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Long-term Outcomes from the HORIZON Randomized Trial for a Schlemm's Canal Microstent in Combination Cataract and Glaucoma Surgery

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Purpose: To present the 5-year results of the HORIZON trial comparing cataract surgery (CS) combined with an intracanalicular microstent with CS alone.

Design: Prospective, multicenter, controlled randomized clinical trial.

Participants: Patients with cataract and primary open-angle glaucoma treated with 1 or more glaucoma medications, washed-out diurnal intraocular pressure (DIOP) of 22 to 34 mmHg, and no prior incisional glaucoma surgery.

Methods: Eyes were randomized 2:1 to receive a Hydrus Microstent (HMS; Ivantis, Inc) or no stent after successful CS.

Main Outcome Measures: Intraocular pressure (IOP), glaucoma medication use, repeat glaucoma surgery, visual acuity, visual field, procedure-related adverse events, and corneal endothelial cell counts.

Results: Three hundred sixty-nine eyes were randomized to HMS treatment, and 187 eyes were randomized to CS only. Study groups were well matched for preoperative IOP, medication use, washed-out DIOP, and glaucoma severity. Five-year follow-up was completed in 80% of patients. At 5 years, the HMS group included a higher proportion of eyes with IOP of 18 mmHg or less without medications than the CS group (49.5% vs. 33.8%; $P = 0.003$), as well as a greater likelihood of IOP reduction of 20% or more without medications than the CS group (54.2% vs. 32.8%; $P < 0.001$). The number of glaucoma medications was 0.5 ± 0.9 in the HMS group and 0.9 ± 0.9 in the CS group ($P < 0.001$), and 66% of eyes in the HMS group were medication free compared with 46% in the CS group ($P < 0.001$). The cumulative risk of incisional glaucoma surgery was lower in the HMS group (2.4% vs. 6.2%; $P = 0.027$, log-rank test). No clinical or statistically significant differences were found in the rate of endothelial cell loss from 3 to 60 months between the HMS and CS alone groups ($P = 0.261$).

Conclusions: The addition of a Schlemm's canal microstent in conjunction with CS was safe, resulted in lowered IOP and medication use, and reduced the need for postoperative incisional glaucoma filtration surgery compared with CS after 5 years. Long-term presence of the implant did not affect the corneal endothelium adversely. *Ophthalmology 2022;129:742-751 © 2022 by the American Academy of Ophthalmology*

Supplemental material available at www.aaojournal.org.

The number of people affected by blindness resulting from age-related cataract and glaucoma remains a major worldwide health problem.[1] Combined glaucoma surgery and cataract surgery (CS) has become increasingly common in North America with the introduction of minimally invasive glaucoma surgery (MIGS) devices and techniques. Although several angle surgery devices and techniques have been described,[2] only Schlemm's canal stents have demonstrated safety and effectiveness in Food and Drug Administration clinical studies.[3,4] As a result, glaucoma surgery is being performed in patients with early- and moderate-stage glaucomatous disease who are not suitable candidates for higher-risk filtration procedures. The near-term impact of these devices has been to reduce medication burden.[5]

Two previously reported randomized studies for the Hydrus Microstent (HMS; Ivantis, Inc) showed that implantation of the device significantly reduced intraocular pressure (IOP) and medication use in patients with primary open-angle glaucoma over the short- and medium-term and that the effectiveness margin improved compared with the control treatment from year 1 to year 2.[3,6] These clinical findings were consistent with laboratory studies that demonstrated that implantation of the HMS device increases outflow facility.[7]

https://doi.org/10.1016/j.ophtha.2022.02.021
ISSN 0161-6420/22

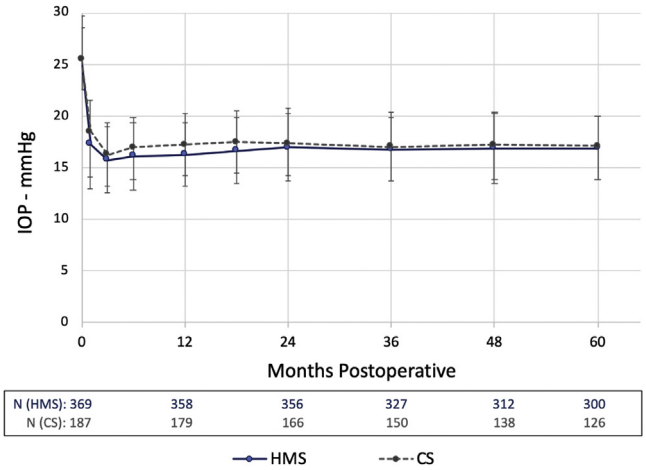

Figure 1. Graph showing the mean intraocular pressure (IOP) at each visit throughout the study. Patients with any secondary IOP-lowering procedure are excluded. Error bars are standard deviations. CS = cataract surgery; HMS = Hydrus Microstent.

In procedures where intervention is performed at an early disease stage, safety outcomes are especially important. The HORIZON trial[8] followed up the randomized cohorts for 5 years to assess long-term outcomes. Three-year follow-up from this study showed that eyes undergoing HMS implantation were less likely to require subsequent incisional glaucoma surgery than eyes randomized to CS alone. The objective of this report is to provide 5-year safety and effectiveness results, including impact on the corneal endothelial cell layer.

Methods

Study Design and Inclusion Criteria

The HORIZON study was a prospective, multicenter, single-masked, randomized controlled clinical trial. The study was conducted at 38 investigational centers worldwide (26 sites in the United States and 12 international sites). The study protocol was approved by the governing institutional review board or ethics committee at all participating centers[3] and by national regulatory agencies where applicable. The study was conducted according to the principles described in the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act and local patient privacy protection regulations. All study participants provided written informed consent before initiating study procedures and including follow-up for 5 years after surgery. The study is registered in the National Library of Medicine database (http://www.clinicaltrials.gov; identifier, NCT01539239).

Study oversight, randomization, washout, and surgical procedures have been described previously.[3] Briefly, patients with age-related cataract and a diagnosis of mild to moderate primary open-angle glaucoma receiving 1 to 4 topical hypotensive medications were enrolled prospectively into the study. Eligible patients demonstrated ophthalmoscopically detectable glaucomatous optic neuropathy, mild to moderate visual field (VF) loss as defined by Hodapp–Anderson–Parrish criteria,[9] best-corrected visual acuity (BCVA) of 20/40 or worse with or without brightness acuity testing, Schaffer grade III or IV angle width in all 4 quadrants, and a medicated IOP of 31 mmHg or less. After washout of all hypotensive medications, continuation to randomization required a mean diurnal IOP (defined as the average of 3 Goldman tonometry measurements obtained at 8 AM, 12 PM, and 4 PM) of between 22 and 34 mmHg.

Patients with angle-closure glaucoma, any secondary glaucoma, a VF mean deviation worse than −12 decibels (dB), exudative age-related macular degeneration, proliferative diabetic retinopathy, or significant risk of glaucomatous progression because of washout of IOP-lowering medications were excluded. Anatomic exclusion criteria were a narrow anterior chamber angle (Shaffer grade I or II) or another angle abnormality visible on gonioscopy, central corneal thickness of < 480 µm or > 620 µm, or clinically significant corneal dystrophy. Patients who underwent prior corneal surgery, cycloablation, or any incisional glaucoma procedure, such as trabeculectomy, tube shunt implantation, deep sclerectomy, or canaloplasty, also were excluded. Prior selective laser trabeculoplasty (SLT) was allowed, but patients who had undergone prior argon laser trabeculoplasty were excluded.

Postoperative study visits were scheduled at 1, 7, and 30 days and then at 3, 6, 12, 18, 24, 36, 48, and 60 months. Follow-up procedures

Table 1. Medication-Free Rates Stratified by Preoperative Medication Count

Preoperative Count	2 Years		3 Years		4 Years		5 Years	
	Hydrus Microstent Group	*Cataract Surgery Alone Group*	*Hydrus Microstent Group*	*Cataract Surgery Alone Group*	*Hydrus Microstent Group*	*Cataract Surgery Alone Group*	*Hydrus Microstent Group*	*Cataract Surgery Alone Group*
No. of patients	357	170	332	153	319	144	308	134
No. of medications (%)								
1	88	48	79	48	71.0	42.3	72.7	47.9
2	79	61	74	56	71.3	44.7	65.4	52.3
3 or 4	51	30	51	33	36.5	27.6	46.8	33.3
Overall medication free (%)	78	48	72	46	64	40	66	46
P value*	< 0.0001		< 0.0001		< 0.0001		0.0002	
IOP (mmHg)†	16.6 ± 3.2	17.4 ± 2.8	16.4 ± 3.2	17.1 ± 3.1	16.7 ± 3.1	17.3 ± 3.2	16.6 ± 3.2	17.6 ± 3.6

IOP = intraocular pressure.
*Overall medication-free rate between groups.
†Mean ± standard deviation IOP of unmedicated eyes with no repeat interventions.

Table 2. Five-Year Effectiveness Outcomes

	Hydrus Microstent Group	Cataract Surgery Alone Group	P Value
No. of patients	308	134	—
Medication-free eyes, %	66	46	< 0.001
Change in IOP vs. before surgery (mmHg), mean ± SD	−8.3 ± 3.8	−6.5 ± 4.0	< 0.001
Medication free, %			
≤ 18 mmHg IOP	49.5	33.8	0.003
≥ 20% IOP reduction	54.2	32.8	< 0.001
≥ 30% IOP reduction	39.6	17.2	< 0.001
≥ 40% IOP reduction	17.5	9.0	0.020

IOP = intraocular pressure; SD = standard deviation; − = *P*-value is not applicable.

included slit-lamp examination with gonioscopy, fundus examination, BCVA measurement, and IOP assessment with Goldmann applanation tonometry. Medications were allowed throughout the study as needed to reach IOP targets. A medication washout was carried out at months 12 and 24 to permit assessment of full unmedicated diurnal IOP. For reasons related to cost and time burden on the patient and investigational site staff, washed-out IOP assessment was not repeated after 24 months. Perimetry testing and specular microscopy were repeated at each annual visit from 2 to 5 years.

Mean central corneal endothelial cell density (ECD) was determined by analyzing specular microscopic images (CellChek; Konan Medical, Inc) obtained at baseline and then repeated at least annually through 5 years. Triplicate images of the central endothelium were obtained for each eye at each time point. Images were analyzed at an independent reading center masked to the treatment assignment of the study eye (Cornea Image Analysis Reading Center, University Hospitals Eye Institute, Cleveland, OH). Cell counts were determined by 2 certified readers masked to the study group using the Konan Center method; ≥ 5% differences were resolved by adjudication with a third reader. The effects of MIGS devices on the corneal endothelium has become an important metric requiring careful monitoring and reporting. Accordingly, it is important to emphasize that, although other components of the HORIZON trial were single masked, readers were masked to the study group for all specular microscopy images.

Outcome Measures

Long-term outcome measures included surgical success rate (20% reduction in IOP without medications or IOP of ≤18 mmHg), mean IOP, need for glaucoma medical therapy, repeat glaucoma surgery, loss of visual acuity, VF progression, procedure-related adverse events, and corneal endothelial cell counts. An adverse event was defined as any surgical complication or untoward finding relating to the patient's vision or ocular health, regardless of whether it was related to the device or the procedure. Loss of 2 lines or more of BCVA or 2.5 dB or more of VF were defined as adverse events. Endothelial cell density findings were expressed as means, percentage change from previous time points, and frequency of 30% loss from baseline at respective follow-up time points.

A repeat glaucoma surgery was defined as a major surgical intervention for IOP lowering, such as trabeculectomy (or gel stent implantation), glaucoma drainage device implantation, or transscleral cyclophotocoagulation. Because investigators were not masked to treatment assignment, a potential for bias existed in the decision to perform subsequent surgery. Therefore, an adjudication committee comprising 5 independent glaucoma specialists (I.I.K.A., D.R., T.W.S., G.G.) masked to the treatment group reviewed each case for surgical necessity (Table S1 and S2, available at www.aaojournal.org). Other IOP-lowering procedures (such as SLT, endoscopic cyclophotocoagulation, needling, and membranectomy or laser goniotomy) were not considered major glaucoma surgery.

Statistical Analysis

Continuous variables were analyzed using means and standard deviations. Between- and within-group differences were tested with the use of 2-sample *t* tests. For categorical variables, counts and percentages are presented according to treatment group; values were compared with the use of the Fisher exact test for binary variables. Hazard ratios were calculated using the Cox proportional hazards model. Comparisons of cumulative rate of failure and reoperation for glaucoma were assessed with Kaplan−Meier survival analysis. Long-term endothelial cell count changes were assessed using linear regression analysis. A *P* value of 0.05 was considered statistically significant in the analysis.

Results

A total of 556 eyes were randomized to either HMS with CS (n = 369) or CS alone (n = 187). Baseline participant demographic and preoperative characteristics were described previously and also are provided in Table S1 (available at www.aaojournal.org). No significant differences were found between the 2 groups with regard to these baseline variables.

Before surgery, mean ± standard deviation IOP was 17.9 ± 3.1 mmHg in the HMS group and 18.1 ± 3.1 mmHg in the CS group ($P = 0.55$). Approximately half of all participants were taking 1 topical medication, with the other half taking 2 or more medications at the time of initial screening (average, 1.7 ± 0.9 in both groups). The mean baseline unmedicated diurnal IOP after washout was 25.5 ± 3.0 mmHg in the HMS group and 25.4 ± 2.9 mmHg in the CS group ($P = 0.89$).

Five-year follow-up was completed for 308 of 369 participants (83.4%) in the HMS group and 134 of 187 participants (71.7%) in the CS group (details of follow-up from 1 to 5 years can be found in Table S2, available at www.aaojournal.org). All patients who completed the 5-year postoperative examination or who demonstrated secondary glaucoma surgery within the follow-up period were included in this analysis. Because patients who underwent secondary procedures were counted as treatment failures using dichotomous success criteria, IOP and medication counts for these patients were not included in the calculation of overall mean IOP and medications use after the secondary procedure.

Throughout the follow-up period, mean IOP was similar and stable between the groups (Fig 1). At 5 years, the mean ± standard deviation IOP was 16.8 ± 3.1 mmHg in the HMS group and 17.2 ± 3.2 mmHg in the CS group ($P = 0.24$). A consistent difference

Table 3. Postoperative Intraocular Pressure-Lowering Procedures (n = 369 Patients Undergoing Hydrus Microstent Implantation and n = 187 Patients Undergoing Cataract Surgery Alone)

	1 Year		2 Years		3 Years		4 Years		5 Years		Cumulative	
	Hydrus Microstent Group	*Cataract Surgery Alone Group*	*Hydrus Microstent Group*	*Cataract Surgery Alone Group*	*Hydrus Microstent Group*	*Cataract Surgery Alone Group*	*Hydrus Microstent Group*	*Cataract Surgery Alone Group*	*Hydrus Microstent Group*	*Cataract Surgery Alone Group*	*Hydrus Microstent Implantation*	*Cataract Surgery Alone*
No. (%) of patients undergoing a major surgical intervention*	**0 (0)**	**1 (0.5)**	**1 (0.3)**	**3 (1.6)**	**1 (0.3)**	**1 (0.5)**	**4 (1.1)**	**4 (2.1)**	**3 (0.8)**	**1 (0.5)**	**8 (2.1)**	**10 (5.3)**
No. of events†												
Trabeculectomy		1	1	1		1	2	3	3		6	6
Tube shunt		1		2	1						1	3
Gel stent							1	1			1	1
Other procedures		1								1	0	2
TSCPC			1								1	0
No. (%) of patients undergoing other IOP-lowering procedures*	**3 (0.8)**	**2 (1.1)**	**1 (0.3)**	**1 (1.1)**	**3 (0.8)**	**3 (1.6)**	**4 (1.2)**	**1 (0.5)**	**1 (0.3)**	**1 (0.5)**	**12 (3.3)**	**8 (5.3)**
No. of events†												
SLT				2	2	3	3	2	1		6	7
ECP							1				1	0
Membranectomy or laser goniotomy	3		1		1					3	5	3
Needling or bleb revisions						1		1		1	0	3
Paracentesis > 7 days after surgery	1	5									1	5

ECP = endoscopic cyclodestructive procedure; IOP = intraocular pressure; SLT = selective laser trabeculoplasty; TSCPC = transscleral cyclophotocoagulation.
Boldface distinguishes the number (and %) of patients with any event from the number of events.
*Patients with at least 1 event. A single patient may have > 1 event.
†Other surgical interventions include deep sclerectomy and express shunt removal. Patients may have multiple events.

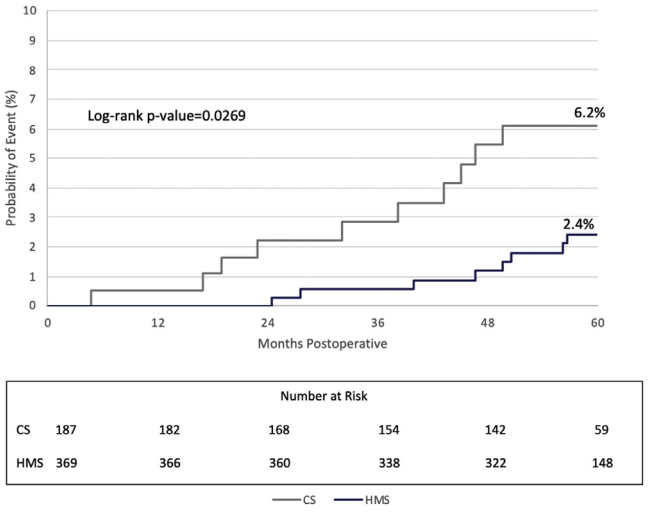

Figure 2. Graph showing the cumulative risk of a major surgical intervention for glaucoma (bleb-forming procedures or transscleral cyclophotocoagulation). CS = cataract surgery; HMS = Hydrus Microstent.

was found in medication count in favor of the HMS group over the period, with mean medications at 0.5 ± 0.9 in the HMS group and 0.9 ± 0.9 in the CS group (difference, 0.4 medications; $P < 0.001$). From the 1-year to 5-year follow-up, the mean medication count increased by 0.2 in both groups, resulting in no change in the between-group margin over the course of the study.

Significantly more eyes in the HMS group remained medication free at 5 years than in the CS group (66% vs. 46%; difference, 20%; $P < 0.001$). Eyes receiving 1 or 2 medications before surgery were more frequently medication free after surgery than eyes receiving 3 or 4 medications (Table 1). Eyes in the HMS group, whether receiving 1, 2, 3, or 4 medications, became medication free more often than eyes in the CS alone group.

Because of the greater reduction in the need for medications, the HMS group demonstrated significantly higher rates of procedure success relative to the CS group. As shown in Table 2, among eyes that remained medication free, a greater mean IOP reduction was found than preoperative washed-out diurnal IOP (−8.3 ± 3.8 mmHg vs. −6.5 ± 4.0 mmHg; $P < 0.001$), and significantly more eyes in the HMS group maintained an IOP of 18 mmHg or less (49.5% vs. 33.8%; $P = 0.003$). Additionally, the fraction of eyes with medication-free reductions in IOP of 20%, 30%, and 40% versus preoperative levels consistently was greater in the HMS group than the CS group.

Secondary IOP-Lowering Procedures

A summary of IOP-lowering procedures is provided in Table 3. Twenty-two events occurred in 18 eyes (4.9%) in the HMS group, and 30 events occurred in 14 eyes (7.5%) in the CS group. As shown in Table 3, through 5 years, 8 eyes in the HMS group and 10 eyes in the CS group required major glaucoma surgery, a significant reduction in the event rate (hazard ratio, 0.365; 95% confidence interval, 0.144−0.926; $P = 0.034$). All glaucoma surgeries were adjudicated as clinically warranted because of worsening glaucoma by the HORIZON Clinical Events Committee. As shown in Figure 2, Kaplan−Meier survival analysis showed a significant increase in the risk of major incisional surgery between groups at 5 years (6.2% vs. 2.4%; $P = 0.027$, log-rank test). Among other IOP-lowering procedures, SLT was the most common procedure in both study groups, occurring twice as frequently in the CS group (1.6% vs. 3.7%; $P = 0.12$). Procedures secondary to trabeculectomy or tube shunts such as bleb needling, revisions, or paracenteses also were less frequent in the HMS group.

Safety

Vision and ocular health were assessed at each visit. As shown in Table 4, very few new adverse findings occurred in the late follow-up period. After 5 years, cumulative BCVA loss of 2 lines or more was 1.9% in the HMS group and 2.1% in the CS group. A loss of 2.5 dB or more in VF mean deviation was defined as an adverse finding in the protocol. This condition was met in 8.4% of HMS eyes and 9.6% of CS eyes. No late observations of inflammation, corneal edema, or a need for device removal were observed. The only long-term findings uniquely related to the device were focal peripheral anterior synechiae (PAS) or tissue adhesions near the trabecular entry point. The percentage of patients with PAS in the CS group was 3.7% and in the HMS group 14.6% ($P = 0.0001$). No differences were found in IOP control between those with and without PAS (16.9 ± 3.3 mmHg vs. 16.6 ± 3.5 mmHg; $P = 0.49$). A patient questionnaire was conducted at 2 years and found no differences in ocular discomfort or pain between study groups. This assessment was not repeated at the 5-year mark; however, no adverse events related to pain or other discomfort were reported.

ECD Findings

Mean central ECD findings are presented in Figure 3. Mean ± standard deviation central ECD at baseline was 2417 ± 390 cells/mm^2 in the HMS group and 2426 ± 371 cells/mm^2 in the CS group ($P = 0.81$). At the first postoperative evaluation (3 months), the mean endothelial cell counts were 2086 ± 519 cells/mm^2 (95% confidence interval, 2032−2140 cells/mm^2) in the HS group and 2162 ± 444 cells/mm^2 (95% confidence interval, 2097−2227 cells/mm^2) in the CS group ($P = 0.09$), representing endothelial cell loss (ECL) of 13% and 11% in the respective groups compared with preoperative measurements. The between-group difference was not statistically significant ($P = 0.08$, t test). A modest but significant decline in ECD was found in both groups from 3 months to 5 years. The last observed mean counts were 1967 ± 522 cells/mm^2 ($P \leq 0.01$ vs. 3 months) and 2117 ± 442 cells/mm^2 ($P < 0.01$ vs. 3 months) in the HMS and CS groups, respectively.

The rate of change in ECD is a better indicator of corneal stability than the cell density value alone.[10] As shown in Figure 4, year-to-year ECL ranged from 0% to 2% in the HMS group and 0% to 1% in the CS group (note that the change indicated in year 1 is from the 3-month postoperative visit). The rate of yearly change was evaluated using linear regression, and no clinical or statistically significant difference was found in the rate of ECL from 3 to 60 months between the HMS and CS groups ($P = 0.261$). Additionally, no shift toward increased ECL was found in years 4 or 5 compared with prior years.

A loss of 30% or more in ECD is considered a threshold for significant change.[11] At 3 months, 30% or more loss was observed in 17.3% of eyes in the HMS group and 9.4% of eyes in the CS group, a between-group difference of 7.9% ($P = 0.01$). Over the 5-year follow-up period, the proportion of eyes with 30% ECL increased to 20.8% ($P = 0.27$ vs. 3 months) in the HMS group and 10.6% ($P = 0.85$ vs. 3 months) in the CS group. A logistic regression analysis showed no difference in the rate of change in 30% or more ECL between the groups in the postoperative period from 3 months to 5 years ($P = 0.82$). None of the eyes with 30% or more ECL in either group had associated corneal edema, decompensation, or other clinical sequelae.

Table 4. Adverse Events

Adverse Event	Cumulative Events								
	2 Years		3 Years		4 Years		5 Years		
							% (95% Confidence Interval)		
	Hydrus Microstent Group	Cataract Surgery Alone Group	Hydrus Microstent Group	Cataract Surgery Alone Group	Hydrus Microstent Group	Cataract Surgery Alone Group	Hydrus Microstent Group, % (95% Confidence Interval)	Cataract Surgery Alone Group,	P Value
BCVA loss of ≥ 2 ETDRS lines ≥ 3 mos	1.4	1.6	1.6	2.1	1.9	2.1	1.9 (0.8–3.9)	2.1 (0.6–5.4)	1.0
Worsening in visual field MD ≥ 2.5 dB	4.3	5.3	6.2	8.6	7.3	9.1	8.4 (5.8–11.7)	9.6 (5.8–14.8)	0.63
Inflammation requiring additional steroids > 1 mo	5.9	3.7	5.9	3.7	5.9	3.7	5.9 (3.8–8.9)	3.7 (1.5–7.6)	0.27
Peripheral anterior synechiae	10.6	2.1	12.4	3.2	13.5	3.2	14.6 (11.2–18.7)	3.7 (1.5–7.6)	0.0001
Device-related events									
Postoperative malposition	1.4	—	1.4	—	1.4	—	1.4 (0.4–3.1)	—	
Peripheral anterior synechiae with device obstruction	3.5	—	4.3	—	5.1	—	5.4 (3.3–8.3)	—	
Device obstruction, partial or complete	7.3	—	7.6	—	8.4	—	8.4 (5.8–11.7)	—	
Device removal	0	—	0	—	0	—	0	—	

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; MD = mean deviation; — = not applicable.
Data are presented as percentages unless otherwise indicated. The most frequent adverse events occurred at 3 years.

Discussion

This study is the longest continuous follow-up of a pivotal MIGS randomized clinical trial; 442 of 556 eyes (80%) completed 5 years of follow-up. The data demonstrate that the implantation of the HMS in conjunction with CS is associated with a sustained, clinically significant reduction in the number of medications required to maintain a therapeutic IOP compared with CS alone over the course of 5 years after surgery. No statistically significant difference was found in medicated IOP between the 2 groups at 5 years. This was expected because clinicians were allowed to add medications to reach target IOP as necessary; however, medication elimination was maintained at significantly higher rates at 5 years in the HMS group than the CS group. There was a greater proportion of eyes without medications and an IOP of 18 mmHg or less, as well as with IOP reductions of 20%, 30%, or 40%, in the HMS group than in the CS alone group. A lower proportion of patients who received the HMS needed to undergo further glaucoma surgery because of glaucomatous disease progression or poor IOP control versus those who underwent CS alone. For these reasons, HMS implantation combined with CS has been shown to be cost-effective and to maintain a favorable quality-adjusted life year compared with CS alone.[12]

The 2-year findings from the HORIZON study showed that HMS implantation combined with CS provided a statistically and clinically significant reduction in unmedicated diurnal IOP compared with cataract CS alone. Although the 5-year results do not include medication washout, the IOP and medication use are consistent with the 1- and 2-year findings. The mean IOP of unmedicated eyes was consistently lower in the HMS versus CS eyes, and mean change in IOP from baseline remained greater, suggesting that investigators treated the study groups similarly in terms of adding medications.

Medication use is an area that is often underestimated when it comes to impact on patient quality of life and is a critical consideration in assessing outcomes for MIGS devices in combination with CS. Adherence has been shown to drop for multiple medication regimens.[13] Reduction in the number of glaucoma medications lessens the burden of medication-related adverse effects and may promote better adherence, which in turn may reduce the risk of disease progression and the need for further surgery. Consistent with the 2- and 3-year findings, the drop-free rate was proportional to the starting medication count, especially for

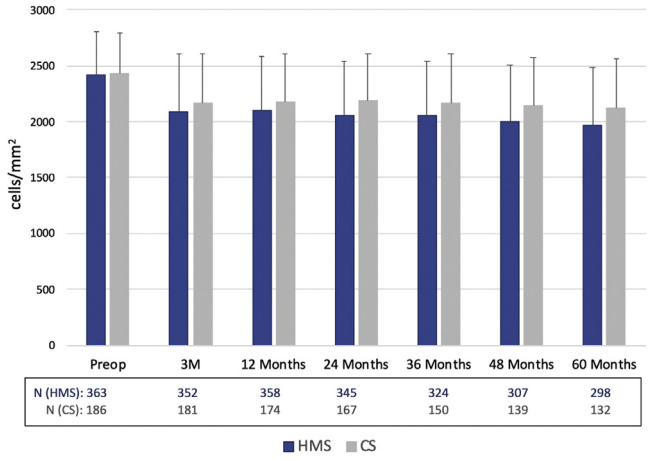

Figure 3. Bar graph showing the mean central endothelial cell density. Error bars are standard deviations. CS = cataract surgery; HMS = Hydrus Microstent; M = months; Preop = before surgery.

the HMS group. Eyes requiring only a single medication for pressure control before surgery reached a higher rate of drop-free IOP control than eyes receiving multiple drops. Even among eyes receiving maximum preoperative medical therapy (3 or 4 classes of medications), 59% were receiving fewer medications at 5 years, and 48% were completely medication free in the HMS group.

A finding of particular interest in this study is that, among a cohort of patients with predominantly mild glaucoma that was controlled with 1 or 2 topical medications, a significant proportion needed invasive glaucoma surgery over 5 years, particularly in the CS group. Filtering surgery is a major escalation in therapy associated with significant side effects, refractive and anatomic alterations, and resultant life-altering behavioral modifications.[14–16] Kaplan–Meier time-to-event analysis demonstrated that the risk of surgery was reduced by more than half in HMS group over the course of follow-up. Combined with reduced dependency on topical medications and lack of significant long-term complications, HMS treatment has a durable, significant impact on the quality of life and the long-term consequences faced by patients with early-stage glaucoma.

A number of possible explanations exist for the difference in secondary surgical intervention rates between the study groups. Poor long-term adherence to treatment regimens is observed commonly in patients with glaucoma[17] and may be associated with subsequent visual loss and irreversible optic nerve damage. The lower average medication use as well as the higher frequency of eyes that achieved drop-free IOP control in the HMS group likely will translate into improved patient well-being both with regard to slowing disease progression and improved patient quality of life.[18] A similar finding was observed in a study comparing the use of first-line SLT versus medical therapy for early-stage glaucoma.[19] An analysis of VF data from this study showed greater VF progression in patients treated first with medical therapy than in those treated first with SLT.[20] This finding could be related to the advantage of more frequent drop-free IOP control in the SLT group.

Reduced diurnal IOP fluctuation in surgically versus medically controlled IOP may be another possible explanation for the lower secondary glaucoma surgery rates in the HMS group. Additionally, a 24-hour assessment of the circadian rhythm of IOP using a contact lens sensor in patients with open-angle glaucoma showed that the signal fluctuation range was significantly smaller in patients treated surgically (e.g., with the EX-PRESS shunt or HMS implantation) than in the medically treated group.[21]

Overall, BCVA and ocular health findings did not differ between the 2 groups. Visual recovery was rapid and loss of 2 lines or more of vision was observed in only 2% of eyes in both groups after 5 years of follow-up. The only adverse finding unique to the HMS group was the formation of PAS or adhesions near the device. It is important to note that the presence of PAS was determined by gonioscopy and was not related to IOP. Potentially obstructive versus nonobstructive status was determined by whether the device inlet could be visualized. Presence of PAS was not associated with loss of device function as determined by IOP or other adverse events.

The authors observed an ECL of 13% and 11% in the HMS and CS groups, respectively, at the first postoperative assessment performed at 3 months. Postoperative ECL of this magnitude is consistent with previous studies on the effect of phacoemulsification in either healthy or glaucomatous eyes.[22,23] Although the between-group difference was not significant, the slightly higher ECL observed in the HMS group may be related to additional surgical manipulation required to place the device or early surgical experience with the device. A gradual decline in cell counts was noted for both groups during the postoperative follow-up period, and the rate of ECL from 3 months to 5 years was similar in both treatment groups. Although the proportion of eyes with 30% ECL was higher in the HMS group by 8.1% at 3 months, no significant increase was found in the rate of ECL in the HMS group compared with the CS group over the 5-year follow-up period. In a previous study, supraciliary microstent implantation was

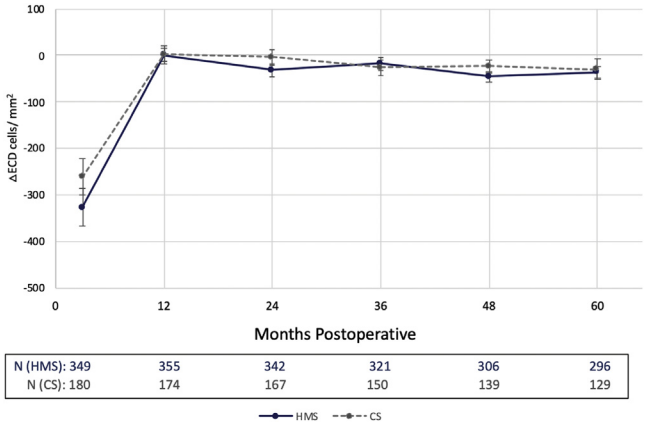

Figure 4. Graph showing the mean endothelial cell loss (ECL) from the prior visit. The 3-month value indicates the ECL compared with the preoperative value. The 12-month value indicates the ECL from the 3-month value. Error bars are 95% confidence intervals for the mean. CS = cataract surgery; ECD = endothelial cell density; HMS = Hydrus Microstent; N = the number of patients at the time point who completed the microscopy examination.

associated with a significant and progressive decline in mean endothelial cell count and frequency of eyes with 30% or more cell loss at the 4- and 5-year follow-up.[24] The authors found no similar pattern of late acceleration of ECL with HMS implantation was found.

The 5-year HORIZON study findings suggest the following: (1) combining HMS implantation with phacoemulsification reduces medication dependence and improves the likelihood of remaining drop-free regardless of preoperative medication count; (2) the percentage of eyes that are medication free is durable; (3) combining HMS implantation with CS reduces the need for further incisional glaucoma surgery compared with CS alone; and (4) no clinically significant differences in safety outcomes exist between the HMS and CS groups, including the long-term rate of ECL. By reducing dependency on topical medications and reducing the risk of further glaucoma surgery without introducing significant complications, HMS treatment has a durable and significant impact on quality of life of and the long-term consequences faced by patients with early-stage glaucoma.

Study Limitations

Despite multiple measures to minimize bias, it was not possible to mask the surgeon to the treatment group during postoperative examinations. It is noteworthy that those interpreting specular microscopy scans at the reading center were masked to the study group. Most surgeons had limited prior experience with the HMS implantation technique. The study excluded patients with secondary open-angle glaucomas, and thus, the results may not be generalizable to these populations. Inclusion was limited to primary open-angle glaucoma eyes with age-related cataract as the only comorbidity, and the procedure was assessed in combination with phacoemulsification. The medication washout requirement enabled a direct assessment of the device alone on IOP not confounded by medication use but simultaneously limited the population to patients with mild and moderate severity of disease who could tolerate the washout procedure safely. Additionally, medication washout was not repeated after 2 years; thus, the possibility of medication introduction bias must be considered for later IOP assessments. Despite these limitations, the authors believe the study is sufficiently powered to demonstrate a significantly reduced need for medication to achieve IOP control and a reduced need for incisional IOP-lowering procedures in patients treated with combined HMS implantation and CS versus with CS alone.

Footnotes and Disclosures

Originally received: August 11, 2021.
Final revision: February 7, 2022.
Accepted: February 15, 2022.
Available online: February 23, 2022. Manuscript no. OPHTHA-D-21-01616.

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Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): I.I.K.A.: Consultant — Aequus, Aerie Pharmaceuticals, Akorn, Alcon, Allergan, Aquea Health, Inc, ArcScan, Bausch Health, Beaver Visitec, Beyeonics, Carl Zeiss Meditec, Centricity Vision, Inc, CorNeat Vision, Costum Surgical, ELT Sight, ElutiMed, Equinox, Genentech, Glaukos, Gore, Iantrek, InjectSense, Iridex, iStar, Ivantis, Johnson & Johnson Vision, LayerBio, Leica Microsystems, Long Bridge Medical, Inc, MicroOptx, MST Surgical, New World Medical, Ocular Instruments, Ocular Therapeutix, Oculo, Omega Ophthalmics, PolyActiva, Radiance Therapeutics, Inc, Ripple Therapeutics, Sanoculis, Santen, Shifamed, LLC, Sight Sciences, Smartlens, Inc, Stroma, Thea Pharma, ViaLase, Vizzario; Financial support — Aerie Pharmaceuticals, Alcon, Allergan, Glaukos, Ivantis, Johnson & Johnson Vision, New World Medical, Santen; Lecturer — Alcon, Allergan, Carl Zeiss Meditec, Johnson & Johnson Vision, MST Surgical, Mundipharma

D.R.: Financial support — Verana, Glaukos, Allergan; Lecturer — Aerie, Ivantis, Allergan, Bausch & Lomb; Expert testimony — Ivantis; Data Safety Monitoring Board or Advisory Board — Ocular Therapeutix

T.D.: Consultant — ViaLase; Lecturer — Santen;

C.M.: Consultant — Alcon, Bausch & Lomb, Allergan, Novartis, Ivantis, Zeiss, Omeros, Ocular Therapeutix, EyePoint Pharma, Sight Sciences, Science Based Health, Imprimis, Dompe, Tarsus, Visus, Orasis, Quidel, Eyevance, Lensar, iSTAR Medical; Lecturer — Alcon, Bausch & Lomb, Allergan, Novartis, Ivantis, Omeros, EyePoint Pharma, Sight Sciences, Lensar, Ocular Therapeutix, Dompe; Data Safety Monitoring Board or Advisory Board — Alcon, Bausch & Lomb, Allergan, Novartis, Ivantis, Zeiss, Omeros, Ocular Therapeutix, EyePoint Pharma, Sight Sciences, Science Based Health, Imprimis, Dompe, Tarsus, Visus, Orasis, Quidel, Eyevance, Lensar, iSTAR Medical

B.F.: Consultant — iStar, Glaukos, Bausch & Lomb, Alcon, Santen; Financial support — Sight Sciences, iStar, Alcon, Santen, Nicox, New World Medical, Arie, Glaukos; Data Safety Monitoring Board or Advisory Board — iStar

G.G.: Consultant — Allergan, Belkin, Equinox, Genentech, Glaukos, Ivantis, McKinsey, Reichert, Santen, Sight Sciences, Thea; Financial support — Thea, Santen, Ivantis; Lecturer — Alcon, Allergan, Belkin, Equinox, Genentech, Glaukos, Ivantis, McKinsey, Reichert, Santen, Sight Sciences, Thea

T.W.S.: Lecturer — Ivantis, Glaukos, Sight Science, New World Medical, Alcon, Microoptix, Johnson & Johnson, Bausch & Lomb; Equity owner — Ivantis, Sight Science

K.S.: Consultant — Ivantis, Glaukos, Alcon, Santen, Allergan, Sight Sciences; Equity owner — Ivantis

Supported by Ivantis, Inc, Irvine, California.

HUMAN SUBJECTS: Human subjects were included in this study. The study protocol was approved by the by the governing Institutional Review Board or Ethics Committee at all participating centers and by national regulatory agencies where applicable. The study was conducted according to the principles described in the Declaration of Helsinki and complied with Health Insurance Portability and Accountability Act and local patient privacy protection regulations. All study subjects provided written informed consent prior to initiating study procedures and including follow-up for 5 years postoperative.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Ahmed, Samuleson, Singh

Analysis and interpretation: Ahmed, De Francesco, Gazzard

Data collection: Rhee, McCabe, Flowers

Obtained funding: N/A; No additional funding was provided for any of the authors for preparation of the manuscript.

Overall responsibility: Ahmed, De Francesco, Rhee, McCabe, Flowers, Gazzard, Samuleson, Singh

Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CS** = cataract surgery; **DIOP** = diurnal intraocular pressure; **ECD** = endothelial cell density; **ECL** = endothelial cell loss; **HMS** = Hydrus Microstent; **IOP** = intraocular pressure; **MIGS** = minimally invasive glaucoma surgery; **PAS** = peripheral anterior synechiae; **SLT** = selective laser trabeculoplasty; **VF** = visual field.

Keywords:
Microinvasive glaucoma surgery, Glaucoma medication usage, Intraocular pressure, Schlemm's canal microstent.

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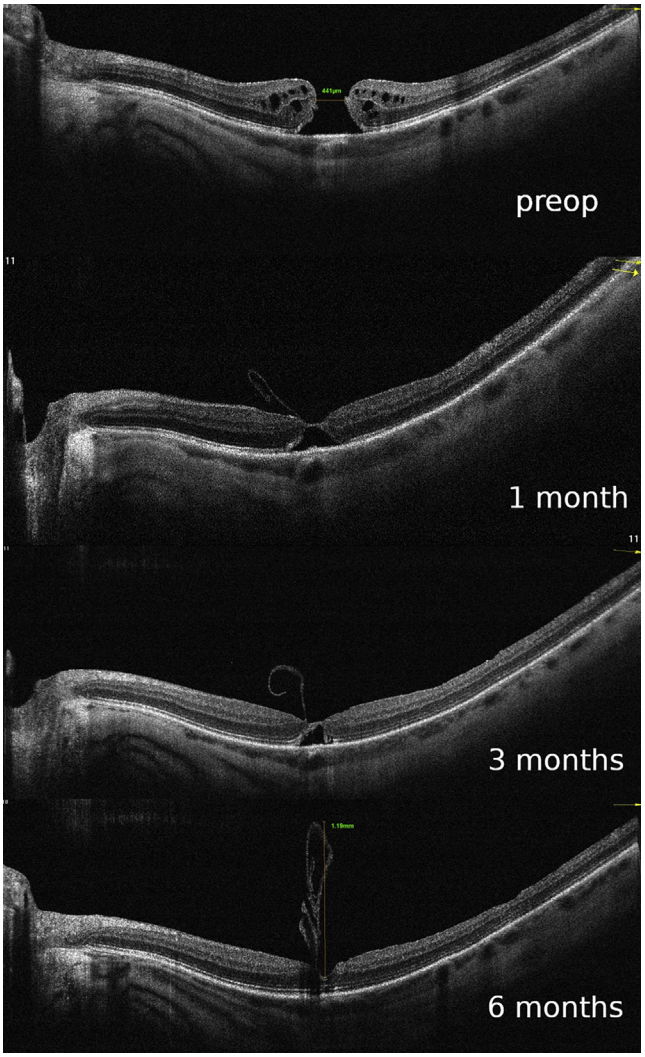
Pictures & Perspectives



Vertical Internal Limiting Membrane Stalk after Macular Hole Surgery

A 62-year-old White woman with a 441-μm wide full-thickness macular hole had a vitrectomy with a temporal inverted internal limiting membrane (ILM) flap in her left eye. After the 6-month follow-up visit, her vision improved to 20/80 with substantially reduced metamorphopsia. She presented with a newly emerged, immobile "dark obscuration" in the center of her visual field. On OCT examination, the macular hole was closed with a complete reconstitution of banded anatomy. A vertical 1.19-mm−long ILM stalk extended from the foveal depression that produced shadowing of underlying layers. A retrospective analysis of images acquired at 1 month and 3 months revealed an asymptomatic gradual rearrangement of the ILM. The patient declined to undergo another intraocular surgery to eliminate the postoperative ILM structure (Magnified version of Fig 1 is available online at www.aaojournal.org).

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