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Five-Year, Prospective, Randomized, Multi-Surgeon Trial of Two Trabecular Bypass Stents versus Prostaglandin for Newly Diagnosed Open-Angle Glaucoma

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Purpose: To evaluate 5-year safety and efficacy of 2 trabecular micro-bypass stents versus prostaglandin as initial stand-alone treatment for newly diagnosed, treatment-naive primary open-angle glaucoma (POAG).

Design: Prospective, randomized, controlled, multi-surgeon clinical trial.

Participants: Enrolled eyes (n = 101) were phakic and had a confirmed POAG diagnosis, normal angle anatomy, mean diurnal intraocular pressure (IOP) 21 to 40 mmHg, and vertical cup-to-disc (C:D) ratio $\leq$0.9.

Methods: Eyes were randomized (1:1) to receive either 2 stents (iStent trabecular micro-bypass; Glaukos Corporation, San Clemente, CA) or once-daily topical travoprost.

Main Outcome Measures: The primary and secondary efficacy end points were the change from screening in mean diurnal IOP at months 12 and 24, respectively, without glaucoma surgery or add-on medication (any medication in stent eyes or a second medication in travoprost eyes). Two additional secondary end points were the proportion of eyes achieving treatment success at months 12 and 24, defined as IOP 6 to 18 mmHg without additional medication or glaucoma surgery. This report shows these efficacy measures through 60 months. Safety measures included best-corrected visual acuity, C:D ratio, visual field, pachymetry, complications, and adverse events.

Results: Of 101 enrolled eyes (54 stent eyes, 47 travoprost eyes), 90 eyes (49 stent eyes, 41 travoprost eyes) completed 5-year follow-up. Five-year mean diurnal IOP was 16.5$\pm$1.2 mmHg in stent eyes (35.3% reduced vs. 25.5$\pm$2.5 mmHg preoperatively; $P < 0.0001$) and 16.3$\pm$1.9 mmHg in travoprost eyes (35.1% reduced vs. 25.1$\pm$4.6 mmHg preoperatively; $P < 0.0001$). During follow-up, add-on medication was initiated in 12 stent eyes (22.2% of the initial 54-eyes) and 18 travoprost eyes (38.3% of the initial 47-eyes). By 5 years, 17% (6/35) of stent eyes and 44% (14/32) of travoprost eyes needed add-on medication to control IOP ($P = 0.017$). Treatment success was achieved in 77% (27/35) of stent eyes and 53% (17/32) of travoprost eyes ($P = 0.04$). Both groups exhibited excellent safety.

Conclusions: This prospective randomized trial demonstrates 5-year effectiveness and safety of 2 trabecular bypass stents in patients with newly diagnosed, treatment-naive POAG, with comparably favorable outcomes as topical prostaglandin. *Ophthalmology Glaucoma 2019;2:156-166 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyglaucoma.org.

The trabecular meshwork is understood to be a major site of resistance to aqueous outflow and contributes to elevated intraocular pressure (IOP) in glaucoma.[1] The iStent (iStent Trabecular Micro-Bypass, Glaukos Corporation, San Clemente, CA) was the first intraocular trabecular bypass stent commercially available to treat open-angle glaucoma of mild to advanced severity (indication based on country) via a micro-invasive glaucoma surgery (MIGS) procedure. Conformité Européenne marked in 2004 and approved by the U.S. Food and Drug Administration in 2012, the L-shaped intraocular stent is designed to create a bypass through the trabecular meshwork to Schlemm's canal to improve physiologic aqueous outflow and consequently decrease IOP. In studies across a variety of clinical settings, the iStent consistently has demonstrated meaningful IOP and medication reductions while maintaining excellent safety. Clinical studies have evaluated iStent implantation with[2-6] or without[7-10] cataract surgery; in mild to moderate and in advanced or refractory open-angle glaucoma;[11-13] in protocol-guided studies and single-surgeon case series;[4,6,10,11,13,14] in

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primary open-angle glaucoma (POAG) and pseudoexfoliative glaucoma[15] or ocular hypertension;[14] in the setting of comparing 1 or multiple stents;[16,17] and in combination with other micro-invasive glaucoma procedures.[12]

It is widely acknowledged that achieving earlier IOP control may reduce progression of vision loss.[18,19] As an initial intervention to achieve early IOP control in newly diagnosed, treatment-naïve patients, there are many potential advantages of using safe micro-invasive trabecular stents. Stents do not have many of the drawbacks of topical IOP-lowering therapy, such as local and systemic hypersensitivities, complex dosing regimens, or preservative-associated toxicities;[20,21] they can reduce dependence on medication adherence, which is frequently suboptimal;[22,23] and they have been shown to be cost-effective over time.[24-27] They also do not carry the same risks as traditional filtering procedures, such as endophthalmitis, hypotony, bleb infections, bleb leaks, or fibrosis.[28-30] The incidence of adverse events (AEs) after combined iStent-cataract surgery has been shown to be comparable to that of cataract surgery alone.[2] When stent-related events do occur, they are often early, related to the surgical procedure itself, or amenable to conservative management.[31] Because of these favorable safety outcomes, iStent surgery may be a preferred option for patients whose disease does not warrant the risks of a filtering surgery, even though the IOP reduction of MIGS procedures is typically more modest than that of filtering surgeries.[31]

Because glaucoma treatment may necessitate additional therapy over time, it would be beneficial if iStent implantation could delay or avoid such therapy, while also preserving ocular tissues in case future intervention is needed. The purpose of this prospective, randomized, controlled, multi-surgeon study was to evaluate the long-term safety and efficacy of 2 trabecular micro-bypass stents compared with prostaglandin therapy as an initial stand-alone treatment in subjects with newly diagnosed POAG who had not received any previous medical or surgical glaucoma therapy. Although the iStent has been evaluated in numerous populations, to our knowledge the present study is the first to evaluate the stand-alone use of the device in newly diagnosed, treatment-naïve patients. The initial results of the study, including primary and secondary efficacy end points, were reported in a prior publication.[32] Briefly, that publication showed that 94% and 90% of stent-treated eyes achieved IOP of 6 to 18 mmHg at 12 and 24 months, respectively, without additional glaucoma surgery or medication; meanwhile, 89% and 87% of travoprost eyes achieved this outcome at 12 and 24 months, respectively. Mean IOP decreased from 25.5 mmHg at screening to 13.7 mmHg at 12 months and 13.8 at 24 months in stent-treated eyes, and from 25.1 mmHg at screening to 13.9 mmHg at 12 months and 15.0 mmHg at 24 months in travoprost eyes.[31] Add-on medication was needed in fewer stent eyes than travoprost eyes, and safety was favorable in both groups.[32] In this study, we report extended outcomes through 5 years of follow-up. To our knowledge, this report is possibly the first 5-year, protocol-driven, randomized evaluation of stand-alone iStent implantation in newly diagnosed glaucoma.

Methods

Trial Design, Participants, Randomization, and Interventions

This prospective, randomized, controlled trial included subjects with POAG; phakic or pseudophakic lens status; cup-to-disc (C:D) ratio ≤0.9; glaucomatous visual field (VF) defects with mean deviation (MD) not worse than −12 decibels (dB); unmedicated mean diurnal IOP by Goldmann applanation of ≥21 and ≤40 mmHg at screening; study eye best-corrected visual acuity (BCVA) of 20/100 (Snellen equivalent) or better; open-angle anatomy assessed by gonioscopy; and absence of peripheral anterior synechiae or other angle abnormalities that could impair proper stent placement. Mean diurnal IOP consisted of the average of 3 IOP measurements taken on a single day (at 9 AM, 1 PM, 5 PM); this was performed at screening and at annual visits during follow-up. Subjects were excluded who had uveitic, neovascular, or angle-closure glaucoma; glaucoma associated with vascular disorders; prior incisional glaucoma surgery; corneal pathology or prior corneal surgery; congenital or traumatic cataract; and non-glaucomatous retinal or optic nerve disorders.

Eyes were randomized within a non-blocked computer-generated, concealed 1:1 random allocation sequence to receive either 2 iStent devices or topical travoprost (0.004% Travatan, Alcon, Fort Worth, TX) 1 drop/day at 8:00 to 9:00 PM for the duration of the study. The sealed, unlabeled randomization envelope was opened at the conclusion of the screening visit if the subject qualified for study participation. The allocation sequence was produced by the study sponsor (Glaukos Corporation); participant enrollment was completed by the highly experienced staff surgeon (L.V., described in next paragraph).

Assessments of efficacy and safety were conducted at day 1, week 1, and months 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60. Measurements of IOP were completed using a 2-observer masked IOP reading technique, with one examiner looking through the slit lamp and turning the dial (masked to reading) and one reader recording the IOP (masked to examination). Over the course of follow-up, ocular hypotensive medication was to be initiated or increased if any patient had concerning clinical findings or IOP >21 mmHg, with the type(s) and number(s) of these medications based on the investigator's discretion on a case-by-case basis. Concerning clinical findings could include worsened optic nerve appearance (per clinical assessment) and VF progression (automated threshold VF, Humphrey 24-2, Swedish Interactive Threshold Algorithm Standard). The protocol advised that if both eyes were eligible to participate, the investigator was to enroll the right eye. Throughout the study, the investigator was allowed to administer any medication as needed in the contralateral eye.

All surgeries and clinical examinations in this study (NCT01443988, clinicaltrials.gov) were conducted over a 6-month period in 2011−2012 at a single site in Yerevan, Armenia. Operations were completed by one local staff surgeon (L.V.) and 12 visiting surgeons (Appendix 1, available at www.ophthalmologyglaucoma.org). The staff surgeon was a highly experienced U.S. glaucoma fellowship-trained ophthalmologist specializing in MIGS; this surgeon also completed subjects' initial diagnosis and ocular examinations during 5 years of follow-up. The visiting surgeons were highly experienced glaucoma specialists from 5 countries who were members of the MIGS Study Group. Ethics Committee approval was obtained from the Armenian Ministry of Health. The study adhered to the Declaration of Helsinki, including all subjects providing written informed consent for their participation.

Stent Implantation Technique

The iStent implantation technique has been detailed previously.[2] Briefly, after anesthetizing the eye and filling the anterior chamber with viscoelastic, the iStent inserter was guided through a temporal clear corneal incision, and the iStent was placed through the trabecular meshwork into the nasal portion of Schlemm's canal. Proper placement of the stents was confirmed intraoperatively with a gonioprism. A second stent was implanted using the same technique approximately 2 clock-hours away from the first stent. Postoperatively, subjects were prescribed a standard antibiotic and anti-inflammatory medication regimen of tobramycin 0.3% plus dexamethasone 0.1% ophthalmic suspension for 1 week, followed by only dexamethasone 0.1% tapered over 3 additional weeks.

Outcomes

The study protocol had prespecified primary and secondary efficacy end points at 12 and 24 months, with planned extension through 5 years to gather long-term safety and efficacy data (the subject of the current report). The primary and secondary efficacy end points were the change from screening in mean diurnal IOP at months 12 and 24, respectively, without glaucoma surgery or add-on medication (any medication in stent eyes or a second medication in travoprost eyes). Two additional secondary end points were the proportion of eyes achieving treatment success at months 12 and month 24, with treatment success being defined as IOP 6 to 18 mmHg without additional medication or glaucoma surgery. Results for these primary and secondary efficacy outcomes were published previously,[32] whereas the present report shows these outcomes through 60 months of follow-up. The rationale behind the upper limit of 18 mmHg for treatment success was the landmark Advanced Glaucoma Intervention Study, which showed that VF decline was limited when IOP stayed below 18 mmHg.[33] In addition, the present report contains a post hoc proportional analysis of eyes achieving IOP of 6 to 15 mmHg (inclusive) without additional medication or glaucoma surgery. Evaluation of safety included BCVA (Snellen equivalent), VF (24-2 Swedish Interactive Threshold Algorithm Standard), vertical C:D ratio, central corneal thickness, optic nerve abnormalities, gonioscopic angle abnormalities, AEs and complications, and secondary surgical interventions.

Statistical Analysis

It was planned that approximately 100 subjects (100 eyes) would be enrolled (50 eyes with 2 iStents and 50 eyes with travoprost) to provide a fair representation of long-term safety. Continuous variables, such as mean diurnal IOP and medications, were assessed using descriptive statistics. An unpaired *t* test was used to evaluate between-group difference in pretreatment screening IOP. Proportional analyses showed the percentage of eyes with IOP $\leq$18 mmHg or IOP $\leq$15 mmHg without the need for add-on medication and the proportion of eyes with varying levels of BCVA through 5 years ($\geq$20/40, 20/100, or 20/200). Pretreatment and month 60 mean diurnal IOP were compared using a paired *t* test. Chi-square tests were used to compare the proportion of eyes in each group achieving treatment success at 5 years and the proportion of eyes requiring add-on medication at 5 years. A Kaplan–Meier analysis was conducted to show post-treatment time to initiating add-on medication. Because cataract surgery itself can reduce IOP,[34-36] to reduce confounding, data from subjects' visits after undergoing such surgery during follow-up were excluded from primary effectiveness analyses. Eyes that required add-on medication or secondary glaucoma surgery were considered nonresponders in proportional analyses.

Results

Accountability

A total of 101 subjects were enrolled and randomized in this study (54 subjects in the stent group and 47 subjects in the travoprost group). A total of 90 eyes (49 and 41 eyes in the 2 groups, respectively) completed follow-up through 5 years. Reasons for study discontinuation included loss to follow-up (2 and 4 subjects in the stent and travoprost groups, respectively), death unrelated to study (2 and 1 subject, respectively), investigator discretion (1 stent subject), and moving out of the country (1 travoprost subject).

Demographic and Pretreatment Ocular Characteristics

The demographic and pretreatment parameters of the subjects are presented in Table 1. Screening IOP was statistically similar in the 2 groups: 25.5±2.5 mmHg in the stent group and 25.1±4.6 mmHg in the travoprost group ($P = 0.58$). Although the protocol allowed for phakic or pseudophakic eyes, only phakic subjects presented for participation and were enrolled. All subjects were white and had newly diagnosed POAG; no eyes had received prior glaucoma medication or surgical procedures.

Effectiveness: Intraocular Pressure and Medications

At all study visits through 5 years after undergoing 2-iStent surgery or using daily travoprost, the mean IOP ranged from 13.5±1.4 mmHg to 16.5±1.2 mmHg in the stent group and 13.8±2.0 mmHg to 16.2±1.9 mmHg in the travoprost group (Fig 1). At 5 years postoperatively in eyes that did not undergo cataract surgery during follow-up, mean diurnal IOP was 16.5±1.2 mmHg in the

Table 1. Demographic and Screening Ocular Parameters

	2-Stent Group (n = 54 eyes)	Travoprost Group (n = 47 eyes)
Age (yrs)		
Mean (SD)	64.5 (11.1)	62.0 (11.3)
Gender		
Male/female	25/29	32/15
Eye		
OD/OS	20/34	24/23
C:D ratio		
Mean (SD)	0.7 (0.2)	0.6 (0.1)
Corneal thickness (μm)		
Mean (SD)	552.6 (41.2)	540.3 (59.2)
Unmedicated IOP (mmHg)*		
Mean (SD)	25.5 (2.5)	25.1 (4.6)
BCVA (Snellen)		
20/40 or better	40 (74%)	39 (83%)
20/100 or better	52 (96%)	47 (100%)
20/200 or better	54 (100%)	47 (100%)

BCVA = best-corrected visual acuity; C:D = cup-to-disc; IOP = intraocular pressure; n = number of eyes; OD = right eye; OS = left eye; SD = standard deviation.
*Between-group difference in screening IOP was not significant ($P = 0.58$).

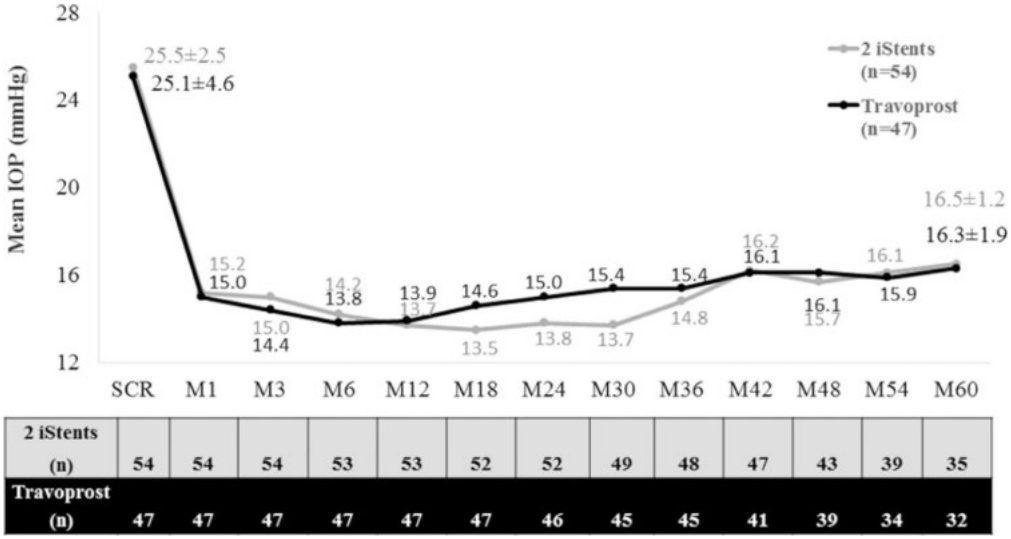


Figure 1. Mean intraocular pressure (IOP) through 5 years postoperatively, regardless of add-on medication. IOP excludes data from eyes after cataract surgery. Add-on medication = any medication in stent group or a second medication in travoprost group; M = month; n = number of eyes; SCR = screening.

stent group (vs. 25.5±2.5 mmHg at screening, a 35.3% reduction, significant, $P < 0.0001$) and 16.3±1.9 mmHg in the travoprost group (vs. 25.1±4.6 mmHg at screening, a 35.1% reduction, significant, $P < 0.0001$). For the entire cohort (including all eyes regardless of whether they had cataract surgery during follow-up), 5-year mean diurnal IOP was 16.4±1.4 mmHg in the stent group and 16.3±1.8 mmHg in the travoprost group.

Over 5 years of follow-up, add-on medication (any medication in stent eyes or a second medication in travoprost eyes) was initiated in 12 stent eyes (22.2% of the initial 54-eye group) and 18 travoprost eyes (38.3% of the initial 47-eye group) (Table 2). In the majority of these eyes, medication was added because IOP exceeded 18 mmHg, whereas in 16.7% of eyes in each group (2/12 stent eyes, 3/18 travoprost eyes), medication was added for optic nerve changes (even though IOP was ≤18 mmHg). The need for add-on medication (regardless of reason) arose at a slower rate for the stent group than the travoprost group (Fig 2). The greatest distinction between groups emerged after 2 years of follow-up: From 2 to 5 years of follow-up, add-on medication was initiated in approximately double the number of travoprost eyes (13) than stent eyes (7). At 5 years of follow-up, less than half the number of stent eyes than travoprost eyes needed add-on medication (17% or 6/35 of stent eyes vs. 44% or 14/32 of travoprost eyes included in effectiveness analyses; statistically significant, $P = 0.017$).

In eyes without add-on medication, month 60 mean diurnal IOP was 16.8±1.0 mmHg in stent eyes and 16.9±1.1 mmHg in travoprost eyes (Fig 3). Treatment success (defined as mean diurnal IOP of 6 to 18 mmHg [inclusive] without the need for add-on medication or secondary glaucoma surgery) was achieved in a significantly higher proportion of stent eyes (77% or 27/35) than travoprost eyes (53% or 17/32) ($P = 0.04$) (Fig 4). Figure 5 shows the proportion of eyes achieving 5-year unmedicated IOP of 6 to 18 mmHg without secondary glaucoma surgery, and it does not exclude eyes that had medication added for non-IOP reasons; as cited in the prior paragraph, this includes 2 stent eyes (with IOP 16 and 18, respectively) and 3 travoprost eyes (all with IOP 18).

Regarding treatment of contralateral eyes, as per the study protocol, no eyes were on medication in either eye before beginning the study. After undergoing study treatment, 1 contralateral eye (subject #220037, stent group) had topical medication added (brimonidine/timolol combination at 1 month). This subject was not excluded from analysis. No other contralateral medications were prescribed in any eye during follow-up.

Safety

A summary of AEs is presented in Table 3. Two eyes in the stent group experienced intraoperative AEs: one eye had a hyphema that resolved without intervention by day 1, and 1 eye had a cyclodialysis that was recorded as mild in severity, necessitated no intervention, resolved the same day, and produced no sequelae. Both intraoperative AEs were due to unexpected subject movement during surgery. In this cohort of phakic subjects with mean baseline age between 62 and 64.5 years, the most common AE over 5 years of follow-up was progression of preexisting cataract. This progression was observed at a similar rate in both groups (16/54 or 30% of stent eyes and 15/47 or 32% of travoprost eyes). The rates of associated BCVA worse than 20/100 were similar in the 2 groups at the time of cataract diagnosis (3/16 stent eyes and 2/15 travoprost eyes). Of the eyes with cataract, cataract surgery was completed in 16 of 16 stent eyes and in 9 of 15 travoprost eyes. Notably, all cases of cataract surgery in both groups occurred after at least 18 months of follow-up (i.e., not in the short term after study treatment).

The only other reported ocular AE was 1 case of conjunctival hyperemia in the travoprost group that occurred 36 months after starting the medication, resulted in no sequelae, and necessitated no intervention or discontinuation of the medication. No eyes in either group required additional glaucoma surgery. There were no stent-related AEs or ocular AEs leading to subject discontinuation from the study.

The BCVA remained stable in both groups throughout follow-up, with more than three-quarters of eyes in both groups having BCVA of 20/40 or better at 5 years, similar to the proportions achieving this level of acuity before treatment (Fig 6). Throughout follow-up, there

Table 2. Detail through 60 Months for Eyes Receiving Add-on Medication (Any Medication in Stent Group or a Second Medication in Travoprost Group)[†]

Subject No.	Preoperative Unmedicated IOP (mmHg)	Postoperative Examination when Medication Added	IOP (mmHg) at Examination Medication Added	Medication Added
Stent Group (54 Eyes Total)				
37	30	Month 1	30	brimonidine, timolol
61	25	Month 1	26	tafloprost
72	26	Month 3	23	travoprost, timolol
07	24	Month 18	16*	tafluprost
82	25	Month 18	18*	timolol
34	28	Month 36	19	timolol
19	28	Month 42	19	tafluprost
38	21	Month 42	19	timolol
52	21	Month 42	20	timolol
75	24	Month 42	20	tafluprost
88	25	Month 42	19	timolol
02	25.3	Month 54	20.7	timolol
Travoprost Group (47 Eyes Total)				
56	38	Month 1	26	brinzolamide, timolol
62	32	Month 1	28	brinzolamide
93	29	Month 1	23	brinzolamide
81	38	Month 3	32	brinzolamide
97	30	Month 3	25	brinzolamide, timolol
41	21	Month 24	20	timolol
76	26	Month 24	18*	timolol
04	23	Month 30	19	betaxolol
35	21	Month 30	19	timolol
65	29	Month 30	18*	betaxolol
10	22	Month 36	19	timolol
14	22	Month 36	19	timolol
05	23	Month 42	18*	timolol
68	28	Month 42	19	timolol
79	25	Month 42	19	timolol
30	24	Month 48	21	timolol
48	28	Month 48	20	timolol
87	24	Month 60	20	timolol

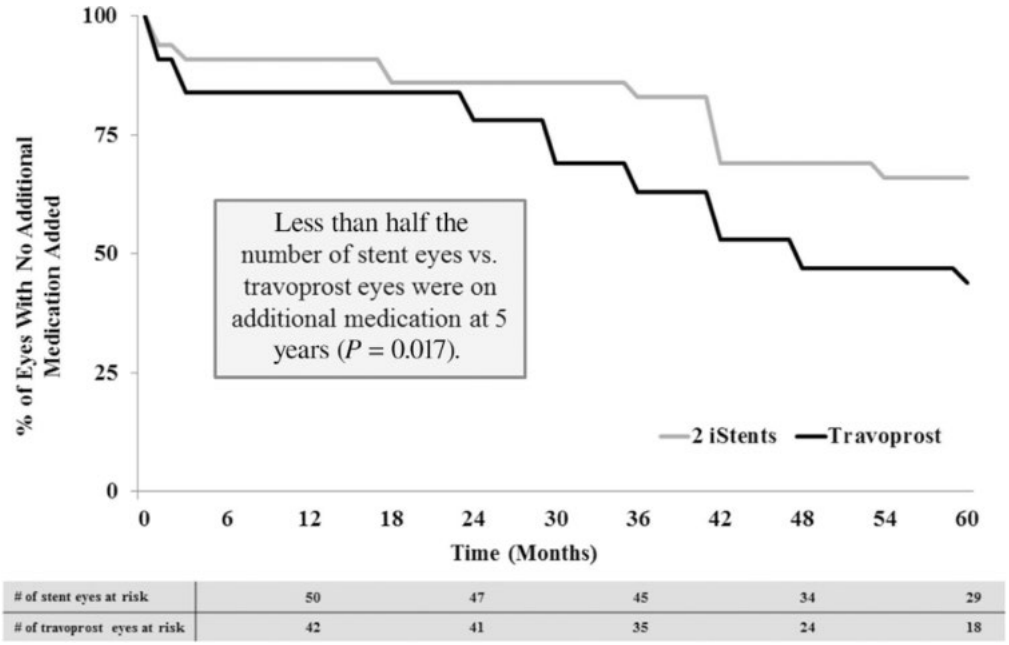
IOP = intraocular pressure.
*Medication added in 2/12 stent eyes and 3/18 travoprost eyes because of optic nerve findings, despite IOP being in range of treatment success (6–18 mmHg inclusive).
[†]Add-on medication = any medication in stent group or a second medication in travoprost group.

were no reports of goniosynechiae, stent obstruction, corneal endothelial compromise, corneal edema, myopic shift, or IOP spike >30 mmHg, and no AEs seen with filtration procedures such as hypotony, choroidal detachment, endophthalmitis, or infection. In the stent group (including all stent eyes regardless of additional medication or cataract surgery), C:D ratio, VFs, and central corneal thickness remained stable over the length of follow-up (Table 4). In the travoprost group (including all travoprost eyes regardless of additional medication or cataract surgery), VF MD worsened slightly over time (MD −7.5 dB at month 60 versus −5.8 dB at screening); this decline likely is because 6 of 15 cataractous eyes in the travoprost group had not undergone cataract surgery by the end of follow-up. All other safety parameters in the travoprost group remained stable (Table 4).

Discussion

This is one of the first studies to ever evaluate the long-term value of iStent as an initial stand-alone treatment in patients newly diagnosed with glaucoma. This prospective, randomized, controlled, multi-surgeon study provides a direct comparison of implanting 2 first-generation iStents versus using a once-daily topical prostaglandin analog medication. Both the stent and travoprost groups demonstrated significant IOP reductions over 5 years (35.3% and 35.1% reductions, respectively, $P < 0.0001$ for both); both groups exhibited favorable rates of treatment success over 5 years (with stent eyes having significantly higher rates than travoprost eyes), and both groups had favorable safety. Medications were added in significantly more travoprost eyes than stent eyes during follow-up.

The IOP-lowering effect of using 2 iStents in treatment-naïve eyes with POAG was similar to a prostaglandin, which often is used as the first line of medication therapy for newly diagnosed POAG.[37] Studies report that prostaglandin analogs produce an IOP reduction of approximately 24% to 35%[38] and that prostaglandin-mediated IOP reduction is expected to endure over the long term.[39,40] The study's observation of approximately 35% IOP reduction in the travoprost group at 5



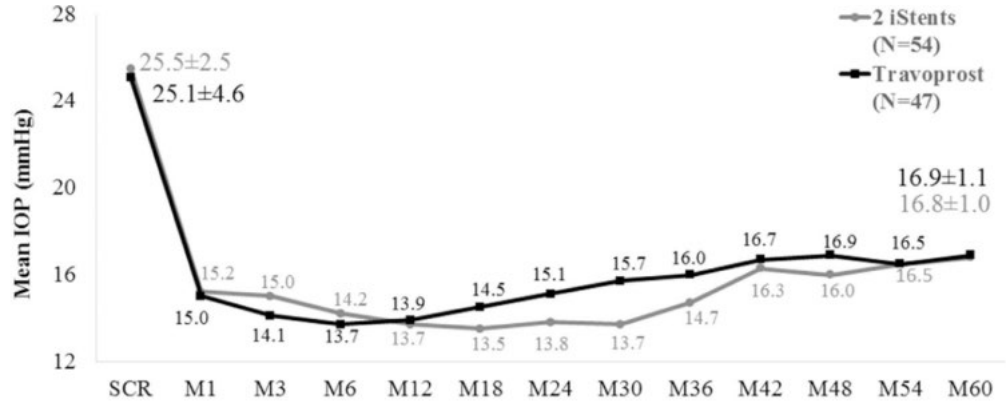
# of stent eyes at risk	50	47	45	34	29
# of travoprost eyes at risk	42	41	35	24	18

Figure 2. Time to starting add-on medication. Excludes data from eyes after cataract surgery. Add-on medication = any medication in stent group or a second medication in travoprost group. IOP = intraocular pressure; SCR = screening.

years is on the higher end of the historical range for prostaglandin therapy. This responsiveness to the first use of medication may be attributed to the fact these newly diagnosed eyes had no prior medication exposure, ocular surgery, or long-standing trabecular dysfunction.

To fully understand the IOP outcomes in this study, one must consider the timing and frequency of initiating add-on medication. Over 5 years of follow-up, add-on medication (any medication in stent eyes or a second medication in travoprost eyes) was initiated in fewer iStent eyes, and at a slower rate, than in travoprost eyes. The greatest distinction between groups began to emerge 2 years post-treatment, after which point add-on medication was initiated in approximately double the number of travoprost eyes than stent eyes. At 5 years post-treatment, although IOP outcomes remained similarly favorable in the 2 groups, approximately half the number of stent eyes versus travoprost eyes were on add-on medication.

It is pertinent to note that even if no additional medication is needed, if the IOP reduction is equivalent (such as the



2 iStents (n)	54	54	52	50	50	49	47	45	45	43	34	32	29
Travoprost (n)	47	47	44	42	42	42	41	38	35	29	24	21	18

Figure 3. Mean intraocular pressure (IOP) through 5 years postoperative for eyes without add-on medication. IOP excludes data from eyes after cataract surgery. Add-on medication = any medication in stent group or a second medication in travoprost group; M = month; n = number of eyes.

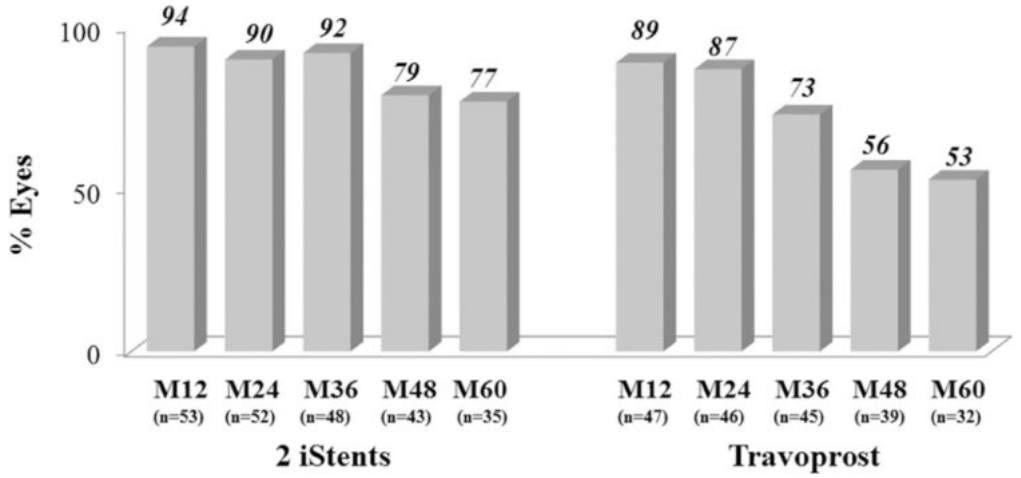


Figure 4. Eyes achieving treatment success through 5 years (intraocular pressure [IOP] 6–18 mmHg inclusive without add-on medication or secondary glaucoma surgery). Excludes data from eyes after cataract surgery. Excludes all eyes with medication added, even if IOP was in success range of 6–18 at the time it was added. Add-on medication = any medication in stent group or a second medication in travoprost group; M = month; n = number of eyes.

results seen in this study), stent eyes already could be considered to be at an advantage because their IOP control is not reliant on medication and adherence. That is, insertion of 2 iStents in treatment-naïve eyes produced prostaglandin-like IOP reductions over the same duration without the same medication side effects or adherence challenges. Furthermore, this medication-free IOP control was delivered with excellent safety and consistency over 5 years, supporting the viability of this treatment as an effective initial intervention in newly diagnosed POAG.

Both the stent and prostaglandin groups exhibited favorable safety. Because the stents were inserted as a stand-alone procedure rather than in combination with cataract surgery, the long-term safety of the device itself could be readily distinguished. In this cohort of aging, phakic subjects, the most frequent (and anticipated) AE was cataract progression. This progression appeared to be age related (rather than treatment related), given that the stent group (operated eyes) exhibited a similar rate as the medication group (nonoperated eyes) and that all cases of cataract surgery occurred at least 18 months after study treatment. In addition, the rates were consistent with U.S. population-based estimates, which report cataract progression in approximately 18% to 33% of phakic, similarly aged subjects over 3.5 years of follow-up.[41] Although rates of cataract progression were similar in the 2 study groups, the rate of cataract surgery was higher in stent eyes than in travoprost eyes. This may be due to increased patient willingness to undergo cataract surgery after undergoing one surgery already (stent implantation). It also could be due to strengthened patient trust in the surgeon after experiencing positive outcomes of the initial stent surgery. No patients experienced

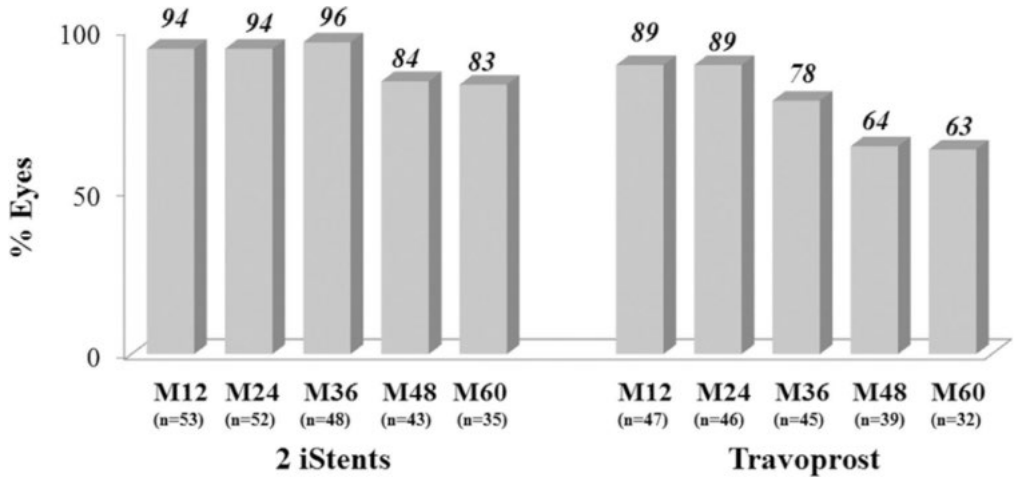


Figure 5. Eyes achieving 5-year unmedicated intraocular pressure (IOP) of 6–18 mmHg without secondary glaucoma surgery, including eyes with medication added for non-IOP reasons. Excludes data from eyes after cataract surgery. Includes data from eyes with medication added because of optic nerve findings, despite IOP within target of 6 to 18 mmHg. This includes 2 stent eyes (IOP 16 and 18, respectively) and 3 travatan eyes (IOP 18). M = month; n = number of eyes; Preop = preoperatively.

Table 3. Adverse Events and Post-treatment Surgery during 60 Months of Follow-up

	Stent Group (54 Eyes Total) n (% of Total)	Travoprost Group (47 Eyes Total) n (% of Total)
Intraoperative Ocular AEs		
Hyphema	1 (2%)	N/A
Iridodialysis	1 (2%)	N/A
Post-treatment Ocular AEs:		
Cataract progression	16 (30%)	15 (32%)
Conjunctival hyperemia	0 (0%)	1 (2%)*
Secondary glaucoma surgery	0 (0%)	0 (0%)
Cataract surgery†	16 (30%)	9 (19%)
Death (unrelated to study)	2 (4%)	1 (2%)

AE = adverse event; N/A = not applicable.
*Occurred 36 months after starting topical travoprost; did not result in any intervention or discontinuation of the medication.
†All cataract surgeries occurred ≥18 months after stent surgery or travoprost initiation.

complications or AEs as would be associated with conventional glaucoma-filtering procedures, such as endophthalmitis, bleb formation, hypotony, and fibrosis.

This study used 2 stents in lieu of 1 stent, which may have contributed to the favorable outcomes. The use of 2 stents is thought to increase circumferential flow and allow access to more collector channels, thereby further increasing the physiologic flow of aqueous humor into the episcleral venous system.[42] This physiologic mechanism is consistent with side-by-side comparative clinical data showing greater IOP and medication reductions with multiple versus single stents, and the suggestion that 3 stents may provide additional benefit over 2 stents for up to 3.5 years after surgery.[16,17] Thus, a possible point for further investigation in our study would be to implant a third stent in lieu of add-on medication in eyes with uncontrolled IOP during follow-up after implanting the initial 2 iStents.

This study has several potential limitations. Endothelial cell data were not included as part of the study protocol; however, there were no cases of corneal edema, decompensation, or surgery over the 5 years of follow-up. Clinical determinations of cataract severity and surgical need were made by the primary investigator and based on patient needs and desires. Standardized cataract grading was not part of the protocol. Despite this possibility for bias, the level of visual impairment was similar in the 2 groups at the time of cataract diagnosis. Inherent to the study design, treatment groups could not be masked; however, measurement bias was limited by completing 2-observer masked IOP readings and mean diurnal IOP measurements. Possible regression to the mean could have occurred because the protocol did not require screening IOP to be measured on 2 separate days before beginning the study, and during follow-up, it did not mandate a second consecutive study visit when IOP fell outside the limits for treatment success. Preoperatively, we expect this should have occurred equally in both treatment arms. Postoperatively, because travoprost efficacy depends on compliance (whereas iStent efficacy does not), measuring IOP at a single postoperative visit (when patients taking travoprost could have missed their drops) could negatively affect the travoprost group more than the iStent group. This limitation reflects real-world clinical practice where medical therapy depends on adherence, an issue that can be avoided or minimized with surgical treatment. The study included an entirely white population in Armenia, and thus the results may not be directly transferrable to other populations. However, any potential impact of race on study outcomes would be expected to occur similarly in both study arms, so the study's observed between-group comparisons still hold weight. The study was conducted at a single site; however, variability was afforded because of the involvement of 13 different highly trained international glaucoma surgeons in the study.

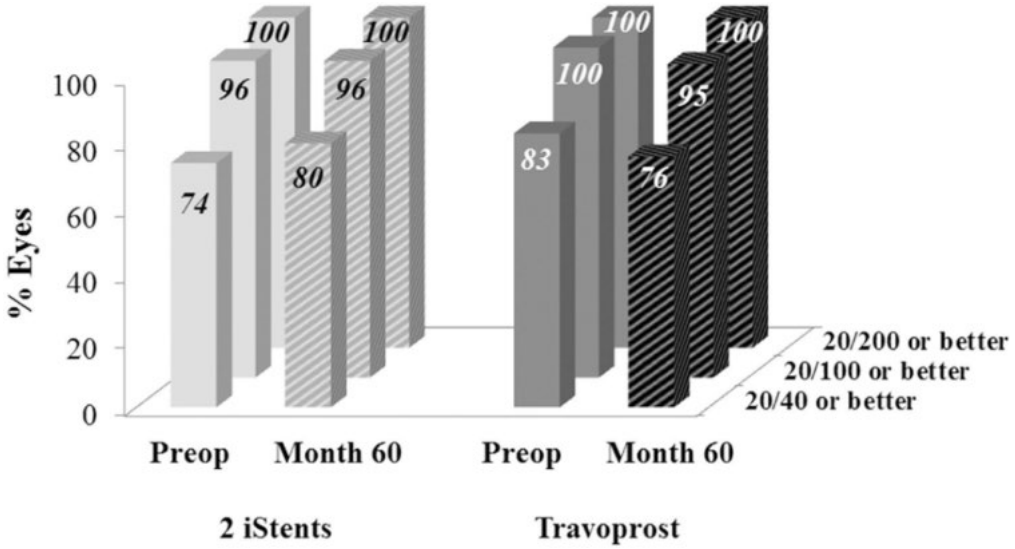


Figure 6. Proportional analysis of best-corrected visual acuity (BCVA) through 5 years postoperative. Preop = preoperative.

Table 4. Screening and Annual Postoperative Cup-to-Disc Ratio, Visual Field, and Central Corneal Thickness in All Available Eyes at Each Visit Regardless of Add-on Medication* or Cataract Surgery

	Screening	Month 12	Month 24	Month 36	Month 48	Month 60
2-iStent Group (Total Number of Eyes = 54)						
n	54	53	53	53	51	49
C:D ratio Mean (SD)	0.7 (0.2)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)
VF - MD (dB) Mean (SD)	−7.5 (8.8)	−7.7 (8.9)	−6.0 (9.7)	−7.2 (8.1)	−7.5 (7.6)	−7.8 (7.9)
VF - PSD (dB) Mean (SD)	4.6 (3.3)	4.4 (3.1)	4.7 (3.2)	4.2 (2.9)	4.4 (2.9)	4.6 (2.9)
Corneal thickness (μm) Mean (SD)	552.6 (41.2)	547.1 (41.6)	549.0 (43.9)	551.0 (43.7)	554.8 (41.6)	555.6 (41.2)
Travoprost Group (Total Number of Eyes = 47)						
n	47	47	47	46	42	41
C:D ratio Mean (SD)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
VF - MD (dB) Mean (SD)	−5.8 (7.7)	−6.3 (7.6)	−5.5 (7.7)	−6.3 (6.5)	−7.5 (7.2)	−7.5 (7.5)
VF - PSD (dB) Mean (SD)	3.5 (2.6)	3.5 (2.6)	3.4 (2.4)	3.6 (2.5)	4.1 (2.8)	4.2 (2.9)
Corneal thickness (μm) Mean (SD)	540.3 (59.2)	544.6 (59.3)	545.2 (59.2)	547.5 (60.4)	551.2 (60.2)	553.3 (60.2)

C:D = cup-to-disc; dB = decibels; MD = mean deviation; n = number of eyes; PSD = pattern standard deviation; SD = standard deviation; VF = visual field.
*Add-on medication = any medication in stent group, or a second medication in travoprost group.

Limitations notwithstanding, the study contributes to our understanding of long-term safety and efficacy of trabecular bypass stents as initial therapy for newly diagnosed open-angle glaucoma. The treatment population is novel; to our knowledge this is possibly the first study evaluating 2 trabecular stents in glaucomatous eyes naïve to medication or surgical treatment. The study includes data from a relatively large patient population with a long duration of follow-up (5 years). The study had an active-control comparator group, a prospective, randomized design, and completion of diurnal IOP measurements. More than a dozen highly experienced glaucoma surgeons were involved, thereby minimizing bias that could result from a single-provider protocol. The data from this long-term, prospective, randomized, controlled, multi-surgeon study support the safety and effectiveness of inserting 2 iStents as an initial stand-alone therapy for patients with newly diagnosed, treatment-naïve, open-angle glaucoma. Over the duration of 5 years, 2 iStents were comparable to travoprost in both safety parameters and controlling IOP and medication burden.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **C:D** = cup-to-disc; **dB** = decibels; **IOP** = intraocular pressure; **MD** = mean deviation; **MIGS** = micro-invasive glaucoma surgery; **POAG** = primary open-angle glaucoma; **VF** = visual field.

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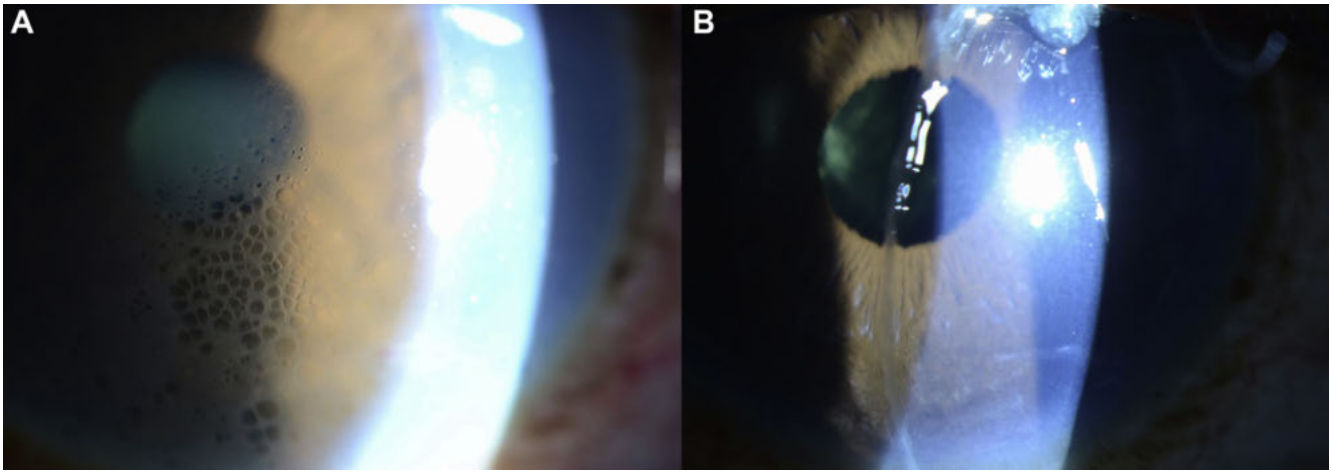
Pictures & Perspectives



Netarsudil-Associated Reticular Corneal Epithelial Edema with Raised Intraocular Pressure

A 55-year-old woman with uveitic glaucoma presented with left eye intraocular pressure (IOP) of 34, visual acuity (VA) 20/30, clear cornea, and quiet anterior chamber. Netarsudil was added to maximum medical therapy. Two weeks later, the patient presented urgently with IOP of 41 and corneal microcystic edema (MCE). Anterior chamber paracentesis was performed, and methazolamide was started. Three days later, VA was 20/60 and IOP 20 with inferior reticular epithelial edema (Fig **A**). Corneal findings resolved with VA 20/20 after netarsudil discontinuation (Fig **B**). Similar corneal findings were reported after netarsudil use in patients with corneal edema and failed corneal endothelial keratoplasty. (Magnified version of Fig **A**-**B** is available online at www.aaojournal.org).

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