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Corneal endothelial safety profile in minimally invasive glaucoma surgery

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Purpose: To compare 5-year corneal endothelial safety of 3 minimally invasive glaucoma surgery (MIGS) devices (iStent *inject*, Hydrus Microstent, CyPass Micro-Stent).

Setting: U.S. multicenter trials.

Design: Post hoc 5-year analysis from prospective randomized single-masked pivotal trials.

Methods: Mild to moderate open-angle glaucoma subjects received a MIGS implant with phacoemulsification (implant + phaco) or phaco alone (control). In addition, 5-year end points comparing the implant and control groups included proportion of eyes with significant endothelial cell loss (ECL) (>30% or ≥30% vs baseline) and mean endothelial cell density (ECD).

Results: Comparable proportions of eyes in the iStent *inject* + phaco and control groups had significant 60-month ECL (9.4% vs 6.3%, respectively, diff: 3.2%, 95% CI, −5.0% to 11.3%, *P* = .77). Hydrus (20.8% vs 10.6%, diff: 10.2%, 95% CI, 3.2% to 17.2%, *P* = .01) and CyPass (27.2% vs 10.0%, diff: 17.2%, 95% CI, 5.6% to 28.7%, *P* = .02) had more eyes with ECL vs controls (iStent *inject* 1.49X, Hydrus 1.96X, CyPass 2.72X vs controls). Mean ECD over 60 months for iStent *inject* was indistinguishable vs control, whereas greater ECL was observed primarily 3 months postoperative (Hydrus) or accelerated after 2 years (CyPass). No iStent *inject* or Hydrus subjects developed persistent corneal edema, whereas 7 CyPass-implanted eyes developed ECL-related complications.

Conclusions: Through 5 years postoperative, there were no differences in proportion of eyes with significant ECL or mean ECD between the iStent *inject* and control groups. There was greater 5-year ECL and lower ECD in the Hydrus and CyPass groups vs controls. The Hydrus ECL rate mirrored control after 3 months; the CyPass ECL rate accelerated vs control.

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Glaucoma is the leading cause of irreversible blindness worldwide and was the primary cause of blindness in over 3 million people in 2020, accounting for approximately 1 in 10 cases of blindness in adults 50 years or older.[1] During treatment selection for patients with glaucoma, surgeons weigh the safety of a therapy against its clinical effectiveness in reducing intraocular pressure (IOP), with the aim of halting or slowing glaucoma progression.[2] Traditional filtration surgeries (eg, trabeculectomy, aqueous tube shunts) can dramatically reduce IOP but have significant risk for serious adverse events.[3] Typically, they are reserved for patients at high risk for vision loss from rapidly progressing or advanced disease.

As an alternative to traditional filtration surgeries, minimally invasive glaucoma surgery (MIGS) emerged as a safer class of procedures enabling earlier surgical intervention for mild to moderate open-angle glaucoma.[2] One of the hallmarks of MIGS is the high degree of safety relative to other procedures.[2] Corneal health is an important factor in glaucoma procedures, especially for patients at high risk for endothelial cell loss (ECL).[4,5] Endothelial cells maintain the optical clarity of the cornea, with the typical corneal endothelial cell density (ECD) ranging from 1800 to 2600 cells/mm^2 in older adults.[6,7] ECL naturally occurs during aging (0.6% loss/year), but in patients with glaucoma, it can be accelerated by elevated IOP or by treatment.[6,8–12] ECL rates vary by treatment type

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and duration of follow-up, at an estimated 4% to 25% after phacoemulsification, 3% to 15% after trabulectomy, 8% to 29% after aqueous shunt implantation, and 5.8% to 14.6% after repeat implantation of a bioerodible bimatoprost-eluting polymer.[6,11,13–17] Since the corneal endothelium does not proliferate, the preservation of ECD is vital for patients with chronic eye diseases requiring surgical intervention.[18] Progressive ECL (defined as accelerated ECL beyond normal attrition or vs control) is a serious concern, as corneal decompensation can occur when ECL rate is accelerated and remaining endothelial cells cannot compensate to maintain epithelial and stromal thickness and clarity.[6,7] Recently, there has been concern about corneal ECL after MIGS implantation because of long-term ECD reductions, resulting in the CyPass Micro-Stent being voluntarily removed from the market.[2] At the present time, however, there is very minimal published long-term data on corneal endothelial outcomes in MIGS devices. To our knowledge, the only rigorous 5-year endothelial data published are from the pivotal trials of the 3 MIGS devices compared in this paper.

In this post hoc analysis, we assess corneal endothelial safety of 3 MIGS devices: iStent *inject* (Glaukos Corp.), Hydrus Microstent (Alcon Laboratories, Inc.), and CyPass Micro-Stent (Alcon Laboratories, Inc.). These devices were chosen because of the similarities in efficacy, study populations, and protocols associated with their pivotal trial data. Two of the studies were extension trials (CyPass and iStent *inject*), and 1 trial was originally designed to follow patients to 5 years after implantation (Hydrus). The objective of this study was to compare the corneal endothelial safety of these 3 MIGS devices combined with phacoemulsification (phaco) vs their respective phaco-only control group.

METHODS

Institutional Review Board/Ethics Committee approval was obtained for the primary studies of all 3 devices included in this post hoc analysis. Each study followed the tenets of the Declaration of Helsinki and HIPAA regulations and included informed consent of all participants. The 3 studies were single-masked, with the subject being masked to treatment assignment.

Study Devices

The iStent *inject*, Hydrus Microstent, and CyPass Micro-Stent have been previously described.[5,19–21] The iStent *inject* decreases IOP by facilitating aqueous outflow through 2 stents that bypass the trabecular meshwork into Schlemm's canal. Each stent has a 230-μm diameter, 360-μm height, 80-μm central lumen diameter, and four 50-μm side outlets. Each stent can carry the average amount of aqueous humor produced by the human body (2.5 μL/min).[19] The Hydrus Microstent is an 8-mm long, curved device (with major and minor axes of 292 μm and 185 μm, respectively) comprised nitinol (a nickel-titanium alloy), which is inserted into Schlemm's canal.[22] The CyPass Micro-Stent is a 6.35-mm fenestrated polyimide device designed to direct aqueous outflow from the anterior chamber into the supraciliary space; its internal and external diameters are 300 μm and 510 μm, respectively.[21]

Data Sources

The data in this post hoc analysis were extracted from publications from 2-year and 5-year follow-up studies of each MIGS device. The iStent *inject* was first studied in a 2-year pivotal trial (NCT00323284), from which every enrolled patient was invited to follow-up through 5 years (NCT04624685).[19,23] All iStent *inject* patients who accepted the extension at 2 years were included in the 5-year follow-up study. The HORIZON randomized trial (NCT01539239) of the Hydrus Microstent planned to study all enrolled patients from baseline to 5 years.[20,24] The CyPass Micro-Stent initially had a 2-year postoperative pivotal trial (COMPASS, NCT01085357), followed by an extension study which continued follow-up through 5 years (COMPASS-XT, NCT02700984).[5,21] The study dispositions from each trial are presented in Figure 1. Study demographics and baseline characteristics were obtained from the 2-year and/or 5-year studies.

Study End Points and Specular Microscopy

Study end points compared the implant + phaco group vs the respective phaco-only group at 60 months postoperative.[5,20] In each study, mean ECD and images of the central corneal endothelium were obtained by specular microscopy (Konan Medical, Inc.) and were completed in triplicate to improve accuracy. All measurements were evaluated at the same reading center (Cornea Image Analysis Reading Center, University Hospitals Eye Institute, Cleveland, Ohio). For each measurement, cell counts were determined by 2 certified readers masked to study group using the Konan Center method, wherein ≥5% differences were resolved by adjudication by a third masked reader. Clinically significant ECL has been characterized as ECL >30%.[5] The rationale for this cutoff is that it allows for a 10% acute surgical loss and subsequent

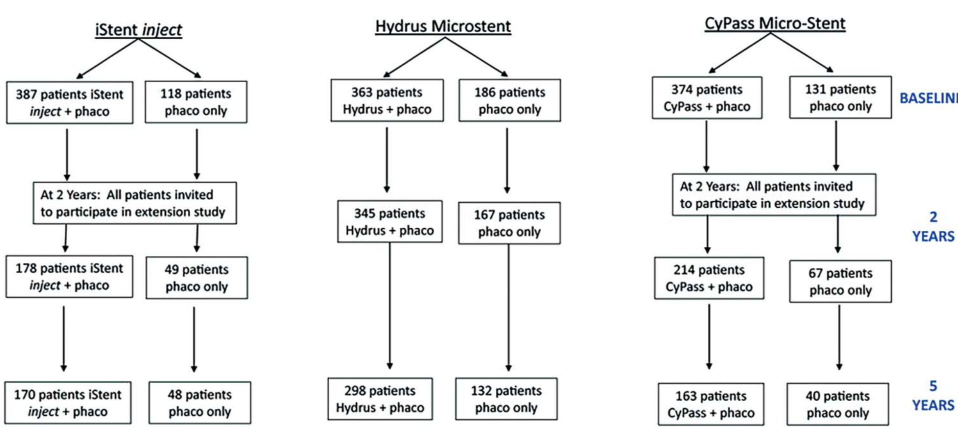

Figure 1. Corneal endothelial cell data in 3 prospective randomized microinvasive glaucoma surgery stent trials. The number of patients is indicative of the patients with ECD data collected, which may differ from the number of patients in Table 1. ECD = endothelial cell density; Phaco = phacoemulsification

annual loss of 2% to have ECD ≥1000 cells/mm^2 at age 72 years; over a 5-year clinical trial, this allows for 20% total ECL from baseline.[25] When combined with inherent measurement variability (up to 10% by specular microscopy), the 30% threshold is reached.[26]

Statistical Analyses

Endothelial safety outcomes of each device were used from the respective publications or Instructions for Use reporting data at baseline and 3 months, 24 months, 36 months, and 60 months, including the proportion of eyes with significant ECL (>30% or ≥30%), and mean ECD.[5,20,23,24,27] Continuous variables were reported as mean ± SD. Categorical variables were represented by frequency, fractions, or percentages. Statistical analyses consisted of 2-sample *t* test for population means (eg, mean ECD) and Pearson chi-square test or Fisher exact test for categorical variables (eg, percentage of eyes with ECL >30% or ≥30%), assuming normal data distribution and correlation over time. Bonferroni correction was not performed due to the positive correlation of measures on the same eyes over time, where Bonferroni is known to be overly conservative. The Hydrus publications reported ECL ≥30%, while the iStent *inject* and CyPass publications reported ECL >30%. For consistency across devices, an additional iStent *inject* data analysis was completed to determine the rates of both ≥30% ECL and >30% ECL. The outcomes for both cutoffs are presented in Table 2 and were identical. A 2-tailed *P* value less than .05 indicated statistical significance in all analyses.

RESULTS

Study Demographics

Full details of study disposition for each trial are shown in Figure 1. The iStent *inject* and CyPass trials were originally designed as 2-year studies, after which all patients were invited to participate in an extension study for 3 additional years, whereas the Hydrus trial was originally designed as a 5-year study. In the iStent *inject* trial, 218 patients had ECD data at 5 years postoperatively, constituting 43.2% (218/505) of the original cohort and 96.0% (218/227) of the extension cohort. In the Hydrus trial, 430 patients had ECD data at 5 years postoperatively, constituting 78.3% (430/549) of the original cohort. In the CyPass trial, 203 patients had ECD data at 5 years postoperatively, constituting 40.2% (203/505) of the original cohort and 72.2% (203/281) of the extension cohort. Patient demographics were comparable across studies, including mean patient age (∼70 years), sex (∼55% female), ethnicity (majority White), study eye (∼50% to 60% right eye), and mean baseline IOP (Table 1). The baseline mean ECDs were comparable as well (2417 to 2450 cells/mm^2 in treatment groups and 2426 to 2453 cells/mm^2 in control groups; Table 1). In addition, to limit potential bias arising from analyzing an extension cohort vs an original cohort, comprehensive baseline demographic and ocular data were compared between treatment and control groups in both the original and extension cohorts (Table 1). No significant differences were detected between treatment and control in either cohort for any of the devices. Efficacy results of these trials have been published previously and are not included in the scope of this endothelial safety analysis.[19,21,24]

Significant ECL

Compared with phaco alone, the iStent *inject* + phaco group had comparable proportions of eyes with significant ECL (>30% vs baseline) at all 3 time points through 60 months (Table 2). The proportion of eyes with significant ECL at 60 months was 9.4% in the iStent *inject* + phaco group vs 6.3% in the phaco group (diff: 3.2%, 95% CI, −5.0% to 11.3%, *P* = .77; Figure 2A, Table 2). The Hydrus + phaco group had a greater proportion of eyes with significant ECL compared with phaco alone (20.8% vs 10.6%, respectively, at 60 months, diff: 10.2%, 95% CI, 3.2% to 17.2%, *P* = .01; Figure 2B, Table 2). This was most marked from baseline to 3 months and then stabilized. The CyPass + phaco group had a greater proportion of eyes with significant ECL at 60 months vs phaco alone (27.2% vs 10.0%, diff: 17.2%, 95% CI, 5.6% to 28.7%, *P* = .02; Figure 2C, Table 2). There was accelerated progressive loss from 2 years to 5 years of follow-up.

Endothelial Cell Density

The iStent *inject* + phaco vs the phaco-alone groups demonstrated comparable mean ECD at all time points through 60 months (2099 vs 2103 cells/mm^2 at 60 months, respectively, diff: −4, 95% CI, −141.8 to 133.8, *P* = .95; Figure 3A, Table 3). The observed decline in mean ECD over time was indistinguishable between groups during both the surgical trauma period (baseline to 3 months) and postsurgical trauma period (3 to 60 months). The Hydrus + phaco group had lower mean ECD vs control at 24 months (2060 vs 2183 cells/mm^2, respectively, diff: −123, 95% CI, −208.7 to −37.3, *P* = .005; Figure 3B, Table 3) and 60 months (1967 vs 2117 cells/mm^2, respectively, diff: −150, 95% CI, −252.5 to −47.5, *P* = .004; Figure 3B, Table 3). The mean ECD showed significant loss at the time of surgery (baseline to 3 months) in the implant group vs control, followed by stable and similar ECL rate thereafter. Patients who underwent CyPass + phaco had lower ECD at 60 months vs those receiving phaco alone (1931 vs 2189 cells/mm^2, respectively, diff: −258, 95% CI, −429.4 to −86.6, *P* = .003; Figure 3C, Table 3). The declining mean ECD trend lines demonstrated minimal between-group difference during the initial postoperative phase; however, a steeper declining slope representing accelerated ECL occurred after 24 months postoperative in the CyPass + phaco group vs phaco-only group.

Corneal Edema

In the iStent *inject* and Hydrus pivotal trials, there were no reported device-related cases of corneal edema or corneal transplant. In the CyPass pivotal trial, 7 eyes had adverse events possibly related to ECL. These included 3 eyes with localized corneal edema and 4 eyes requiring device trimming for anterior chamber protrusion. Of these, only 1 eye exhibited ECL-related clinical symptoms (loss of >2 lines of best-corrected visual acuity), and no eyes were reported to have undergone corneal transplantation.

Table 1. Demographics and preoperative characteristics of patients in each study

Clinical study	iStent *inject*		Hydrus Microstent	CyPass Micro-Stent	
	Baseline of 24-mo study	Baseline of 60-mo study	Baseline[a] of 60-mo study	Baseline of 24-mo study	Baseline of 60-mo study
Patients, n					
Treatment group	387	178	369	374	215
Control group	118	49	187	131	67
Age (y), mean (SD)					
Treatment group	69.0 (8.2)	69.0 (7.8)	71.1 (7.9)	70.0 (8.0)	69.4 (7.9)
Control group	70.1 (7.7)	69.3 (7.0)	71.2 (7.6)	70.0 (8.0)	70.8 (7.5)
P value (treatment vs control)	0.16	0.82	0.89	>0.99	0.20
Diff (95% CI) (treatment − control)	−1.2 (−2.8, 0.5)	−0.3 (−2.6, 2.0)	−0.1 (−1.5, 1.3)	0.0 (−1.6, 1.6)	−1.4 (−3.6, 0.8)
Sex (F), n (%)					
Treatment group	225 (58.1)	95 (53.4)	206 (55.8)	197 (52.7)	116 (54.0)
Control group	64 (54.2)	30 (61.2)	105 (56.1)	72 (55.0)	37 (55.2)
P value (treatment vs control) (FE)	0.46	0.42	>0.99	0.69	0.89
Diff % (95% CI) (treatment − control)	3.9 (−6.3, 14.1)	−7.9 (−23.3, 7.6)	−0.3 (−9.1, 8.4)	−2.3 (−12.2, 7.6)	−1.3 (−14.9, 12.4)
Ethnicity, n (%)					
Treatment group					
White	282 (72.9)	133 (74.7)	291 (78.9)	314 (84.0)	191 (88.8)
Black	77 (19.9)	32 (18.0)	45 (12.2)	36 (9.6)	21 (9.8)
Other	28 (7.2)	13 (7.3)	33 (8.9)	24 (6.4)	3 (1.4)
Control group					
White	86 (72.9)	40 (81.6)	153 (81.8)	108 (82.4)	58 (86.6)
Black	19 (16.1)	5 (10.2)	15 (8.0)	11 (8.4)	7 (10.4)
Other	13 (11.0)	4 (8.2)	19 (10.2)	12 (9.2)	2 (3.0)
P value (treatment vs control)	0.30	0.46	0.31	0.52	0.60
Diff % White (95% CI) (treatment − control)	−0.0 (−9.2, 9.2)	−6.9 (−19.5, 5.7)	−3.0 (−9.9, 4.0)	1.5 (−6.5, 9.5)	2.3 (−6.9, 11.5)
Study eye (right), n (%)					
Treatment group	205 (53.0)	104 (58.4)	178 (48.2)	196 (52.4)	116 (54.0)
Control group	64 (54.2)	32 (65.3)	92 (49.2)	64 (48.9)	27 (40.3)
P value (treatment vs control) (FE)	0.83	0.42	0.86	0.28	0.07
Diff % (95% CI) (treatment − control)	−1.3 (−11.5, 9.0)	−6.9 (−22.0, 8.3)	−1.0 (−9.8, 7.8)	3.6 (−6.4, 13.5)	13.7 (0.2, 27.2)
Unmedicated IOP at baseline (mm Hg), mean (SD)					
Treatment group	24.8 (3.3)	NR	25.5 (3.0)	24.4 (2.8)	24.5 (2.9)
Control group	24.5 (3.1)	NR	25.4 (2.9)	24.5 (3.0)	24.8 (3.1)
P value (treatment vs control)	0.33	n/a	0.71	0.73	0.47
Diff (95% CI) (treatment − control)	0.3 (−0.3, 1.0)	n/a	0.1 (−0.4, 0.6)	−0.1 (−0.7, 0.5)	−0.3 (−1.1, 0.5)
Medicated IOP at baseline, mean (SD)					
Treatment group	17.5 (3.0)	NR	17.9 (3.1)	NR	NR
Control group	17.5 (2.8)	NR	18.1 (3.1)	NR	NR
P value (treatment vs control)	0.99	n/a	0.47	n/a	n/a
Diff (95% CI) (treatment − control)	0.0 (−0.6. 0.6)	n/a	−0.2 (−0.7, 0.3)	n/a	n/a

(continued on next page)

Table 1. Continued

Clinical study	iStent *inject* Baseline of 24-mo study	iStent *inject* Baseline of 60-mo study	Hydrus Microstent Baseline[a] of 60-mo study	CyPass Micro-Stent Baseline of 24-mo study	CyPass Micro-Stent Baseline of 60-mo study
Preoperative ECD (cells/mm^2), mean (SD and/or 95% CI)					
Treatment group	2514 (SD: 363)	2450.2 (SD: 355.7)	2417 (SD: 390)	2429 (SD: 403.2; 95% CI: 2388-2470)	2432.6 (SD: 370.46; 95% CI: 2382.8-2482.4)
Control group	2493 (SD: 379)	2441.4 (SD: 344.4)	2426 (SD: 371)	2453 (SD: 358.7; 95% CI: 2391-2515)	2434.5 (SD: 319.78; 95% CI: 2356.5-2512.4)
P value (treatment vs control)	n/a	0.88	0.81	0.55	0.97
Diff (95% CI) (treatment − control)	n/a	8.9 (−102.5, 120.3)	−0.2 (−0.7, 0.3)	−24.0 (−102.2, 54.2)	−1.9 (−100.8, 97.0)

ECD = endothelial cell density; FE = Fisher exact test; n/a = not applicable; NR = not reported
[a]Patient demographics could not be separated at 2 years and 5 years for Hydrus, since the data at each time point was published together in the same trial

DISCUSSION

The corneal endothelium plays a vital role in maintaining the visual clarity of the cornea. A clinically significant loss of endothelial cells after device implantation, defined as >30% from preoperatively, is a meaningful safety outcome. Of particular importance is device-related progressive ECL over time (ie, beyond normal aging-related attrition or vs control); research has shown that when the rate of ECL is accelerated and remaining endothelial cells cannot compensate to maintain epithelial and stromal thickness and clarity, corneal decompensation and/or corneal edema can ensue.[6,7]

In this study, we collected data from publications of the pivotal trial (Hydrus Microstent) and respective extension studies (iStent *inject* and CyPass Micro-Stent) on the proportion of eyes with significant ECL and mean ECD through 5 years (60 months) after implantation of these MIGS devices with phaco vs phaco alone. After iStent *inject* + phaco, no significant ECL or ECD differences were observed vs the phaco-only group at any time point. Furthermore, the mean ECD trend lines over time were indistinguishable between groups, suggesting no additional ECD impact after iStent *inject* during either the surgical trauma or postsurgical trauma periods. Ahmed et al. estimated the annualized rate of change in ECD to be clinically and statistically insignificant between groups from 3 to 60 months postoperatively in the iStent *inject* extension study.[23]

After Hydrus + phaco, a greater proportion of eyes had ECL ≥30% and reduced ECD vs the phaco-only group. The

Table 2. Proportion of eyes with >30% or ≥30% central ECL from preoperative

Parameter	Time: 3 mo	24 mo	60 mo
iStent *inject* + phaco (% eyes with > 30% ECL)	11.2 (19/170)	9.4 (16/171)	9.4 (16/170)
iStent *inject* + phaco (% eyes with ≥ 30% ECL)[a]	11.2 (19/170)	9.4 (16/171)	9.4 (16/170)
Phaco control	14.3 (7/49)	4.3 (2/47)	6.3 (3/48)
P value	.55	.37 FE	.77 FE
Diff % (95% CI) (treatment − control)	−3.1 (−14.0, 7.8)	5.1 (−2.1, 12.3)	3.2 (−5.0, 11.3)
Hydrus Microstent + phaco	17.3 (61/352)	13.6 (47/346)	20.8 (62/298)
Phaco control	9.4 (17/181)	7.2 (12/167)	10.6 (14/132)
P value	.01*	.03*	.01*
Diff % (95% CI) (treatment − control)	7.9 (2.1, 13.7)	6.4 (1.1, 11.7)	10.2 (3.2, 17.2)
CyPass Micro-Stent + phaco	9.6 (20/209)	8.5 (18/212)	27.2 (44/162)
Phaco control	6.2 (4/65)	3.0 (2/67)	10.0 (4/40)
P value	.39	.18 FE	.02*
Diff % (95% CI) (treatment − control)	3.4 (−3.7, 10.5)	5.5 (0.0, 11.0)	17.2 (5.6, 28.7)

ECL = endothelial cell loss; FE = Fisher exact test; phaco = phacoemulsification
Values are listed as % (n/N). Calculations of CyPass ECL >30% 2-sided *P* value are from FE, assuming normal data distribution and correlation of data over time. Bonferroni correction was not performed due to the positive correlation of the measures on the same eyes over time, where Bonferroni is known to be overly conservative. By contrast, the *P* values reported in Table 3 of the 5-year CyPass paper used a Bonferonni correction.
*Statistically significant

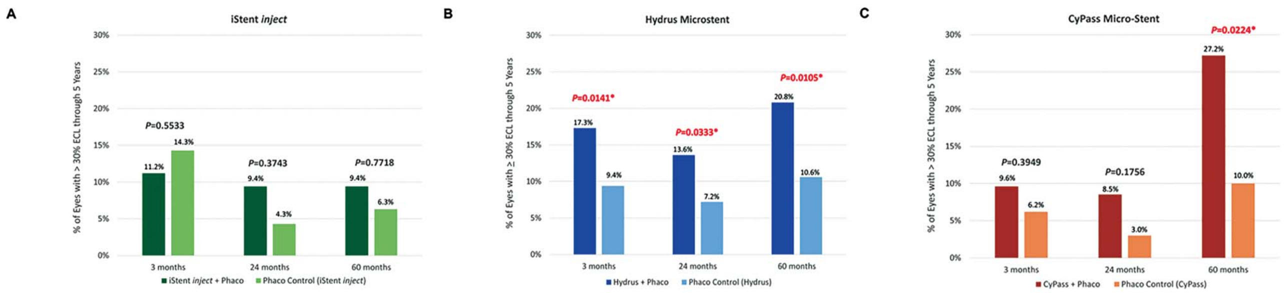

Figure 2. Proportion (%) of eyes with >30% (iStent *inject*, CyPass) or ≥30% (Hydrus) ECL. *A*: iStent *inject*. *B*: Hydrus Microstent. *C*: CyPass Micro-Stent. The Hydrus publications reported ECL ≥30%, while the iStent *inject* and CyPass publications reported ECL >30%. For consistency across devices, an additional analysis of the iStent *inject* data was completed to determine the rates of both ≥30% ECL and >30% ECL. The outcomes for both cutoffs were identical (presented in Table 2). *Denotes statistically significant difference between treatment and control groups. ECL = endothelial cell loss; Phaco = phacoemulsification

mean ECD showed a significant change during the initial postoperative period with Hydrus + phaco vs phaco alone, followed by a similar rate of ECL progression between both groups. The 5-year trial demonstrated no statistically significant difference in the annualized rate of ECD change between groups from the 3- to 60-month period, indicating no additional influence on ECD from the device after 3 months.[20]

After CyPass + phaco, a greater proportion of eyes with ECL >30% and reduced ECD were reported at 60 months postoperative vs phaco alone. Mean ECD over time revealed accelerated ECL in the implant group after 24 months. The effects of device malpositioning on ECL were reported in the COMPASS-XT extension study, with a correlation found between CyPass device protrusion in the anterior chamber and increased ECL.[5] Indeed, when the proportions of eyes with ECL >30% were grouped by the number of exposed rings, differences between the groups were significant at 60 months (P = .01). The authors noted this was likely attributable to a mechanical effect caused by intermittent device-cornea touching, as the ECL rate was comparable with control when the CyPass was placed in its optimal location. The association between device position and ECL was also observed by Fili et al., who published a case series of patients with corneal decompensation associated with CyPass malpositioning, and by Ibarz-Barbera et al., who found a clear association between Preserflo-endothelium distance and ECL, but not by Lenzhofer et al., who observed no such association with XEN positioning.[29–31]

Throughout the 5-year follow-up, compared with their control groups, the iStent *inject* was associated with the least decrease in mean ECD compared with the other devices, while the CyPass Micro-Stent was associated with the greatest ECD decrease.

Regarding ECL over time, patients implanted with any of the 3 MIGS devices, as well as patients undergoing phaco alone, showed an initial decrease in mean ECD from baseline to 3 months (the first postoperative ECD measurement). From 3 to 60 months, the long-term effect of MIGS device implantation was considered the driving force of ECL rather than the short-term effects of surgical trauma between 0 and 3 months. After 3 months, the slope in mean ECL for iStent *inject* and Hydrus was comparable with control, but the slope in mean ECL was greater in the CyPass group vs control. Indeed, no device-related ECL adverse events (corneal edema or surgery) were found in the iStent *inject* or Hydrus pivotal trials but were reported in some patients in the CyPass trial. The endothelial outcomes reported in the present paper are more comprehensive than what was summarized in the systematic reviews of Obuchowska et al. and Seah et al., since the current analysis incorporates all published endothelial end points from the 3 pivotal trials rather than only the end

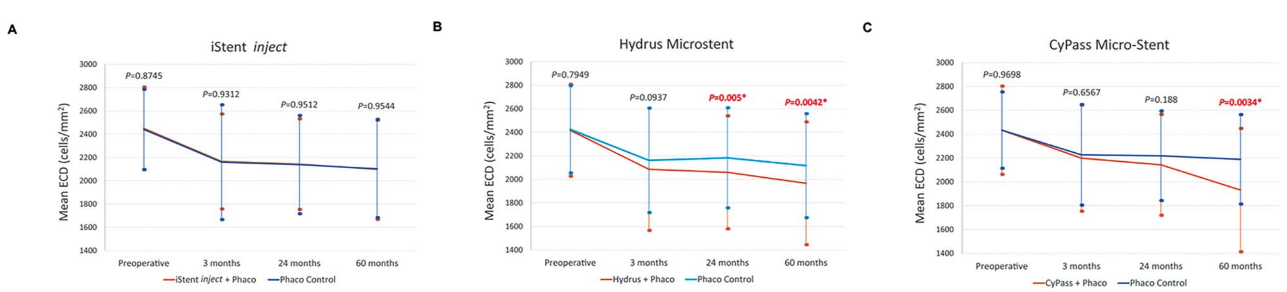

Figure 3. Mean ECD (cells/mm^2). *A*: iStent *inject*. *B*: Hydrus Microstent. *C*: CyPass Micro-Stent. *Denotes statistically significant difference between treatment and control groups. ECD = endothelial cell density; Phaco = phacoemulsification

Table 3. Mean ECD across trials compared with internal control groups

Parameter	Time			
	Preop	3 mo	24 mo	60 mo
iStent *inject* + phaco	2450.2 ± 355.7	2166 ± 408 (170)	2143 ± 389 (171)	2099 ± 430 (170)
Phaco control	2441.4 ± 344.4	2160 ± 493 (49)	2139 ± 422 (47)	2103 ± 419 (48)
P value	.87	.93	.95	.95
Diff (95% CI) (treatment − control)	8.9 (−102.5, 120.3)	6 (−130.9, 142.9)	4 (−124.6, 132.6)	−4 (−141.8, 133.8)
Hydrus Microstent + phaco	2417 ± 390 (363)	2086 ± 519 (352)	2060 ± 480 (345)	1967 ± 522 (298)
Phaco control	2426 ± 371 (186)	2162 ± 444 (181)	2183 ± 425 (167)	2117 ± 442 (132)
P value	.79	.09	.005*	.004*
Diff (95% CI) (treatment − control)	−9 (−77.0, 59.0)	−76 (−164.9, 12.9)	−123 (−208.7, −37.3)	−150 (−252.5, −47.5)
CyPass Micro-Stent + phaco	2433 ± 370 (214)	2199 ± 445 (210)	2143 ± 423 (213)	1931 ± 517 (163)
Phaco control	2434 ± 320 (67)	2227 ± 422 (65)	2219 ± 376 (67)	2189 ± 375 (40)
P value	.97	.66	.19	.003*
Diff (95% CI) (treatment − control)	−1 (−99.9, 97.9)	−28 (−150.9, 94.9)	−76 (−189.7, 37.7)	−258 (−429.4, −86.6)

ECD = endothelial cell density; phaco = phacoemulsification
Values are listed as mean ± SD (n). Mean ECD 2-sided *P* value is from *t* test, assuming nonmultiple measures and normal data distribution and correlation over time. Standard deviation for mean ECD of CyPass was back-calculated from 2-sided 95% CI (from Table 2 in Lass et al.[5]), assuming construction used a normal *t* distribution.
*Statistically significant

points highlighted by the authors of those original publications.[32,33]

Given that corneal endothelial cells do not regenerate, any ECL incurred is additive over the lifetime of the patient. The results of this study indicate that iStent *inject* exhibited the highest endothelial safety both in surgical trauma and long-term placement, contributing the least additional ECL vs control. Hydrus was noted to have increased ECL vs control at the first postoperative ECD measurement, which was believed to be attributable to intraoperative surgical trauma; thereafter, the device exhibited stable endothelial safety. CyPass's chronic progressive ECL implied device-related endothelial safety concerns which ultimately led to its withdrawal from the market.

A strength of this MIGS comparison is the remarkably similar cohort of patients across trials for iStent *inject*, Hydrus Microstent, and CyPass Micro-Stent, including study protocols and control arms, patient demographics, and baseline IOP and ECD measurements. In addition, the masked specular microscopy images were measured in the same reading center across trials, were taken in triplicate to improve accuracy, and were evaluated by 2 to 3 masked readers. A study limitation is that different sites and surgeons with varying techniques between the trials were compared. Another limitation is the discrepancy of trial extension vs continuation through 5 years in the iStent *inject* and CyPass Micro-Stent trials, respectively, compared with the Hydrus Microstent trial, due to the potential risk for selection bias in extension trials. However, both the iStent *inject* and CyPass extension trials discussed this concern in their papers, and neither trial found any significant differences between the 2-year and 5-year patient cohorts.[5,23] This study also compared comprehensive baseline demographic and ocular parameters between treatment and control groups in the 2-year and 5-year cohorts and found no significant differences for any of the 3 devices. Thus, selection bias likely had minimal if any impact. Another limitation is that the trials excluded patients with low baseline ECD, while patients with low baseline ECD and glaucoma can be eligible for cataract surgery in the real-world setting. Such patients are likely more vulnerable than the patients in these studies. Given that there is minimal long-term endothelial data currently available in the MIGS literature, the scope of the present paper was limited to the 3 specific pivotal trials mentioned (the only studies currently available with long-term ECD MIGS data). However, in future years, as more long-term studies are available, a systematic literature review or meta-analysis may be informative.

In conclusion, in the respective pivotal studies, patients who received the iStent *inject* + phaco showed no differences in the proportion of eyes with significant ECL or in mean ECD through 5 years postoperative vs eyes with phaco alone. Eyes with Hydrus + phaco had increased ECL and reduced mean ECD vs eyes with phaco alone. This was noted at 3 months (the first postoperative ECD measurement) and was thought to be attributable to surgical trauma; however, the trends of the Hydrus and control groups were consistent from 3 to 60 months, implying device tolerability. Eyes with CyPass + phaco had increased ECL and reduced mean ECD vs eyes with phaco alone, and the between-group difference increased over time, implying a device-related progressive mechanism of loss.

Each MIGS device has its own comparative efficacy and safety, so device selection is a balance of both factors for each individual patient. This study did not evaluate relative efficacy but sheds light on comparative corneal endothelial safety among MIGS implants. Especially for those with compromised corneal endothelium and/or risk, the impact of intervention and device selection on corneal endothelial cells is an important consideration.

WHAT WAS KNOWN

- Corneal endothelial cell loss (ECL) naturally occurs during aging but can be accelerated in patients with glaucoma due to elevated IOP or treatment. ECL rates vary by treatment type and duration of follow-up.
- At the present time, there is minimal published long-term data on corneal endothelial outcomes after MIGS device surgery. The only rigorous 5-year endothelial data published are from the pivotal trials of the 3 MIGS devices compared in this report.

WHAT THIS PAPER ADDS

- The present analysis assesses 5-year corneal endothelial safety outcomes of 3 MIGS devices (iStent *inject*, Hydrus Microstent, CyPass Micro-Stent) combined with phacoemulsification (phaco) vs their respective phaco-only control group.
- Through 5 years postoperative, there were no differences in proportion of eyes with significant ECL or mean endothelial cell density (ECD) between the iStent *inject* and control groups. Meanwhile, there was greater 5-year ECL and lower ECD in the Hydrus and CyPass groups vs controls. The Hydrus ECL rate mirrored control after 3 months, while the CyPass ECL rate accelerated vs control.
- The present analysis is the first to directly compare all published endothelial datapoints from the 3 pivotal trials, rather than only the datapoints highlighted by the authors of the original publications. Surgeons may use this information to assess the risks and benefits of MIGS surgical options.

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