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Two-Year COMPASS Trial Results: Supraciliary Microstenting with Phacoemulsification in Patients with Open-Angle Glaucoma and Cataracts

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Purpose: We evaluated 2-year safety and efficacy of supraciliary microstenting (CyPass Micro-Stent; Transcend Medical, Inc., Menlo Park, CA) for treating mild-to-moderate primary open-angle glaucoma (POAG) in patients undergoing cataract surgery.

Design: Multicenter (24 US sites), interventional randomized clinical trial (RCT) (ClinicalTrials.gov identifier, NCT01085357).

Participants: Subjects were enrolled beginning July 2011, with study completion in March 2015. Subjects had POAG with mean diurnal unmedicated intraocular pressure (IOP) 21−33 mmHg and were undergoing phacoemulsification cataract surgery.

Methods: After completing cataract surgery, subjects were intraoperatively randomized to phacoemulsification only (control) or supraciliary microstenting with phacoemulsification (microstent) groups (1:3 ratio). Microstent implantation via an ab interno approach to the supraciliary space allowed concomitant cataract and glaucoma surgery.

Main Outcome Measures: Outcome measures included percentage of subjects achieving ≥20% unmedicated diurnal IOP lowering versus baseline, mean IOP change and glaucoma medication use, and ocular adverse event (AE) incidence through 24 months.

Results: Of 505 subjects, 131 were randomized to the control group and 374 were randomized to the microstent group. Baseline mean IOPs in the control and microstent groups were similar: 24.5±3.0 and 24.4±2.8 mmHg, respectively ($P > 0.05$); mean medications were 1.3±1.0 and 1.4±0.9, respectively ($P > 0.05$). There was early and sustained IOP reduction, with 60% of controls versus 77% of microstent subjects achieving ≥20% unmedicated IOP lowering versus baseline at 24 months ($P = 0.001$; per-protocol analysis). Mean IOP reduction was ↓7.4 mmHg for the microstent group versus ↓5.4 mmHg in controls ($P < 0.001$), with 85% of microstent subjects not requiring IOP medications at 24 months. Mean 24-month medication use was 67% lower in microstent subjects ($P < 0.001$); 59% of control versus 85% of microstent subjects were medication free. Mean medication use in controls decreased from 1.3±1.0 drugs at baseline to 0.7±0.9 and 0.6±0.8 drugs at 12 and 24 months, respectively, and in the microstent group from 1.4±0.9 to 0.2±0.6 drugs at both 12 and 24 months ($P <$ 0.001 for reductions in both groups at both follow-ups vs. baseline). No vision-threatening microstent-related AEs occurred. Visual acuity was high in both groups through 24 months; >98% of all subjects achieved 20/40 best-corrected visual acuity or better.

Conclusions: This RCT demonstrated safe and sustained 2-year reduction in IOP and glaucoma medication use after microinterventional surgical treatment for mild-to-moderate POAG. *Ophthalmology 2016;123:2103-2112 © 2016 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Glaucoma is a progressive optic neuropathy that remains the second leading cause of blindness globally,[1] affecting 64.3 million persons.[2] In North America, the 2015 estimated glaucoma prevalence was 3.3 million people of the population aged ≥40 years.[3] The only treatment for glaucoma is lowering intraocular pressure (IOP) to reduce optic nerve damage progression. Medical therapy is the first-line glaucoma treatment,[4] but lifelong hypotensive eye drop administration fails in >50% of patients who require multiple medications and may eventually progress to conventional filtering glaucoma surgery.[5–7]

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Conventional glaucoma surgery (e.g., trabeculectomy, nonpenetrating glaucoma surgery, or shunt implantation) is invasive and associated with significant ocular morbidity and a high failure rate.[7–10] For example, trabeculectomy complications cause visual acuity loss in 10% to 20% of eyes and include subconjunctival fibrosis, blebitis, hypotony, endophthalmitis, and filtration failure.[7–10] Surgical treatment is usually required when topical medication or laser procedures are not tolerated or do not sufficiently reduce IOP.

Despite the observation that approximately 20% of the 3.6 million annual cataract surgeries in the United States are in patients with comorbid glaucoma,[11] combined glaucoma-cataract intervention is infrequently performed even though it can streamline patient care. This is because the risks associated with conventional glaucoma surgery do not outweigh the medication burden in many patients with glaucoma with mild-to-moderate disease, and its safety profile preempts concomitant adjunct intervention alongside cataract surgery.[7–10] Thus, most patients with glaucoma continue to require lifelong medication after receiving cataract surgery.[6–8]

New microinvasive glaucoma surgery (MIGS) approaches are emerging. One example is supraciliary microstenting, the first MIGS intervention to successfully target nontrabecular meshwork/Schlemm's canal–mediated aqueous outflow by creating a conduit from the anterior chamber to the suprachoroidal space.[8,9]

In nonrandomized studies, supraciliary microstenting demonstrated significant IOP lowering both alone[12] and in combination with phacoemulsification cataract surgery/intraocular lens (IOL) implantation,[13–15] without the major complications of conventional glaucoma surgery. Microstenting alongside cataract surgery reduced the IOP of those with glaucoma by 30% to 35% through 24 months, with >40% reduction in necessary IOP-lowering medications.[13–15]

The COMPASS trial is a US Food and Drug Administration (FDA) pivotal randomized clinical trial (RCT) on supraciliary microstenting for the surgical treatment of primary open-angle glaucoma (POAG) and the first study on nontrabecular stenting with 2-year follow-up on >500 subjects. It is also the largest interventional study of MIGS yet to be completed. We report COMPASS trial results on the long-term efficacy and safety of supraciliary microstenting in subjects with POAG undergoing concurrent cataract surgery.

Methods

Study Design and Participants

The CyPass Micro-Stent (Transcend Medical, Inc., Menlo Park, CA) is an investigational device in the United States that recently completed FDA trials and has already received the CE mark from the European Union. COMPASS (ClinicalTrials.gov identifier, NCT01085357) is a prospective, randomized, multicenter, controlled, interventional trial conducted at 24 US sites. A complete list of study site primary investigators is provided in Supplemental Appendix 1 (available at www.aaojournal.org). One eye of each subject was randomized to microstent implantation concurrent with cataract surgery or cataract surgery alone. The study protocol was approved by the institutional review board or ethics committee at all study sites and conformed to both Helsinki Declaration tenets and Health Insurance Portability and Accountability Act regulations.

Subjects were examined at 2 preoperative visits to confirm study eligibility, with written informed consent obtained before or during the first screening visit. Subjects then underwent full glaucoma medication washout before the second unmedicated baseline evaluation. Two-person Goldmann applanation tonometry was used to measure diurnal IOP; the means of duplicate IOP measurements, each determined at approximately 8AM, noon, and 4PM, were averaged to provide mean diurnal IOP. Subjects meeting inclusion criteria were scheduled for surgery.

Inclusion Criteria

Inclusion criteria were as follows: (1) age ≥45 years; (2) diagnosed or confirmed POAG (Shaffer grade ≥3 in all quadrants of the study eye) within 90 days of screening; (3) screening medicated IOP ≤25 mmHg or unmedicated IOP between 21 and 33 mmHg; (4) baseline unmedicated diurnal IOP between 21 and 33 mmHg, and ≥3 mmHg higher than screening IOP; and (5) age-related cataract with best-corrected visual acuity (BCVA), or acuity testing with a Brightness Acuity Meter, of 20/40 or worse that was eligible for phacoemulsification cataract surgery with IOL implantation.

Exclusion Criteria

Exclusion criteria were as follows: (1) >3 ocular hypotensive medications; (2) significant risk associated with ocular hypotensive medication washout; (3) previous corneal or glaucoma surgery (except laser trabeculoplasty); (4) clinically significant ocular pathology other than cataract and glaucoma; and (5) diagnosis of acute angle closure or traumatic, congenital, malignant, uveitic, pseudoexfoliative, pigmentary, or neovascular glaucoma.

Patient Follow-up

Subjects were all scheduled for follow-up examinations at postoperative days 1 and 7 and months 1, 3, 6, 12, 18, and 24. Subjects using glaucoma medication(s) at months 12 and 24 underwent appropriate medication washout before unmedicated diurnal IOP measurements were taken throughout the study day. Safety data were reviewed on an ongoing basis by an independent medical monitor and periodically by a study data safety monitoring board.

Study Device

The CyPass Micro-Stent is a fenestrated microstent made of biocompatible polyimide material (Fig 1). The device is 6.35 mm long, with 300-μm and 510-μm internal and external diameters, respectively. During insertion, the flexible microstent assumes the curvature of the specialized applier guidewire to follow the scleral contour along the supraciliary space. When inserted into the supraciliary space, the microstent's mechanical/physical properties and a series of protruding retention rings at the proximal end ensure the device's positional stability in the angle and the supraciliary space. The microstent is designed to increase aqueous outflow from the anterior chamber into the supraciliary space via the uveoscleral pathway.

Randomization and Masking

Subjects enrolled at all study sites were centrally randomized to the microstent or control groups (≈3:1 ratio), with no site allocated more than 25% of subjects/eyes in the study. Randomization was

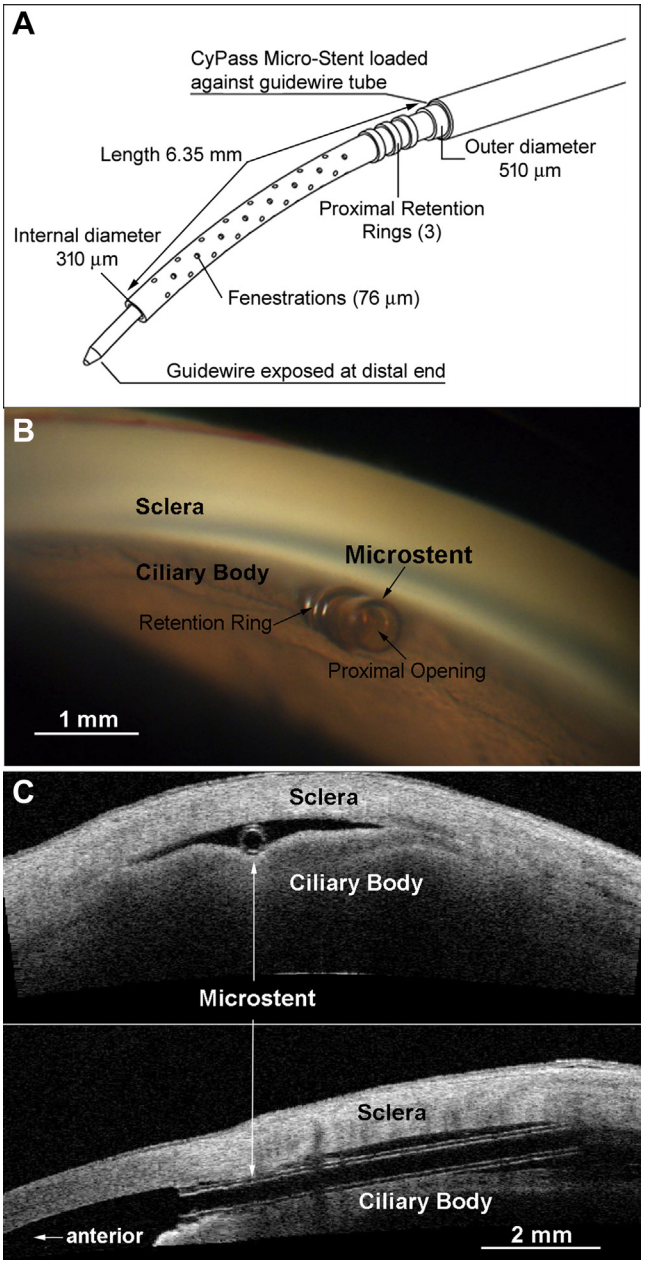

Figure 1. CyPass Micro-Stent (Transcend Medical, Inc., Menlo Park, CA) implantation. **A**, Illustration of the CyPass Micro-Stent threaded on the guidewire of the applier. The slight curvature of the flexible microstent on the guidewire facilitates insertion along the camber of the supraciliary space. Fenestrations in the microstent allow aqueous outflow from the anterior chamber into supraciliary and suprachoroidal spaces. Representative example of CyPass Micro-Stent positioning within the supraciliary space by (**B**) gonioscopic visualization and (**C**) ocular coherence tomography (top image shows the transverse view; bottom image shows the longitudinal view).

stratified by site, and group assignment was revealed intraoperatively immediately after the completion of uncomplicated cataract surgery. Although the surgeon/investigator could not be effectively masked to treatment assignment, subjects did remain masked to treatment group throughout follow-up, and IOPs were recorded by masked technicians.

Surgical Implantation Technique

Surgeons used their standard topical/local anesthesia regimen for cataract surgery. For microstent subjects, acetylcholine was instilled to achieve miosis, and the anterior chamber was filled with a viscoelastic agent to maintain the chamber and expand the angle. The microstent was implanted through a single phacoemulsification corneal incision. Bilateral microstenting was not performed in any subject.

Direct gonioscopy guided microstent implantation, which was initiated by a bluntly dissected plane between the ciliary body and the sclera with the guidewire tip. The microstent was inserted into the supraciliary space until retention features were engaged. The guidewire was then retracted, and the applier was withdrawn from the eye. Viscoelastic was evacuated using irrigation and aspiration, and self-sealing of the clear corneal incision was confirmed. Implant positioning was verified with gonioscopy.

Postoperative Medications

A postoperative regimen of topical antibiotics, nonsteroidal anti-inflammatory drugs, and a steroid was prescribed consistent with cataract surgery, involving topical antibiotics (1 week), nonsteroidal anti-inflammatory drugs (3 weeks), and a steroid (tapered over 1 month). Reintroduction of topical hypotensive medication(s) was indicated if IOP was >21 mmHg at 2 consecutive visits within a 2-week period after the 1-month postoperative visit. Administering ocular hypotensive medication in subjects with IOP >18 and <21.0 mmHg was considered on a case-by-case basis. Reintroduction of hypotensive medication was standardized such that the same medication class(es) used preoperatively was reintroduced, and only 1 medication class was reintroduced at any single visit or within a 2-week window. Dependent on preoperative IOP medication use, the reintroduction or addition of IOP medications postoperatively followed the order (1) prostaglandin analogues, (2) α-agonists, (3) β-blockers, and (4) carbonic anhydrase inhibitors.

Outcome Measures

The primary efficacy outcome measure was the proportion of eyes with unmedicated diurnal IOP reduction ≥20% at 24 months versus unmedicated baseline IOP. Secondary efficacy outcome measures included (1) mean unmedicated IOP reduction at 24 months and (2) the proportion of eyes with unmedicated IOP between 6 and 18 mmHg inclusive at 24 months. The number of ocular hypotensive medications required to maintain target IOP at 24 months versus baseline was an exploratory end point. The primary safety outcome measure was the frequency and nature of any ocular adverse events (AEs) that occurred through 24 months. A secondary safety-related outcome was the proportion of patients with BCVA of 20/40 or better at 24 months.

Statistical Analyses

Categoric variables were compared by the Fisher exact test, and continuous variables were compared by the Student *t* test. *P* values <0.05 indicated statistically significant differences. Efficacy data were assessed using per-protocol (PP) analyses. The 24-month PP population included randomized subjects who met all eligibility criteria, received treatment consistent with the randomization schedule, had no major protocol deviations, and completed the 24-month follow-up examination. Primary outcome parameters were also evaluated by intention-to-treat (ITT) analysis,[16] comprising all subjects who were randomized; safety data were assessed in the ITT population who were randomized and received allocated treatment.

Power analyses indicated that to identify a 20% effect differential of microstent versus control in primary effectiveness outcome (≥20% IOP reduction) by Fisher exact test with a binomial distribution, selecting a power of 90% and a significance level (2-sided) of 0.05, the sample size at 24 months required at least 266 microstent subjects and 95 cataract-only subjects. However, to detect at least 1 safety event through 24 months with a probability of ≥0.95 if the safety event rate is ≥1%, and assuming a 10% annual dropout rate, required randomizing 505 subjects to the microstent (n = 372) and control (n = 133) groups. This cohort size met the statistical criteria for assessing both primary efficacy and safety parameters.

Results

Of 897 consenting subjects who were screened, 505 eyes of 505 subjects received study-related surgery at 24 sites across the United States. Of the 392 subjects who initially provided consent for study participation but ultimately were not enrolled, the most prevalent reasons for nonparticipation were failure to meet study eligibility criteria (n = 308/392; 78.6%) and consent withdrawal (n = 53; 13.5%). Cataract surgery-related posterior capsule rupture occurred in 6 of 392 consenting prospective subjects and precluded their study randomization. At the conclusion of uncomplicated cataract surgery, subjects were randomized at an approximately 3:1 ratio; 374 subjects (74.1%) were randomized to undergo cataract surgery with subsequent microstent implantation (microstent group), and 131 eyes (25.9%) were randomized to cataract surgery only (controls). More than 95% of randomized subjects (n = 480/505) completed the entire 24-month follow-up. The PP population comprised 332 microstent subjects and 116 controls, totaling 448 subjects, or 88.7% of the randomized cohort. Study enrollment began July 1, 2011, and the study ended on March 31, 2015.

No significant differences existed in demographic or baseline ocular parameters between the microstent and control groups (Table 1). Mean age was 70 years, with most subjects (76%) aged 60 to 79 years at the time of enrollment; 53% were female. Most subjects were white (84%), with black/African-American the second most frequently enrolled race/ethnicity (9%). The numbers of left and right eyes randomized were similar.

The microstent and control groups were well balanced in terms of baseline ocular characteristics (Table 1). Most subjects (82%) were using ≥1 ocular hypotensive medication at enrollment; mean (±standard deviation) medications numbered 1.4±0.9 and 1.3±1.0 in the microstent and control groups, respectively. For all randomized subjects, mean BCVA was 20/67 Snellen equivalents, visual field mean deviation was −3.47±2.95 decibels, corneal thickness was 550±36 μm, and diurnal mean unmedicated IOP was 24.4±2.8 mmHg. No subject had pre-perimetric glaucoma. Baseline diurnal IOP after medication washout was similar between the microstent and control groups.

Microstenting with the CyPass device with cataract surgery significantly reduced IOP compared with cataract surgery alone. Significantly more microstent subjects (77%) than controls (60%) achieved a ≥20% reduction in unmedicated diurnal IOP at 24 months postoperatively (PP analysis, $P = 0.001$; ITT analysis, microstent 73%, control 58%, $P = 0.002$) (Fig 2A). Mean unmedicated IOPs at 24 months were 17.0±3.4 mmHg in microstent subjects and 19.3±3.3 mmHg in controls (data not shown).

Secondary efficacy outcomes included mean unmedicated IOP change and the proportion of subjects maintaining unmedicated IOP between 6 and 18 mmHg inclusive at study terminus. Postoperative IOP was reduced from baseline in the microstent and control groups by a mean of 7.9±4.1 mmHg (↓32%) and 6.2±3.8 mmHg (↓26%) at 12 months, and by 7.4±4.4 mmHg (↓30%) and 5.4±3.9 mmHg (↓21%) at 24 months, respectively ($P < 0.001$ within each group vs. baseline values at both times, and $P < 0.001$ for microstent vs. control comparisons at both times) (Fig 2B). This reflected a 1.7-mmHg treatment difference in the PP population (95% confidence interval [CI], 0.9−2.5) favoring microstent treatment at 12 months, which increased to a 2.0-mmHg treatment difference (95% CI, 1.1−2.8) at 24 months ($P < 0.001$ for microstent vs. control comparisons at both times) (Fig 3B). This difference at 24 months remained significant in ITT population analysis (1.8 mmHg; 95% CI, 1.0−2.6; $P < 0.001$). By PP analysis, 67% of all microstented patients maintained washout IOP between 6 and 18 mmHg inclusive at 12 months and 65% remained within this clinically relevant range at 24 months, whereas significantly fewer control subjects maintained this unmedicated IOP range (53% and 44% at 12 and 24 months, respectively) (Fig 2C). In the ITT population, the 24-month proportions of microstent and control subjects maintaining 6 to 18 mmHg IOP were 61% and 44%, respectively ($P < 0.001$).

Microstenting significantly reduced hypotensive ocular medication use. From baseline to 12 months, mean topical glaucoma medication use markedly decreased in the ITT population microstent group, from 1.4±0.9 to 0.2±0.6 drugs, and was maintained through 24 months (Fig 3A) ($P < 0.001$ for intragroup comparisons vs. baseline). Medication use in the control group was 1.3±1.0 medications at baseline and 0.7±0.9 and 0.6±0.8 medications at 12 and 24 months postoperatively, respectively ($P < 0.001$). Thus, at the 2-year study end point, control subjects required a 3-fold greater number of IOP-lowering medications than microstent recipients ($P < 0.001$) (Fig 3A, B).

Whereas 84.8% of microstent subjects required no rescue medication through 24 months, only 59.1% of control subjects achieved this goal (Fig 3B, C). Subjects who achieved ≥20% IOP reduction without requiring rescue medication through 24 months comprised 68.2% of microstent subjects versus 45.7% of controls ($P < 0.001$) (Fig 3C). Subjects who maintained IOP ≤18 mmHg without the need for hypotensive IOP medications through 2 years comprised 66.7% of microstent subjects compared with 40.9% of controls ($P < 0.001$) (Fig. 3C). Thus, the microstent significantly reduced the requirement for IOP-lowering medication.

More than 98% of subjects in both cohorts achieved 20/40 or better BCVA through 24 months. Only 1.1% of CyPass subjects and 0.0% of controls displayed a BCVA reduction of ≥2 lines at 24-month follow-up compared with baseline values. No vision-threatening ocular AEs occurred in either group through 24 postoperative months. No cases of endophthalmitis, hypopyon, choroidal detachment or suprachoroidal hemorrhage, or retinal detachment occurred. Because of the ab interno nature of the procedure, there was no possibility of bleb-related complications typical of conventional glaucoma surgery.[6–10]

Of the 505 randomized subjects, 39% of microstent subjects and 36% of controls experienced ocular AEs through 24 postoperative months (Table 2; ITT population). Most frequently reported minor AEs were transient (≤30-day duration), BCVA loss ≥2 lines (8.8% microstent; 15.3% control), visual field loss progression (6.7% microstent; 9.9% control), iritis (8.6% microstent; 3.8% control), and corneal edema (3.5% microstent; 1.5% control). Acuity loss was largely transient, and only 6 microstent and 3 control subjects completed the study with unresolved BCVA loss, primarily due to posterior capsular opacification. All corneal edema cases were transient, nonfocal, and unrelated to corneal touch. Iritis was transient and resolved in all cases with topical steroid administration. Eleven microstent subjects (2.9%) experienced transient hypotony (3 cases were considered clinically significant, i.e., not associated with acuity loss, but with signs of

Table 1. Demographic and Baseline Ocular Parameters of the Study Population

Parameter	Randomized Group		Total (N = 505)
	Stent (n = 374)	*Control (n = 131)*	
Age, yrs			
Mean ± SD	70±8	70±8	70±8
Range	45–89	48–93	45–93
<60	40 (11%)	12 (9%)	52 (10%)
60–<70	132 (35%)	50 (38%)	182 (36%)
70–<80	148 (40%)	54 (41%)	202 (40%)
≥80	54 (14%)	15 (11%)	69 (14%)
Gender			
Male	177 (47%)	59 (45%)	236 (47%)
Female	197 (53%)	72 (55%)	269 (53%)
Race/ethnicity			
American Indian or Alaska Native	4 (1%)	2 (2%)	6 (1%)
Asian	5 (1%)	1 (1%)	6 (1%)
Black or African American	36 (10%)	11 (8%)	47 (9%)
Hispanic or Latino	15 (4%)	7 (5%)	22 (4%)
Native Hawaiian or other Pacific Islander	0 (0%)	1 (1%)	1 (0%)
White	314 (84%)	108 (82%)	422 (84%)
Other (Caribbean)	0 (0%)	1 (1%)	1 (0%)
Study eye			
OD	196 (52%)	64 (49%)	260 (51%)
OS	178 (48%)	67 (51%)	245 (49%)
IOP medications at screening			
0	63 (17%)	26 (20%)	89 (18%)
1	152 (41%)	59 (45%)	211 (42%)
2	101 (27%)	26 (20%)	127 (25%)
3	58 (16%)	20 (15%)	78 (15%)
Screening medium BAT or BCVA*			
n	373	131	504
Mean logMAR (SD)	0.517 (0.263)	0.541 (0.268)	0.524 (0.264)
Mean Snellen	20/66	20/70	20/67
Minimum, maximum	20/30, 20/800	20/40, 20/400	20/30, 20/800
Visual field, mean deviation, dB			
n	374	131	505
Mean dB (SD)	−3.37 (2.90)	−3.77 (3.07)	−3.47 (2.95)
Minimum, maximum	−15.5, 2.03	−15.5, 0.79	−15.5, 2.03
Pachymetry at screening, corneal thickness (μm)			
n	374	131	505
Mean (SD)	550 (36)	550 (35)	550 (36)
Minimum, maximum	452, 654	467, 619	452, 654
Unmedicated baseline IOP, mmHg			
n	374	131	505
Mean (SD)	24.4 (2.8)	24.5 (3.0)	24.4 (2.8)
Minimum, maximum	21.0, 33.0	21.0, 32.3	21.0, 33.0

BAT = brightness acuity test; BCVA = best-corrected visual acuity; dB = decibels; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; OD = right eye; OS = left eye; SD = standard deviation.
Only one eye per subject was enrolled. All values are provided as n (%), unless otherwise indicated; n-values for age, gender, and ethnicity refer to number of subjects, and n-values for all other parameters refer to number of eyes. All percentages are rounded to the nearest integer. There were no significant differences ($P > 0.05$) in any demographic or baseline ocular parameter between groups. Smaller sample sizes (n) for some clinical parameters were due to missing values.
*Screening BCVA was used for unavailable screening BAT values. In those instances, Snellen visual acuity was converted to logMAR as log10(Snellen/20), followed by mean and SD calculation.

early maculopathy), and 16 microstent subjects (4.3%) and 3 control subjects (2.3%) displayed transient IOP ≥10 mmHg above baseline values. All cases resolved, although 3 microstent subjects and 4 control subjects required additional glaucoma intervention for IOP control. Seven stented eyes developed a cyclodialysis cleft with a >2-mm circumference during implantation; however, this was not associated with hypotony or other sequelae and did not require stent replacement. Cleft closure occurred within 1 and 6 months in 5 and 1 of these subjects, respectively. In the 7th subject, the cleft remained open through study terminus, and 24-month BCVA was 20/40 with unmedicated IOP 9.8 mmHg.

Of microstent-related AEs, 8 stent obstructions (2.1%), 2 instances of malpositioning, and 2 instances of migration/dislodgement occurred. Stent obstructions were not related to migration but to the formation of focal peripheral anterior synechiae without any specific relation to inflammation/iritis. No microstent-related AE caused permanent untoward visual sequelae.

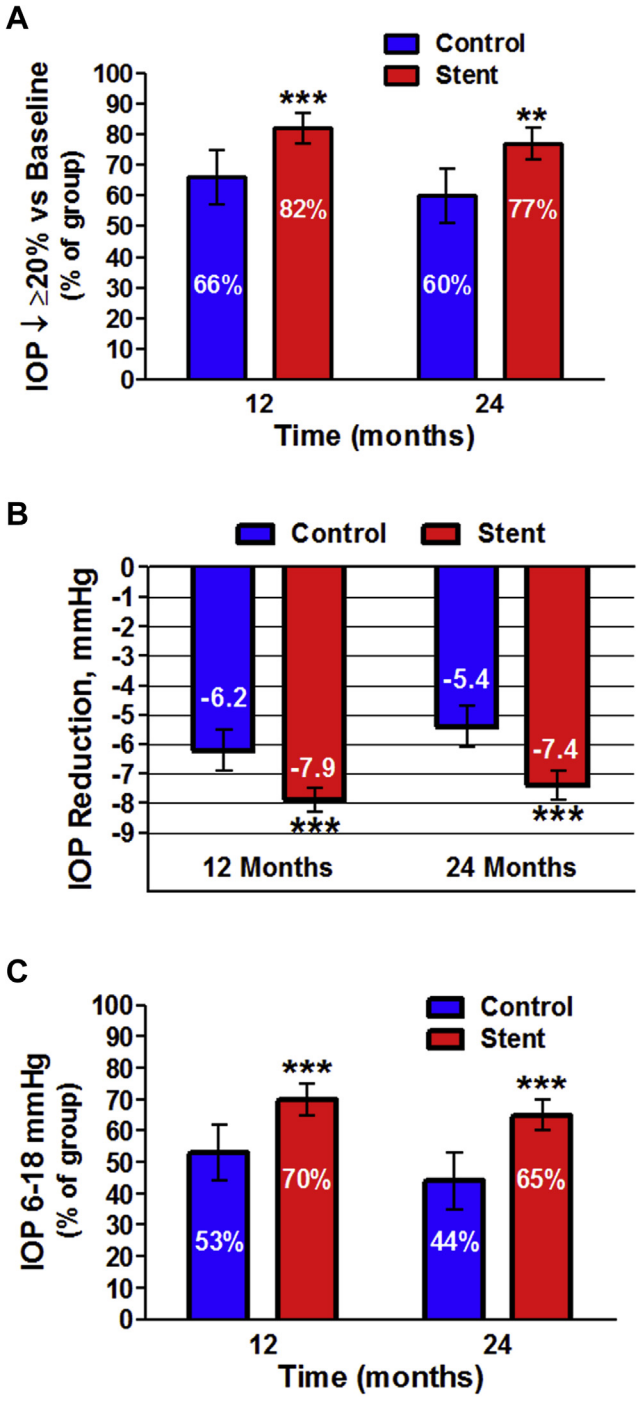

Figure 2. Microstenting reduces intraocular pressure (IOP) in glaucoma subjects. **A**, Microstent implantation performed in conjunction with cataract surgery better increased the percentage of glaucoma subjects who achieved a ≥20% decrease in unmedicated baseline IOP versus phacoemulsification alone. **B**, Unmedicated mean IOP was reduced to a greater extent by microstenting versus phacoemulsification only. **C**, Microstenting increased the proportion of glaucoma subjects who achieved unmedicated IOPs between 6 and 18 mmHg. Data are presented as means ± 95% confidence intervals. $^{**}P < 0.01$ and $^{***}P < 0.001$ in stent versus control comparisons.

A total of 78 nonocular serious AEs were reported in 55 subjects through 24 months postoperatively (43 microstent, 8.5%; 12 control, 9.2%). Twelve subjects died during the study (11 microstent; 1 control). No serious AEs or deaths were related to the microstent or cataract surgery intervention, and all were consistent with participants' ages and comorbidities.

Discussion

This pivotal study of microincisional glaucoma surgery in mild-to-moderate POAG demonstrated a sustained 2-year efficacy benefit for IOP control in subjects undergoing concurrent cataract surgery. Ab interno stenting of the supraciliary space demonstrated safety comparable to the phacoemulsification cataract/IOL procedure alone and to other MIGS interventions.[8,9] The supraciliary microstent showed sustained 24-month efficacy benefit over phacoemulsification across several outcomes, including reducing both IOP and glaucoma medication use.

Phacoemulsification cataract surgery itself can lower IOP, possibly by widening the anterior chamber angle.[17] For example, in a study that included 55 open-angle glaucoma (OAG) eyes and 59 control eyes, the 5-year post-phacoemulsification IOPs in OAG and control eyes were significantly reduced by 1.8±3.5 and 1.5±2.5 mmHg, respectively.[18] The current RCT showed a clear additional IOP-lowering benefit of concomitant microstenting versus cataract surgery alone in those with OAG. In the COMPASS study, although both microstent subjects and control subjects maintained a significant IOP reduction at 2 years (↓7.4±4.4 and 5.4±3.8 mmHg, respectively), a 2.0-mmHg treatment benefit favored the microstent group. Thus, supraciliary microstenting performed concurrently with cataract surgery showed considerable additional efficacy in 2-year IOP control compared with cataract surgery alone.

In regard to the effect of cataract surgery alone on glaucoma medication use, a 2014 report indicated that although cataract surgery decreased mean IOP in 157 patients with OAG through 12 months' follow-up, 38% of eyes with medication-controlled OAG had worsened IOP control after surgery, with 24% requiring additional drugs or laser trabeculoplasty.[19] One long-term study indicated no significant difference in IOP medication use in OAG eyes 3 and 5 years after cataract surgery,[18] whereas another report indicated that phacoemulsification reduces hypotensive medication use in patients with OAG by 0.4±0.9 medications at 24 months.[20] This value approximates the 0.7 mean medication decrease that we observed in the control group in the COMPASS study. However, microstenting conferred significant glaucoma medication reduction over cataract surgery alone, with a mean decrease of 1.2 medications at 24 months. Microstenting reduced long-term glaucoma medication use to one third of that required by control subjects.

The iStent (Glaukos Corp., Laguna Hills, CA) is a trabecular micro-bypass device approved for use in the United States, although it is mechanistically different from

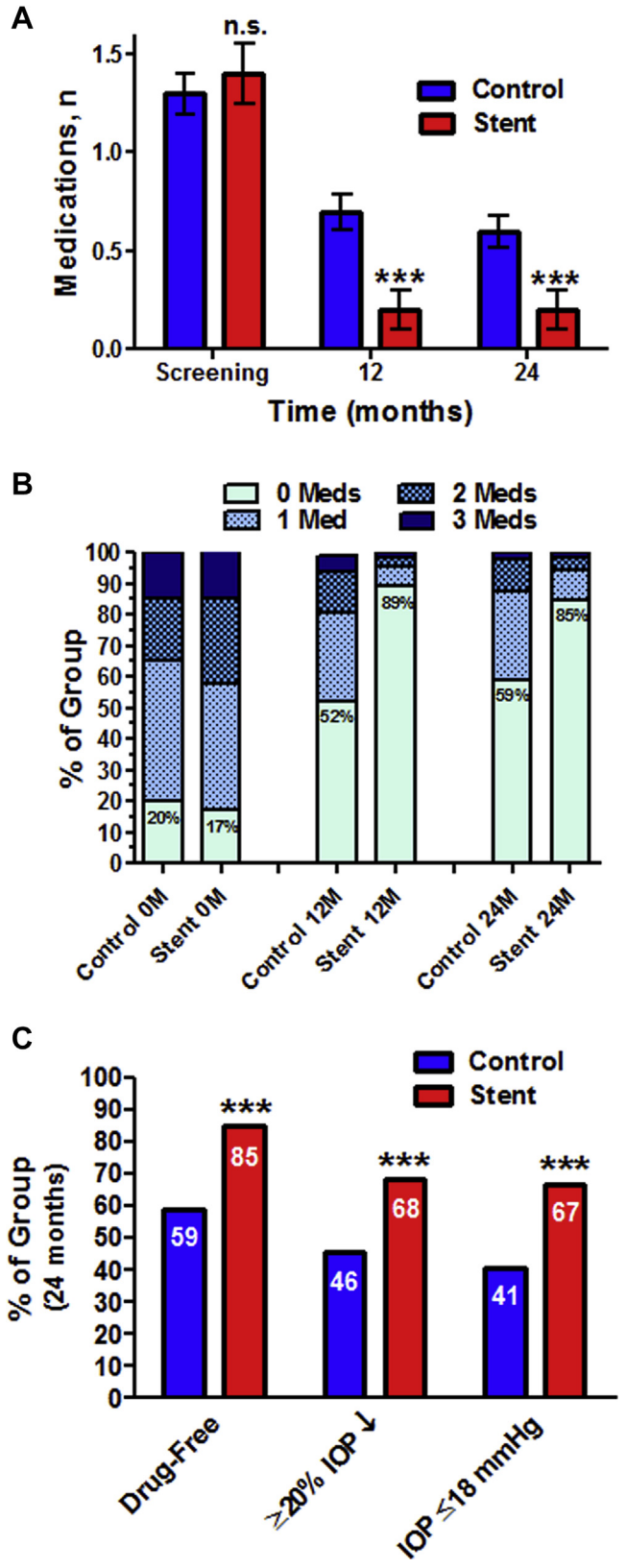

Figure 3. Microstenting reduces hypotensive glaucoma medication use. Microstent implantation performed in conjunction with cataract surgery better lowered intraocular pressure (IOP) medication requirements versus phacoemulsification alone. **A**, From baseline to 24 months, mean topical glaucoma medication use decreased from 1.4±0.9 to 0.2±0.6 drugs in the stent group ($P < 0.001$). Medication numbers decreased in the control group from a baseline mean of 1.3±1.0 to 0.6±0.8 medications at 24 months postoperatively ($P < 0.001$). At the 2-year study end point, IOP control in controls required a 3-fold greater number of drugs than in stent recipients ($P < 0.001$). **B**, Two years after surgery, 85% of stent recipients with glaucoma maintained target IOP without any hypotensive medications, whereas only 59% of phacoemulsification-only subjects were drug-free. **C**, Of subjects who did not require rescue medication through the 24-month study end point, significantly greater proportions of stent versus control group subjects maintained IOP at levels decreased from baseline by ≥20%. In drug-free subjects, microstenting significantly increased the likelihood that IOP would be maintained at ≤18 mmHg. Error bars in **A** show means ± 95% confidence intervals, M = months; n.s. = not significant. ***$P < 0.001$ in stent versus control.

the supraciliary microstent. The iStent is implanted through the trabecular meshwork to target the Schlemm's canal and enhance trabecular outflow.[21] The FDA clinical study for the trabecular micro-bypass device was similar in design, population (although a smaller N value), and inclusion/exclusion criteria as the COMPASS study, and was also performed in conjunction with phacoemulsification cataract extraction/IOL implantation.[22] However, that iStent study did not include medication washout, so rescue medication use was a significant confounder of the IOP-lowering results. In addition, the study was designed and powered to detect efficacy differences through postoperative year 1, but not year 2.

The iStent study primary end point was the proportion of subjects with IOP ≤21 mmHg who did not require medication.[22] At 24 months, this proportion was significantly higher in the iStent group (61%) than in the control group (50%). In the COMPASS study, we applied a more stringent criterion of achieving unmedicated IOP ≤18 mmHg, which occurred in 67% of CyPass subjects and 41% of controls. The iStent secondary efficacy end point was achieving medication-free IOP reduction ≥20% below baseline, which was also evaluated in the current study. At 24 months, this proportion trended higher in the iStent group (53%) than in their control group (44%), although this difference was not significant ($P = 0.09$).[22] In contrast, in the current RCT, a significantly larger percentage of microstent subjects (68%) met this criterion at 24 months compared with controls (46%).

The iStent RCT demonstrated significant 12-month hypotensive medication reduction in stented subjects compared with phacoemulsification-only controls, but this difference dissipated by 24 months.[22] By contrast, the CyPass study showed significant, sustained reduction in the use of IOP-lowering medications through 2 years.

The Hydrus device (Ivantis Inc., Irvine, CA) is a curved metal microstent that targets the Schlemm's canal to increase aqueous outflow. A 2015 report detailed findings from an RCT (N = 100 subjects) that was similar to the COMPASS study in study groups, inclusion/exclusion parameters, outcome parameters, duration, and use of unmedicated diurnal IOP measurements.[23] The primary 2-year efficacy end point, unmedicated IOP reduction by ≥20% of

Table 2. Ocular Adverse Events through 24 Months of Follow-up

AE	Stent (n = 374)	Control (n = 131)	P Value*
BCVA loss ≥10 letters	33 (8.8%)	20 (15.3%)	0.0466
Corneal abrasion	7 (1.9%)	2 (1.5%)	0.9999
Corneal edema	13 (3.5%)	2 (1.5%)	0.3741
Conjunctivitis	4 (1.0%)	3 (2.3%)	0.3828
Cyclodialysis cleft >2-mm circumference	7 (1.9%)	0 (0.0%)	0.1985
Hyphema, transient intraoperative	10 (2.7%)	0 (0.0%)	0.0706
Iritis	32 (8.6%)	5 (3.8%)	0.0809
Hypotony (IOP <6 mmHg)	11 (2.9%)	0 (0%)	0.0744
IOP ≥10 mmHg over baseline	16 (4.3%)	3 (2.3%)	0.4263
Maculopathy, cystoid edema	6 (1.3%)	1 (0.8%)	0.6829
Stent obstruction	8 (2.1%)	N/A	N/A
Subconjunctival hemorrhage	6 (1.6%)	1 (0.8%)	0.6829
Secondary ocular surgical intervention	20 (5.5%)	7 (5.3%)	0.9999
Visual field loss progression, confirmed	25 (6.7%)	13 (9.9%)	0.2488

AE = adverse event; BCVA = best-corrected visual acuity; IOP = intraocular pressure; N/A = not applicable.
Shown are any ocular AE that occurred in at least 1% subjects in either experimental group, either intraoperatively or through 24 postoperative months. Data are n (%) unless otherwise indicated.
*P values calculated by the Fisher exact test using 2×2 contingency tables.

baseline values, occurred in 46% of cataract surgery controls and 80% of stented subjects in the Hydrus study; this compares to 62% of control and 77% of CyPass subjects in the current study.

Medication-free rates at 2 years in the Hydrus RCT[23] were 38% and 73% in controls and stented subjects, respectively; in the CyPass RCT, 59% of controls and 85% of CyPass subjects were medication-free at 2 years. In the Hydrus study, IOP mean baseline medications numbered 2.0 in both groups, decreasing to 0.5 and 1.0 medications in control and microstented subjects; in the CyPass trial, respective 2-year IOP medication use was reduced from 1.3 to 0.6 medications in controls and from 1.4 to 0.2 medications in microstent subjects.

Compared with conventional glaucoma surgery, supraciliary microstenting offers concomitant intervention during cataract surgery, with a low rate of complications. CyPass microstenting is an ab interno, "bleb-less," conjunctiva-sparing technique accomplished through the same corneal incision used for phacoemulsification. Minimal tissue trauma and controlled IOP reduction lessen surgical morbidity, evidenced by the low rate of AEs and the absence of bleb-related complications, such as blebitis, leakage, chamber collapse, choroidal hemorrhage, and persistent hypotony.[2,5–9]

Although CyPass cases experienced ocular AEs, such as iritis (7.8%), corneal edema (3.2%), hypotony (2.9%), and IOP elevation (4.0%), the majority of these events were transient and did not negatively affect functional outcomes such as visual acuity.

Incidents of BCVA reduction and visual field loss affected a smaller proportion of CyPass versus control group subjects. Best-corrected visual acuity loss ≥10 letters occurred in 8.0% of microstent subjects versus 13.7% of controls and was primarily transient. At 24 months, only 1.1% of microstent and 0.0% of control eyes had a BCVA that was ≥2 lines below the baseline value. More than 98% of both groups had acuity better than 20/40 at study terminus, which is similar to previous findings with other MIGS.[22]

Eleven subjects died during the course of the study, with 10 deaths in the microstent group and 1 death in the control group. No deaths were related to the CyPass device; of the microstent subjects, 4 died of cancer, 3 died of heart failure, 1 died of intracranial hemorrhage, 1 died of pneumonia, and 1 died of septic shock secondary to a methicillin-sensitive *S. aureus* urinary tract infection. The single death in the control group was of unknown cause. This subject was aged 86 years at the time of surgery, with no known next of kin. These mortality causes were consistent with the natural history of the age group that participated in this study.

Study Limitations

Findings from this study are generalizable to men and women aged >45 years, with Shaffer grade ≥3 POAG and baseline unmedicated IOP 21 to 33 mmHg, and demographics typical of the enrolled US subpopulation. We appreciate that the Latino/Hispanic ethnicity category constituted only 4% of our cohort and may be underrepresented. Another study limitation was that the principal investigator at each study site was not masked to treatment randomization during patient follow-up examinations. Nonetheless, we believe that this study was sufficiently powered to provide important new insights into glaucoma surgical treatment.

Conclusions

Supraciliary implantation of the CyPass Micro-Stent during routine cataract surgery safely and sustainedly reduces IOP and glaucoma medication use in subjects with mild-to-moderate POAG and comorbid cataracts.

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References

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004;82:844–51.
2. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 2014;121:2081–90.
3. Kapetanakis VV, Chan MP, Foster PJ, et al. Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. Br J Ophthalmol 2016;100:86–93.
4. Sambhara D, Aref AA. Glaucoma management: relative value and place in therapy of available drug treatments. Ther Adv Chronic Dis 2014;5:30–43.
5. Nordstrom BL, Friedman DS, Mozaffari E, et al. Persistence and adherence with topical glaucoma therapy. Am J Ophthalmol 2005;140:598–606.
6. Crawley L, Zamir SM, Cordeiro MF, Guo L. Clinical options for the reduction of elevated intraocular pressure. Ophthalmol Eye Dis 2012;4:43–64.
7. Razeghinejad MR, Spaeth GL. A history of the surgical management of glaucoma. Optom Vis Sci 2011;88:E39–47.
8. Saheb H, Ahmed II. Micro-invasive glaucoma surgery: current perspectives and future directions. Curr Opin Ophthalmol 2012;23:96–104.
9. Brandão LM, Grieshaber MC. Update on minimally invasive glaucoma surgery (MIGS) and new implants. J Ophthalmol 2013;2013:705915.
10. Landers J, Martin K, Sarkies N, et al. A twenty-year follow-up study of trabeculectomy: risk factors and outcomes. Ophthalmology 2012;119:694–702.
11. Tseng VL, Yu F, Lum F, Coleman AL. Risk of fractures following cataract surgery in Medicare beneficiaries. JAMA 2012;308:493–501.
12. García-Feijoo J, Rau M, Grisanti S, et al. Supraciliary microstent implantation for open-angle glaucoma failing topical therapy: 1-year results of a multicenter study. Am J Ophthalmol 2015;159:1075–81.
13. Hoeh H, Vold SD, Ahmed IK, et al. Initial clinical experience with the CyPass Micro-Stent: Safety and surgical outcomes of a novel supraciliary microstent. J Glaucoma 2016;25:106–12.
14. Höh H, Grisanti S, Grisanti S, et al. Two-year clinical experience with the CyPass Micro-Stent: safety and surgical outcomes of a novel supraciliary micro-stent. Klin Monbl Augenheilkd 2014;231:377–81.
15. Hoeh H, Ahmed II, Grisanti S, et al. Early postoperative safety and surgical outcomes after implantation of a suprachoroidal micro-stent for the treatment of open-angle glaucoma concomitant with cataract surgery. J Cataract Refract Surg 2013;39:431–7.
16. Gupta SK. Intention-to-treat concept: a review. Perspect Clin Res 2011;2:109–12.
17. Vizzeri G, Weinreb RN. Cataract surgery and glaucoma. Curr Opin Ophthalmol 2010;21:20–4.
18. Shingleton BJ, Pasternack JJ, Hung JW, O'Donoghue MW. Three and five year changes in intraocular pressures after clear corneal phacoemulsification in open angle glaucoma patients, glaucoma suspects, and normal patients. J Glaucoma 2006;15:494–8.
19. Slabaugh MA, Bojikian KD, Moore DB, Chen PP. The effect of phacoemulsification on intraocular pressure in medically controlled open-angle glaucoma patients. Am J Ophthalmol 2014;157:26–31.
20. Mathalone N, Hyams M, Neiman S, et al. Long-term intraocular pressure control after clear corneal phacoemulsification in glaucoma patients. J Cataract Refract Surg 2005;31:479–83.
21. Le K, Saheb H. iStent trabecular micro-bypass stent for open-angle glaucoma. Clin Ophthalmol 2014;8:1937–45.
22. Craven ER, Katz LJ, Wells JM, Giamporcaro JE, iStent Study Group. Cataract surgery with trabecular micro-bypass stent implantation in patients with mild-to-moderate open-angle glaucoma and cataract: two-year follow-up. J Cataract Refract Surg 2012;38:1339–45.
23. Pfeiffer N, Garcia-Feijoo J, Martinez-de-la-Casa JM, et al. A randomized trial of a Schlemm's canal microstent with phacoemulsification for reducing intraocular pressure in open-angle glaucoma. Ophthalmology 2015;122:1283–93.

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Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **FDA** = Food and Drug Administration; **IOL** = intraocular lens; **IOP** = intraocular pressure; **ITT** = intention-to-treat; **MIGS** = microinvasive glaucoma surgery; **OAG** = open-angle glaucoma; **POAG** = primary open-angle glaucoma; **PP** = per-protocol; **RCT** = randomized controlled trial.

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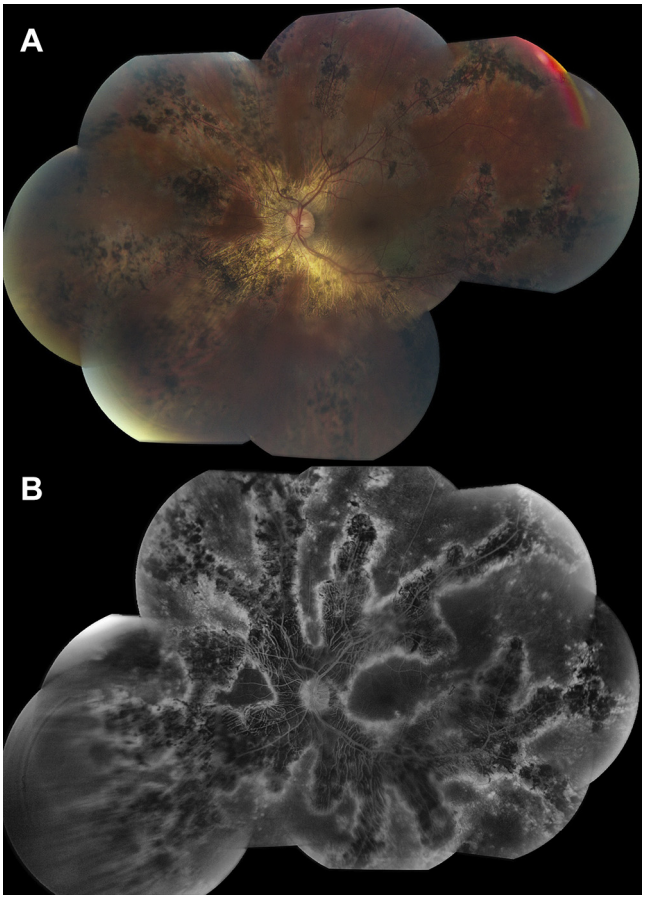
Pictures & Perspectives



Pigmented Paravenous Retinochoroidal Atrophy

A 50-year-old man presented with gradual worsening vision. He denied any history of measles, other infectious illnesses, or autoimmune disease. His visual acuity was 20/20 in the right eye (OD) and 20/30 in the left eye (OS) at presentation. He had mild cataract OS. The fundus photograph (Fig 1**A**) of the left eye demonstrated prominent atrophy of the retina and choroid surrounding the retinal venous circulation. The red-free image (Fig 1**B**) highlighted the atrophic changes. A diagnosis of pigmented paravenous retinochoroidal atrophy was confirmed. This is thought to be secondary to degeneration of the retinal pigment epithelium of unknown etiology.

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