls,[11-13] and local production of NO by TM and Schlemm canal cells is also reduced.[13] In the ciliary body, the number of anterior longitudinal muscle fibers, responsible for mechanical opening of the TM through tension on the scleral spur, is also reduced.[13] This can affect the contractile tone of the TM which, as described previously,

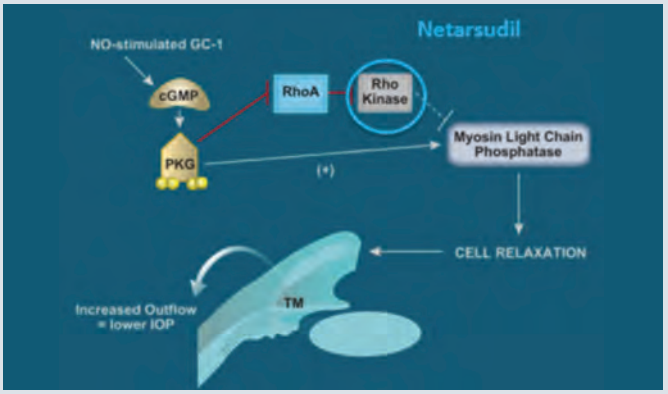

Figure. A simplified illustration of the cyclic guanosine monophosphate pathway and the effects of nitric oxide and Rho kinase inhibition on the trabecular meshwork

Abbreviations: cGMP, cyclic guanosine monophosphate; GC-1, guanylate cyclase 1; IOP, intraocular pressure; NO, nitric oxide; PKG, protein kinase G; TM, trabecular meshwork

can contribute to TM stiffness, reduced aqueous outflow, and elevated IOP.[14]

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Case 2: Newly Diagnosed Primary Open-Angle Glaucoma

From the Files of I. Paul Singh, MD

A 60-year-old white woman was referred by her optometrist for glaucoma evaluation on the basis of suspicious-appearing optic discs. She had no prior history of glaucoma or any family history of glaucoma. Her general health was good, with medically controlled systemic hypertension and hyperlipidemia. On examination, her best-corrected VA was 20/20 in both eyes, IOP was 24 mm Hg in both eyes, her angles were open on gonioscopy, and her CCT was 515 µm in both eyes. **Figure 3** shows her VFs, optic nerves, and RNFL optical coherence tomography (OCT) images. Corneal hysteresis was 8 OU, which is considered to be low and has been shown to be an independent risk factor for progression to OAG.[7]

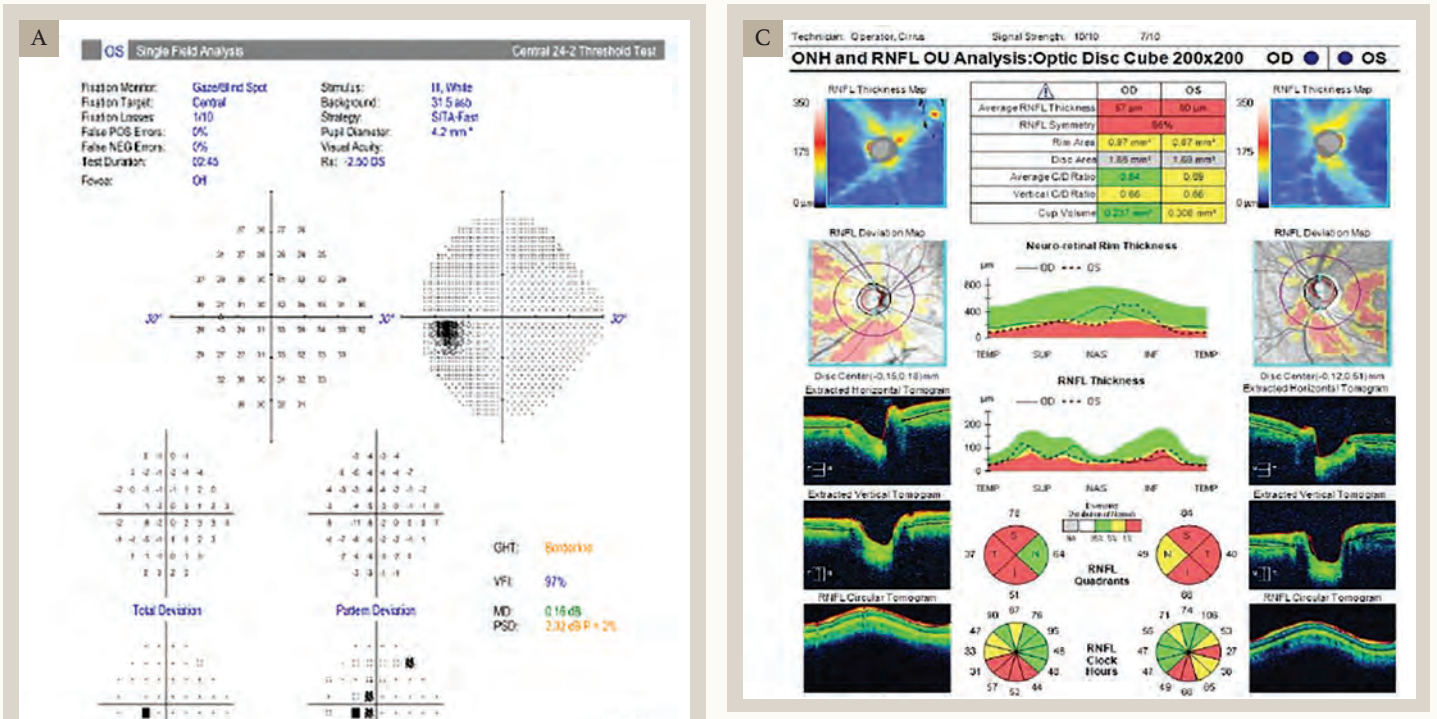

Figure 3. Visual fields (A), optic nerves (B), and retinal nerve fiber layer optical coherence tomography images (C) of the patient presented in Case 2

There were subtle signs of RNFL thinning in both eyes (difficult to appreciate in the images, but more evident on examination) corresponding to the defects seen on the VFs. RNFL OCT revealed more widespread RNFL dropout in both eyes, mostly inferiorly, which corresponds to the fundus photographs that demonstrate loss of RNFL striations inferiorly. The diagnosis of POAG was made when correlating visual field defects with the optic nerve head and OCT findings. Although it is common to ignore the visual field defects as "artifact", pattern defects do correlate with optic nerve head findings.[8] On the basis of this patient's relatively young age and relatively advanced disease (with paracentral VF loss in both eyes), a 30% to 35% IOP reduction was set as her target. This is consistent with the American Academy of Ophthalmology's guidelines for treatment of more advanced and/or higher-risk POAG.[1]

Treatment options included prostaglandins, LBN, a beta blocker, a fixed combination, or SLT. This patient preferred medical therapy over laser. Given the need for a substantial IOP reduction to achieve target IOP (~16 mm Hg) and her desire for monotherapy, she was started on once-daily LBN, 0.024%. LBN has been shown in clinical trials to produce superior IOP reduction compared with latanoprost[9] and with timolol,[10] and has a favorable safety profile (less hyperemia) compared with netarsudil vs timolol.[11] It is important to address the pathology associated with IOP rise, and the effect of LBN on TM outflow has been demonstrated.[12] One month after initiating treatment, her IOP was reduced to 15 mm Hg, and at 3 months, her IOP reduced further to 13 mm Hg, where it remained for at least 1 year. She exhibited good tolerability to the medication without any adverse events. It is unknown if the additional decrease in IOP at 3 months is the result of the time it takes to maximize outflow through the uveoscleral pathway or the result of increased outflow through the TM, but this case might be an example of the benefit of using medications that improve TM outflow in patients with early glaucoma.

Latanoprostene Bunod Clinical Studies

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

Table 1. Summary of the Phase 3 APOLLO and LUNAR Studies of LBN 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	7.7-9.1	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.[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.[4] Adverse events were primarily mild to moderate (> 99.5%) and included conjunctival hyperemia (5.9%), eye irritation (4.6%), and eye pain (3.5%).

The VOYAGER study was a phase 2 dose-finding comparison of LBN to latanoprost **(Table 2)**.[5] 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 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.[6]

The single-arm, open-label JUPITER study evaluated LBN in 130 Japanese patients with ocular hypertension, primary open-angle glaucoma, and normal-tension glaucoma.[7] 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%).

Table 2. Efficacy and Safety Outcomes at Week 4 in the VOYAGER Phase 2 Study of LBN vs Latanoprost[5]

	n	Mean Baseline IOP, mmHg	Mean IOP Reductions, mm Hg	Significance vs Latanoprost	Common Side Effects	
					Eye Irritation, %	Conjunctival Hyperemia, %
LBN, 0.006%	82	26.12	7.81	$P = .913$	1.2	1.2
LBN, 0.012%	85	26.25	8.26	$P = .258$	2.4	3.6
LBN, 0.024%	**83***	**26.01**	**9.00**	***P* = .005**	**3.6**	**4.8**
LBN, 0.040%	81	26.04	8.93	$P = .009$	6.2	3.7
Latanoprost	82	26.15	7.77	–	0	0

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

* n = 82 for safety analysis

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Case 3. Treated Primary Open-Angle Glaucoma Progressing at Low Intraocular Pressure

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

A 71-year-old white woman had a 5-year history of POAG managed with prostaglandin monotherapy. She had SLT twice previously—the first time with a significant and lasting IOP reduction, but the second time with little response. On examination, her VA was 20/30 in both eyes. Her IOP was 13 mm Hg in both eyes. She had mild cataracts, and her angles were open on gonioscopy. **Figure 4** shows her serial optic disc photographs, VFs, and RNFL OCT images of the right eye.

The disc photographs demonstrated progressive erosion of the inferior neuroretinal rim, confirmed by similar findings on OCT and correlating with the progressive VF defect in the superior hemifield. Collectively, these findings indicated progression of POAG, despite IOP in the low teens.

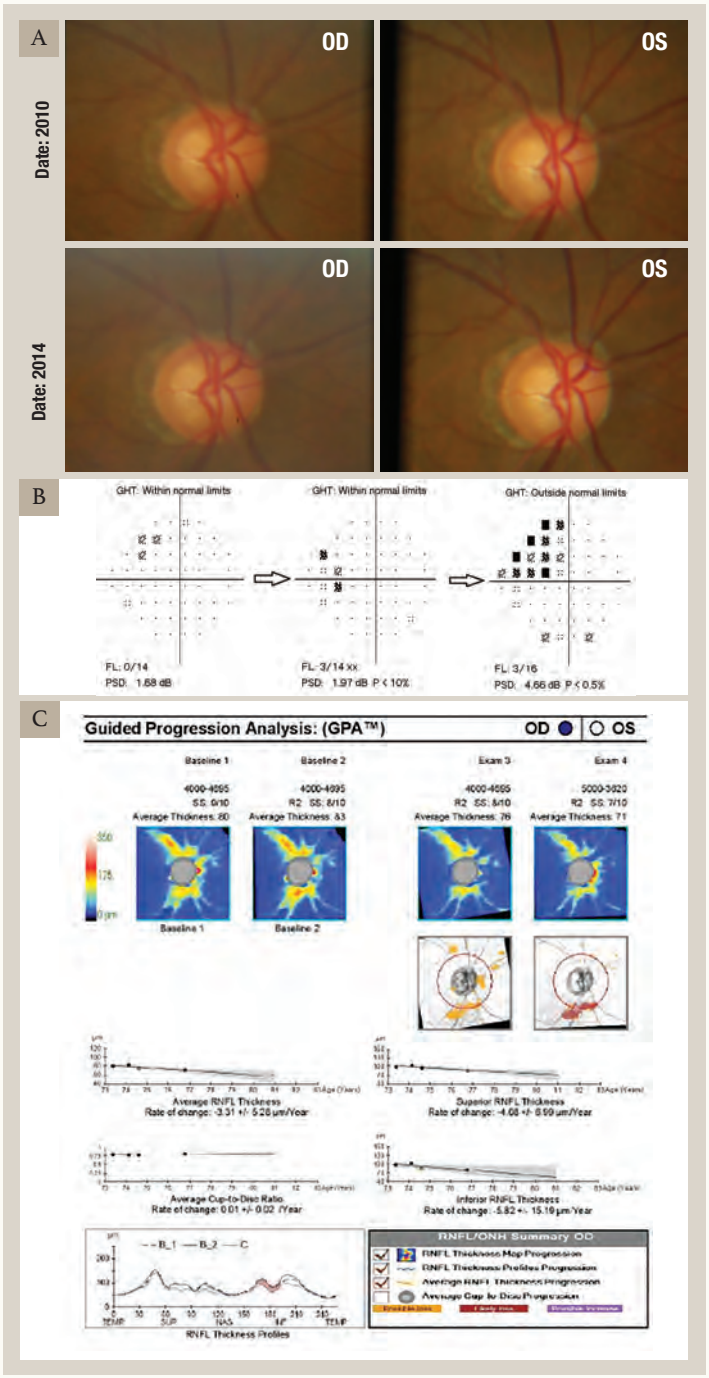

Figure 4. Serial optic disc photographs (A), visual fields (B), and retinal nerve fiber layer optical coherence tomography images (C) of the right eye of the patient presented in Case 3

There are several important factors to consider when progression occurs in the setting of low IOP. The most common issue is adherence. Nonadherence is a well-described phenomenon in glaucoma.[13] Patients often forget to administer medications, leading to elevated IOP between visits. As the time for follow-up approaches, patients are often more attentive to adherence, either because the impending visit serves as a reminder to take their medications or because they do not wish to disappoint the physician with their nonadherence. This scenario leads to low IOP at the time of office visits, but higher IOP—and potential progression—between visits. Suboptimal adherence should be suspected whenever progression occurs in seemingly well-controlled eyes.

Intraocular pressure variability is another factor to consider. Intraocular pressure is often highest at night when patients are in the supine position for sleep.[14] Intraocular measurements at these peak times are difficult to obtain clinically and can undermine perceptions of the adequacy of glaucoma control. Home tonometry, while technically feasible, is difficult from a practical standpoint and expensive to perform and so remains primarily a research tool rather than a clinical tool. Corneal biomechanics should also be considered when progression occurs at low IOP. A thin central cornea can produce artifactually low IOP by applanation tonometry, and low corneal hysteresis—a measure of the viscoelastic properties of the cornea—can do likewise. Finally, changes to the optic nerve in eyes with low IOP can be nonglaucomatous in origin. Findings such as reduced central acuity, color vision abnormalities, and optic disc pallor can be indicative of nonglaucomatous processes that might warrant additional investigations.[15]

When these other issues have been ruled out and progression at low IOP has been confirmed, the target IOP must be revised downward. The Canadian Glaucoma Study demonstrated that a 20% further reduction in progressing eyes significantly reduced the rate of future VF decline.[16] Likewise, lowering IOP to < 10 mm Hg with trabeculectomy with mitomycin C has been shown to halt advancing disease in most eyes progressing with IOP in the low teens.[17]

For this patient, a target IOP of 10 mm Hg (a 20% reduction from 13 mm Hg) was set. Options for establishing this new target IOP included repeat SLT, adding a medication, switching to a different medication, or surgery. A suboptimal response to SLT is not necessarily predictive of a similar response to subsequent SLT[18]; however, the patient preferred not to have a third SLT. Switching to LBN might be expected to add an additional 1 to 1.5 mm Hg[7] which would not achieve the new target IOP. Switching to netarsudil would also be unlikely to achieve target IOP, but adding netarsudil to her current prostaglandin therapy would be a reasonable next step. One month after adding netarsudil, her IOP was 10 mm Hg (a 23% reduction from 13 mm Hg). Despite some mild hyperemia, the treatment was well tolerated. Four months later, she developed bilateral corneal verticillata. These pigment deposits in the basement membrane of the corneal epithelium are similar to those seen with amiodarone and other systemic drugs.[19] They are typically visually insignificant and do not usually justify discontinuation of therapy, particularly in eyes with a satisfactory clinical IOP response.

Netarsudil Clinical Studies

ROCKET-1 and ROCKET-2 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 was assessed through 6 months.[2] All 3 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 the efficacy and safety outcomes of these studies. In ROCKET-1, mean IOP reductions in the timolol group were greater than those in the once-daily netarsudil group in 3 of the 9 time points, and the criteria for noninferiority were not met.[1] However, a post hoc analysis

Table. Efficacy and Safety Outcomes of the 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	3.5-5.1	3.9-4.7	3.8-5.2
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

Abbreviation: IOP, intraocular pressure.
* Netarsudil statistically inferior to timolol

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 receiving netarsudil and 357 patients receiving timolol, 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 with netarsudil and 6.8 mm Hg with 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 by 2.6 mm Hg more than did netarsudil monotherapy, with hyperemia rates of 40% in both the netarsudil and 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 a 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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Case 4. Normal-Tension Glaucoma

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

A 58-year-old white woman was referred by an optometrist for evaluation of glaucoma on the basis of suspicious-appearing optic nerves. She had systemic hypotension and sleep apnea. She underwent bilateral LASIK (laser-assisted in situ keratomileusis) for high myopia 17 years ago. On examination, her VA was 20/25 OD and 20/20 OS without correction. Her pupillary examination result was normal. Her IOP was 14 mm Hg OD and 15 mm Hg OS. CCT was 475 µm OD and 480 µm OS. Her angles were open on gonioscopy. **Figure 5** shows her optic discs, VFs, and OCT images.

Although there was asymmetry of the cup:disc ratio between eyes, both eyes demonstrated concentric cups with intact neuroretinal rim. The RNFL OCT image was normal OD and borderline OS (the eye with the larger cup). The VF was essentially full in both eyes. The patient was diagnosed as a normal-tension glaucoma suspect, and observation was recommended. Confounding this diagnosis was a history of corneal refractive surgery, which thinned the cornea and likely induced artifacts in applanation tonometry. Her true IOP was likely somewhat higher than measured.

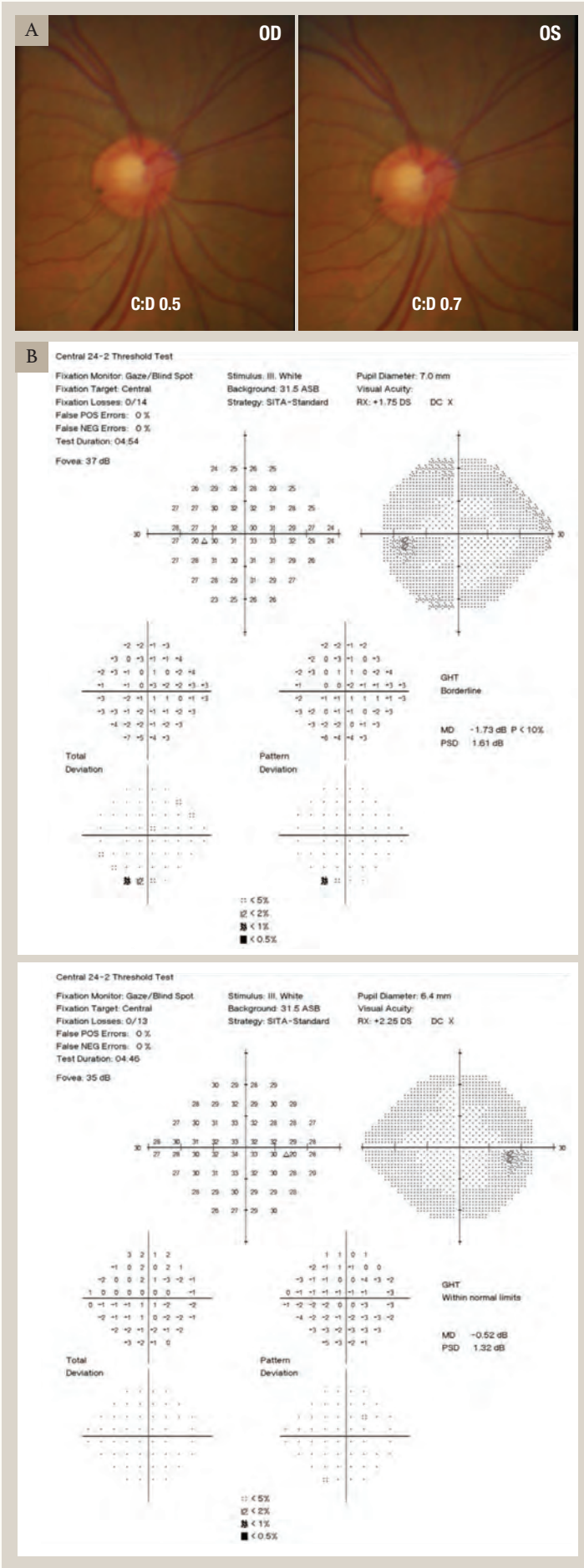

Figure 5. Optic discs (A), visual fields (B), and optical coherence tomography images (C) of the patient presented in Case 4. Average retinal nerve fiber layer thickness was 88 µm OD and 77 µm OS.

Normal-tension glaucoma (NTG) is an entity initially described in the 1930s as having all the clinical hallmarks of POAG despite IOP consistently in the normal range.[20] Initially, the condition was called low-tension glaucoma, but NTG better represents the fact that IOP, while low, is typically in the normal range in these eyes. Whether NTG is a distinct entity from POAG is controversial. In fact, there are no findings of NTG that are pathognomonic; some findings (such as disc hemorrhages and paracentral field defects) are more common in NTG, but also occur in POAG. It is likely that NTG and POAG are the same entity occurring across the spectrum of IOP. Because glaucoma is multifactorial in pathophysiology, different factors might be at play at different IOP levels.

Approximately 18 months after her initial evaluation, the patient presented with acute onset of flashes and floaters and was diagnosed with a posterior vitreous detachment OS. On examination, a new disc hemorrhage was noted OS **(Figure 6)**. Although the posterior vitreous detachment alone could have caused the hemorrhage, the appearance of a disc hemorrhage is considered a sign of progressing glaucoma and was an indication for treatment in the Collaborative Normal-Tension Glaucoma Study (CNTGS).[21] It was also considered a risk factor for progression in that study,[22] but the benefit of IOP reduction in eyes with NTG with disc hemorrhages was insignificant,[23] suggesting that progression is more related to vascular factors than to IOP in these eyes.

Given that the disc hemorrhage occurred in the eye with the larger cup, the likelihood that this represented early NTG justified the initiation of treatment in the left eye. Pursuant to the findings of CNTGS, a 30% IOP reduction was warranted.[21] During the 18 months of observation, IOP of this patient ranged from 15 to 19 mm Hg, so a target IOP in the range of 11 to 13 mm Hg was set. The patient declined laser therapy.

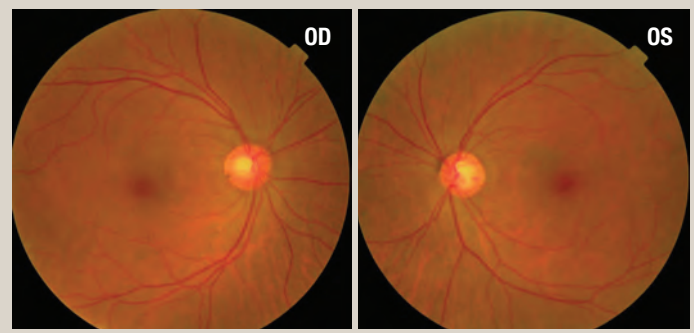

Figure 6. Disc hemorrhage in the left eye in Case 4 upon follow-up

In considering medical therapy for NTG, it is important to recognize that the IOP reductions reported in phase 2 and 3 studies in high-tension POAG might not apply to eyes with lower baseline IOP. Most treatments are more effective when starting at a higher IOP and less effective when starting at a lower IOP. A pair of meta-analyses makes this point.[24,25] In a meta-analysis of studies of prostaglandin monotherapy in eyes of Japanese patients with NTG, mean IOP reductions were on the order of 15% to 20%,[24] whereas in a meta-analysis of similar studies in high-tension POAG, mean IOP reductions of 30% were seen.[25]

In the hopes of a better-than-expected outcome, generic latanoprost therapy was commenced in the left eye. Over the next 2 visits, IOP was 14 to 16 mm Hg, which was not at target. Both LBN[26] and netarsudil[5] have been shown to be effective in eyes with low baseline IOP. Therapy was switched to once-daily LBN, which produced IOP readings in the range of 12 to 13 mm Hg over the next several visits, with acceptable tolerability.

Summary and Take-Home Points

- Nitric oxide plays a key role in IOP regulation; activating the NO signaling pathway lowers IOP.
- When following a patient with OHT or a glaucoma suspect who has a newly abnormal VF, repeat the VF test. Most of the time, the VF will return to normal.
- Three new agents lower IOP by improving outflow through the TM: LBN, netarsudil, netarsudil/latanoprost.
- According to individual clinical trial data, monotherapy with LBN, among other single-agent options, may provide the best option to lower IOP with greater efficacy than that of timolol and latanoprost and greater tolerability (less hyperemia) than that of netarsudil.
- There are many choices for adjunctive therapy, including netarsudil, to a prostaglandin analogue when IOP is inadequately controlled. Prospective comparative trials are needed to determine which treatments work best.
- Some patients with NTG might have POAG, but IOP measurements are artifactually low owing to thin corneas. This does not change management. The goal is still to achieve a 30% IOP reduction.
- Optic disc hemorrhages can be a warning sign of future progression. Visual field, OCT image, and optic nerve comparisons should be performed 4 to 6 months after a hemorrhage is identified to determine if therapy needs to be advanced.
- Both LBN and netarsudil are effective in eyes with low baseline IOP, although the magnitude of effect might be smaller than that seen in eyes with high baseline IOP.

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1. A patient has an IOP of 25 mm Hg in both eyes, with normal VFs and optic nerves. Ocular hypertension is diagnosed. Which is the best approach to manage this patient?
   a. The patient has an IOP > 21 mm Hg and should be treated with IOP-lowering medications to prevent glaucoma
   b. The risk of developing glaucoma is so low that the patient should not be treated until glaucoma appears
   c. Treatment should be reserved for those with a high risk for developing glaucoma
   d. The patient should be treated with a goal of 30% IOP reduction

2. A patient with OHT has had normal VFs for 3 years. The most recent VF shows a new defect. How should this patient be managed?
   a. Patient has developed glaucoma and should be treated
   b. Because the patient has been stable, this is not likely glaucoma, and neuroimaging should be performed to rule out central nervous system lesions
   c. VFs are poorly reliable and this finding should be ignored. The diagnosis of glaucoma should be based on RNFL OCT images instead.
   d. Patient should be retested because the VF has a high likelihood of being normal on repeat testing according to the Ocular Hypertension Treatment Study

3. The TM in eyes with glaucoma is ____ times stiffer than that in healthy eyes.
   a. 7
   b. 13
   c. 20
   d. 35

4. NO lowers IOP by relaxing cells in the TM and Schlemm canal. This effect is mediated by:
   a. Inhibition of the complement cascade
   b. Enhancing actin-myosin interactions
   c. Activating the cyclic guanosine monophosphate signaling pathway
   d. Raising episcleral venous tone

5. Which treatment has no demonstrable effect on trabecular outflow?
   a. Netarsudil
   b. LBN
   c. Netarsudil/latanoprost fixed combination
   d. Timolol

6. LBN lowers IOP by:
   a. Decreasing uveoscleral outflow and increasing trabecular outflow
   b. Increasing both uveoscleral and trabecular outflow
   c. Decreasing aqueous humor formation
   d. Increasing episcleral venous pressure

7. In a pooled analysis of 2 phase 3 studies, LBN lowered mean diurnal IOP by ____ at 3 months.
   a. 15%
   b. 24%
   c. 32%
   d. 44%

8. Which was a result of the pair of phase 3 trials evaluating the netarsudil/latanoprost fixed combination?
   a. IOP reduction with the fixed combination was noninferior to that with latanoprost alone
   b. IOP reduction with the fixed combination was superior to that with both latanoprost alone and netarsudil alone
   c. The fixed combination was associated with fewer adverse events compared with latanoprost alone
   d. 35% of eyes in the fixed combination group experienced conjunctival hyperemia

9. Which of the following should be considered when glaucoma progresses at low IOP?
   a. CCT might be higher than average
   b. Neuroimaging should be considered in most cases
   c. Patients might not be taking their medications consistently as prescribed
   d. Most medications work better in eyes with low baseline IOP

10. According to CNTGS, the goal of therapy in newly diagnosed NTG is to lower IOP by ___.
    a. 20%
    b. 25%
    c. 30%
    d. 35%