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REVIEW

Corneal Endothelial Cell Loss in Patients After Minimally Invasive Glaucoma Surgery: Current Perspectives

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Abstract: Minimally invasive glaucoma surgery (MIGS) is a rapidly expanding category of surgical glaucoma treatment options that offer a superior safety profile compared with traditional approaches for reducing intraocular pressure. However, MIGS may cause corneal endothelial cell loss; therefore, it has been receiving increasing attention. This systematic review aimed to evaluate and compare the rate and degree of corneal endothelial loss after MIGS. First, this paper presents an overview of the theoretical effectiveness of MIGS, the fundamental aspects regarding the roles of endothelial cells, and the effect of cataract surgery on the quality and count of endothelial cells. Further, we detail the various surgical techniques involved in MIGS, the development of these techniques over the time, and clinical aspects to consider with respect to the endothelial cell count. We discuss in detail the COMPASS-XT study, which was based on data collected over 5 years, reported that withdrawal of the CyPass Micro-Stent (Alcon Laboratories) yielded increased corneal endothelial cell loss. Generally, MIGS procedures are considered safe, with the incidence of complications ranging from 1% to 20% depending on the surgery type; however, there is still need for studies with longer follow-up. Thus, an adequate count of endothelial cells in the central cornea portion is recommended as necessary for candidate patients for MIGS.

Keywords: minimally invasive glaucoma surgery, endothelial cell loss, corneal decompensation, glaucoma surgery

Introduction

Worldwide, glaucoma is a primary cause of irreversible blindness and is treated by decreasing the intraocular pressure (IOP) to prevent glaucomatous optic neuropathy (GON). Although it remains possible to effectively control IOP with glaucoma eye drops in many patients, for some of them only effective treatment remains glaucoma surgery. (eg, non-compliance with medical recommendations, allergy to eye drops treatment costs. However, topical drop therapy often involves poor adherence (incidence rate: 5–80%), with independent risk factors including lack of education regarding the risk of irreversible vision loss. Moreover, complex dosing regimens involving one or more medications place high demands on patients' daily routines. Furthermore, the chronic use of glaucoma drops, especially those containing preservative agents, is associated with an increased incidence of meibomian gland dysfunction and ocular surface toxicity. Additionally, daily use of topical drops can cause symptoms of burning, photophobia, and irritation. Taken together, these factors promote the discontinuation of or intolerance to the prescribed therapy.[1,2] For these reasons, glaucoma surgery is the only effective treatment alternative for some patients.

Despite considered very effective, classical incision surgical glaucoma procedures, including trabeculectomy, glaucoma shunt implantation (Ex-PRESS), and glaucoma valve implantation (Ahmed, Molteno, Baerveldt), cannot be used in place of pharmacotherapy, thus involve a risk of vision-threatening complications. However, these limitations have been mitigated with the advent of minimally invasive glaucoma surgeries (MIGS).[3,4]

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MIGS seek to decrease the IOP and number of administered glaucoma eye medications with minimal invasiveness and maximal safety manner. This can be achieved by avoiding conjunctival incisions; moreover, this procedure is traditionally performed using an *ab interno* approach and a clear corneal incision, which results in fewer complications and a relatively short recovery period. Safety and effectiveness are the critical factors to account for when considering MIGS. In many cases, MIGS are combined with phacoemulsification, which further reduces the IOP. Since MIGS cannot extensively reduce the IOP as traditional incisional glaucoma surgery, they are mainly used for patients with mild-to-moderate glaucoma.[5,6] Specifically, MIGS are usually used to treat open-angle glaucoma (OAG), including primary open-angle glaucoma (POAG), pseudoexfoliation glaucoma (PXG), and pigmentary glaucoma (PG). Additionally, there have been some papers of MIGS that have been used for primary angle-closure glaucoma (PACG), normal-tension glaucoma (NTG), and uveitic glaucoma; however, minimally invasive procedures are not routinely considered for these glaucoma types.[6] The incidence of complications depends on the type of surgical technique and ranges from 1% to 20%, with an approximate average of 3–5%. The most common early postoperative complication is anterior chamber hemorrhage.[12–14] Compared with MIGS, traditional glaucoma surgeries involve a substantially higher rate of complications. Since MIGS have a moderate effect on the IOP and reduced invasiveness, they are often performed in patients with less advanced glaucoma, younger age, and patients seeking to discontinue or reduce the burden of pharmacotherapy. In these patients, anti-glaucoma surgery is not considered a last-choice treatment after other treatments fail; instead, it is considered as one of the stages in the therapeutic process. Further, the postoperative endothelial quality and activity are of crucial significance. This study aimed to analyze the long-term effects of different MIGS types on corneal endothelial cell loss (CECL). We assumed that increased CECL may result from the chronic presence of a titanium foreign body in the trabecular meshwork, which is rich in phagocytic and antigen-presenting cells;[7,15] extensive manipulation within the anterior chamber during the implantation; and the postoperative contact between the blood and endothelium. Therefore, there is a need to consider how different MIGS procedures, categorized according to the mechanism of IOP reduction, affect corneal endothelial cell density.

MIGS reduce IOP through the following four main mechanisms:

Improved Aqueous Humor Outflow Through the Conventional Pathway (Schlemm's Canal/Trabecular MIGS)

MIGS mainly improve outflow through the conventional pathway, which is based on the premise that the greatest resistance to aqueous humor outflow occurs in the juxtacanalicular trabecular meshwork in most patients with OAG.[7] Specifically, MIGS seek to remove or bypass the inner wall of the Schlemm's canal (SC), which allows improved aqueous humor drainage from the anterior chamber to the collector channels, located in the outer wall of the SC.[5,7] Accordingly, these MIGS procedures reduce the resistance of aqueous humor outflow in the juxtacanalicular system without affecting the outflow resistance at the more distal pathways (ie, episcleral veins). MIGS procedures based on the aforementioned mechanism of action generally are not recommended for normal tension glaucoma since they will not reduce IOP below the episcleral venous pressure.

MIGS procedures with the aforementioned mechanisms include Trabectome, Kahook Dual Blade, iStent and iStent inject, Hydrus microstent, gonioscopy-assisted transluminal trabeculotomy (GATT), and excimer laser trabeculotomy (ELT).[4,8]

Improving Aqueous Humor Outflow Through the Unconventional Pathway (Suprachoroidal MIGS)

Improving aqueous humor outflow through unconventional pathways involves increasing uveoscleral outflow via the suprachoroidal pathway, which accounts for 50% of aqueous humor drainage in the healthy human eye.[9] Regarding the mechanism of action of this outflow pathway, a negative pressure gradient (3–4 mm Hg) between the suprachoroidal space and anterior chamber, creates a potential driving force for aqueous humor outflow from the chamber into the suprachoroidal space.[10] This pressure gradient is positively correlated with IOP. MIGS procedures for improving the uveoscleral pathway for aqueous humor outflow involve implantation of suprachoroidal shunts, which allow improved

outflow of the aqueous humor directly from the anterior chamber into the suprachoroidal space.[5] These MIGS procedures include CyPass microstent and iStent Supra.

Creating the Non-Physiologic Aqueous Humor Outflow Pathway (Subconjunctival MIGS)

In these MIGS procedures, an alternative non-physiological pathway for aqueous humor outflow from the anterior chamber into the subconjunctival space is established using an implant that bypasses the conventional outflow pathway.[7] These procedures are only possible in eyes with preserved mobile conjunctiva, without any adhesions, caused by surgeries, inflammation or injuries. These MIGS procedures include the XEN Gel Stent and PRESERFLO Micro Shunt.

Reducing the Production of Aqueous Humor

Reducing the IOP by decreasing the production of aqueous humor is applied in pharmacological interventions for glaucoma and in procedures for destroying ciliary processes involved in the production of aqueous humor. Traditional approaches are extrasclerally performed, while the most recent procedure being endocyclophotocoagulation (ECP) performed with *ab interno* approach. ECP is recommended for mild-to-moderate glaucoma; contrastingly, transscleral cyclocryotherapy or photocoagulation are recommended for advanced glaucoma and in cases where other surgical methods were unsuccessful. ECP can be combined with cataract phacoemulsification or performed in pseudophakic eyes. In ECP, a curved laser endoscopic probe is introduced into the anterior chamber and then into the sulcus space through a 2.4-mm temporal incision in the clear cornea.[11] Subsequently, the anterior ciliary processes are irradiated using an 810-nm diode laser, which provides light best absorbable by the ciliary body. During one session, approximately 270–360° of the ciliary processes is irradiated, which causes tissue fading and shrinking.[11]

Materials and Methods

Two researchers independently performed a PubMed search for articles published between 2015 and 2022 using the following search terms: corneal endothelial loss, corneal decompensation, minimally invasive glaucoma surgery, trabecular microbypass stent, iStent Supra® (Glaukos, San Clemente, California, USA), Schlemm's canal scaffold, Hydrus® (Ivantis, Irvine, California, USA), suprachoroidal microstent, CyPass® Micro-Stent (Alcon, Fort Worth, Texas, USA), XEN® Gel Stent (Allergan, Irvine, California, USA), and PRESERFLO® Micro Shunt (Santen, Osaka, Japan). The inclusion criteria for the articles were as follows: 1) original research papers, randomized clinical trials, observational studies, and other methodologies; 2) papers describing both procedures combined with phacoemulsification and solo procedures; 3) patients undergoing MIGS (irrespective of age, sex, or ethnicity); and 4) papers published in English until January 2022. The exclusion criteria were review papers, case reports, and articles published in languages other than English. The reviewers browsed the references of included articles to identify potentially relevant articles.

Corneal Endothelium – Anatomy, Physiology, and Natural History

The corneal endothelium is a single layer of cubic cells with high metabolic activity. The cells are located on the posterior corneal surface and anchored to Descemet's membrane. The endothelium borders the aqueous humor of the anterior chamber; moreover, its main function is maintaining optimal corneal translucency by preventing water entry from the anterior chamber to the cornea. This is achieved by an active ion pump system and the carbonic anhydrase enzyme, which remove both water and ions from the corneal stroma into the anterior chamber. However, since the cornea lacks vessels, the endothelial cells have to remain permeable to nutrients and the waste products of keratocyte metabolism.[16,17]

Endothelial cells cannot divide and proliferate; accordingly, their numbers decrease with age by approximately 0.6% per year.[17] At birth, the endothelial cell density (ECD) in the healthy human eye is approximately 6000–7500 cells/mm^2. In childhood, it fluctuates between 3000 and 4000 cells/mm^2, with a gradual decreasing tendency. It reaches approximately 2500 cells/mm^2 at the age of 40 years. In elderly people (aged ≥70 years), who are potential at risk of requiring glaucoma surgery, the number of endothelial cells roughly ranges from 1500 to 2000 cells/mm^2. The exact number of the

ECD, which ensure the safety of intraocular surgery within the anterior eye segment, specifically in terms of avoiding postoperative corneal decompensation, remains unclear. Patients with an ECD of 500–800 cells/mm^2 are at a high risk of endothelial decompensation and postoperative corneal edema. Specifically, the critical value is 500 cells/mm^2, below which corneal decompensation certainly occurs. This may cause corneal opacity and edema, bullous keratopathy, and blindness, which can be solely treated using corneal transplantation.[18]

Corneal Endothelium in Glaucoma

Compared with healthy individuals, patients with glaucoma have a decreased number of corneal endothelial cells, which is dependent on the disease type, duration, progression, and stability. The IOP value is considered the most important determining factor for the extent of CECL in patients with glaucoma.[19] Yu et al[20] reported that patients with POAG had a 6.8% lower ECD than healthy individuals. Furthermore, patients with POAG without and with previous pharmacological treatment had a 3.5% and 9.2% lower ECD, respectively, than healthy individuals. This suggests that topical treatment can also cause changes in the corneal endothelium of patients with glaucoma. Anti-glaucoma medications may have toxic effects on corneal endothelial cells, which are mainly considered to result from the contained preservatives. Pseudoexfoliation syndrome (PEX) and PXG are also associated with a decreased ECD. Compared with healthy individuals, patients with PEX without glaucoma and PXG have 8.2% and 10.4% lower ECD values, respectively.[21] Similar to POAG, elevated IOP is considered to be the cause of CECL in patients with PXG. Nonetheless, local accumulation of pseudoexfoliative material within the anterior chamber, including the cornea, is considered as a crucial contributing factor.[21] This is demonstrated by the large ECD decrease in patients with PEX without glaucoma, where increased IOP is not a crucial factor. Furthermore, ACG has a significant impact on endothelial status. Compared with healthy individuals, patients with acute and chronic ACG have a 9.4% and 35.1% smaller number of endothelial cells, respectively.[22] Additionally, these patients have shown increased pleomorphism and polymegathism of the corneal endothelial cells. Patients with acute ACG have significantly greater corneal thickness than healthy individuals and patients with chronic glaucoma. The greater CECL in patients with ACG than in patients with OAG could be attributed to their higher IOP values, which have been mainly associated with acute glaucoma.[19] The duration of the acute angle closure is positively correlated with CECL. When the angle closure duration is >72 h, it causes 62% greater CECL than that in patients with angle closure duration <72 h.[19] Regarding acute angle closure, endothelial damage occurs due to direct contact between the cornea and iris, as well as impaired aqueous humor outflow. This causes hypoxia and impaired corneal nutritional status.

As aforementioned, topical glaucoma treatment can affect the corneal endothelial status; however, the detrimental effects of any single or combined medication on ECD and endothelial morphology remain unclear.[17] Yu et al[20] suggested that topical medications have toxic effects on the corneal endothelium after comparing treated and untreated patients with glaucoma; however, different conclusions can be drawn from the same study. Specifically, patients with untreated POAG have better endothelial parameters than those treated with pharmacotherapy since they mainly comprise newly diagnosed glaucoma cases and patients with mild stages of the disease. Other studies have reported a 0.68% and 0.6% annual CECL rate in pharmacologically treated patients with glaucoma and healthy individuals without any drops, respectively, which suggests that topical treatment has little effect on the ECD.[23]

Although pharmacological glaucoma treatment has a probable effect on the corneal endothelial status, the effect of surgical treatment is certain. The extent of this effect is strongly dependent on the invasiveness of the procedure. However, when comparing the effects of different surgical techniques related to ECD, it is important to note that more invasive surgeries are performed in advanced glaucoma stages. Accordingly, the more advanced the glaucoma, the worse the baseline corneal endothelial status.

Corneal Endothelial Cell Loss Related to Cataract Phacoemulsification

Cataract surgery affect endothelial cells, with the damage depending on several intraoperative factors, including contact with lens masses, surgical instruments, intraocular implant (IOL), impact of irrigation solutions, and ultrasound activity, as well as postoperative factors, such as IOP elevation,[24] contact between the endothelium and IOL, vitreous body, inflammatory reaction, hemorrhage into the anterior chamber, presence of peripheral anterior adhesions, and post-surgical

alterations in the aqueous humor composition.[25–27] Further, the most significant cell loss is observed during the early perioperative period (up to 1 postoperative month), with the rate of cell loss being greater than the physiological loss even after 10 postoperative years. Furthermore, the postoperative increase in central corneal thickness (edema) is positively correlated with subsequent cell loss.

The Effect of Traditional Incisional Glaucoma Surgery on Endothelial Cell Density

Before the introduction of MIGS, most patients underwent traditional trabeculectomy for glaucoma treatment, which still remains the gold standard in surgical armamentarium. Moreover, patients with OAG frequently underwent other surgery methods, including Ex-PRESS implantation, deep sclerectomy and Ahmed valve, Molteno, or Baerveldt implants being used for more advanced stages. These procedures are relatively invasive and are associated with significant CECL. After 2 postoperative years, the Ahmed valve (New World Medical, Rancho Cucamonga, CA, USA) caused a CECL of 11.5–18.6%,[28–30] which is most extensive in the superior temporal quadrant close to the valve location (22.6%). Two years after placing Molteno implants (Molteno Ophthalmic Limited, Dunedin, New Zealand), the CECL was 12.37%.[30] Additionally, the Baerveldt implant (Johnson and Johnson, New Brunswick, NJ, USA) causes a CECL of 13.7% within 3 postoperative years, with an average annual CECL rate of 4.54% and 6.57% in the corneal center and perimeter, respectively.[31] EX-PRESS shunt implantation and trabeculectomy have slightly fewer adverse effects on corneal density. Specifically, within a short follow-up period (1–3 postoperative months), EX-PRESS did not affect ECD while trabeculectomy caused a CECL of 3.5% and 4.2% after 1 and 3 months, respectively.[32] After 2 follow-up years, the ECD loss after EX-PRESS shunt implantation and trabeculectomy was 2.5% and 6.1–9.1%, respectively.[33] Within 2 postoperative years, solo EX-PRESS shunt implantation was found to have a generally little effect on ECD; however, when combined with phacoemulsification, the CECL was 5.3% greater than that after phacoemulsification alone. Compared with trabeculectomy alone, trabeculectomy combined with phacoemulsification yielded an approximately 5% higher CECL.[33] After 2 follow-up years, Tajo et al[34] reported that the average CECL after EX-PRESS implantation was 7%, with this value depending on the shunt position. Specifically, a CECL of 15% and 5.2% was observed upon EX-PRESS insertion into the cornea and trabecular meshwork, respectively. A 1-year follow-up study on patients after trabeculectomy alone and trabeculectomy combined with phacoemulsification reported the following respective CECL values: 9.6% and 12.3% in the central cornea, and 11.9% and 11.8% in the upper quadrants. Similarly, after deep sclerectomy alone and deep sclerectomy combined with phacoemulsification, the CECL within 1 postoperative year was 4.5% and 7.8% in the central cornea, respectively, and 5.2% and 12.2% in the upper quadrants, respectively.[35]

The Effect of Minimally Invasive Glaucoma Surgery on Endothelial Cell Density

Schlemm's Canal/Trabecular MIGS

Trabectome

Trabectome (NeoMedix Inc, Tustin, California, USA) is an *ab interno* trabeculectomy procedure approved by the US Food and Drug Administration (FDA) in 2004.[36] It involves ablation of the trabecular meshwork with a 550-kHz bipolar electrode to facilitate irrigation, aspiration, and electrocauterization. The 19.5-gauge-tip is designed to fit through a 1.6-mm-or-larger corneal incision. Goniotomy is performed over an area covering 30–180° of the filtration angle, with simultaneous aspiration of the resulting deposits and tissue debris. Simultaneous irrigation maintains the stability of the anterior chamber depth. A retrospective observational study on 159 operated eyes reported no significant CECL throughout the cornea at 3 postoperative years.[37] Trabectome combined with phacoemulsification caused ECD loss in the superior and inferior temporal quadrants by 13.6% and 9.6%, respectively, at 12 postoperative months. Trabectome did not affect the coefficient of variation (CV) or the percentage of hexagonal cells (%HEX). Similarly, Maeda et al[38] reported no significant effect of trabectome on the ECD in their study.

Kahook Dual Blade

The Kahook Dual Blade (KDB, New World Medical Inc., Rancho Cucamonga, California, USA) was introduced in 2015 as an *ab interno* goniotomy and trabeculectomy method.[6] It was designed to allow trabecular meshwork removal with minimal damage to adjacent tissues. It comprises a handle and sharp blade that allows gentle entrance into Schlemm's canal at a 10° angle to the trabecular meshwork plane. Under gonioscope guidance, the blade is inserted *ab interno* into the Schlemm's canal, followed by trabecular meshwork removal within an area of 3–4 clock hours using several available techniques.[8] In a prospective multi-center study, a 3.4% decrease in ECD at 6–29 months after KDB combined with phacoemulsification. There was no correlation between CECL and the postoperative follow-up duration. KDB did not significantly affect the size of CV, %HEX, or central corneal thickness (CCT). Further KDB did not cause corneal edema, corneal decompensation, or other corneal complications.[39] Contrastingly, Ventura-Abreu et al[40] reported that KDB combined with phacoemulsification and phacoemulsification alone yielded a CECL of 25.2% and 11.8%, respectively. These varying CECL values could be dependent on differences in the lens nucleus fragmentation technique and operators. Taken together, although the KDB procedure is safe, it can cause corneal decompensation in patients with low baseline ECD.

Hydrus Microstent

The Hydrus Microstent (Ivantis, Inc., Irvine, California, USA) is a sickle-shaped implant placed in the Schlemm's canal, where it entirely fits given its curvature.[41] An 8-mm-long implant comprised of a flexible, biocompatible material, nitinol®, which is a nickel-titanium alloy, was introduced using an ab interno approach through a clear corneal incision. The implant is directly placed in Schlemm's canal from a preloaded dispensing injector. Upon penetration of the proximal implant tip 1 mm deep into the trabecular meshwork, it is circularly injected into the canal lumen. By positioning the implant within the canal lumen, it is possible to expand the canal at approximately 3 clock hours. The distal end of the implant remains within the anterior chamber lumen. A 6-month follow-up study on the effect of Hydrus poses on the corneal endothelium reported a CECL of 11.7% and 17.4% after combined microstent implantation with phacoemulsification and after phacoemulsification alone, respectively.[42] Taken together, the MIGS (Hydrus) procedure did not significantly affect the postoperative endothelial status and the CECL is entirely dependent on the cataract surgery. Hydrus microstent implantation did not influence the CV or %HEX. Ahmed et al[43] reported that within the first 3 postoperative months, Hydrus combined with phacoemulsification yielded a minimally greater CECL than phacoemulsification alone (13 vs 11%, respectively, with no significant difference). Within 3 postoperative years, CECL increased by 2% in the Hydrus procedure group, reaching 15%, while it remained unchanged in the cataract surgery alone group (11%), with no significant differences. The ECD in the central cornea in the combined and phacoemulsification groups increased by 9 and 13 cells/mm^2, respectively, between 3 and 12 postoperative months.[38] Additionally, both procedures were evaluated with respect to significant endothelial damage based on an ECD loss of ≥30% as the cut-off threshold. At 3 postoperative months, significant CECL was observed in 17.3% and 9.4% of eyes with implanted Hydrus microstent and phacoemulsification, respectively ($p = 0.014$). Throughout the follow-up period, these differences tended to change; additionally, at 3 postoperative years, 14.2% and 10% of patients in the combined surgery group and phacoemulsification alone group, respectively, had a CECL ≥ 30% ($p = 0.239$).[43] The authors concluded that additional manipulation associated with stent implantation and further removal of viscoelastic material yielded a relatively more significant ECD loss after the Hydrus procedure; however, it was not significant compared with that after cataract surgery alone. In contrast, a 3-year clinical follow-up revealed that the presence of the device alone did not compromise the corneal endothelium.

iStent

The iStent (Glaukos Corporation, Laguna Hills, California, USA) is a first-generation trabecular microbypass that directly connects the anterior chamber to Schlemm's canal. It was approved by the FDA for use in 2012. It has an L-shaped design, with a pipe-shaped inlet located in the anterior chamber and a truncated tip mounted in the trabecular meshwork. Given its dimensions (1 mm long, 0.33 mm wide, 0.25 mm pipe length), it is the smallest implant used in humans. Separate iStent orientations are available for the right (OD) and left eye (OS). The iStent is made using heparin-coated biocompatible titanium. To achieve better results, it is possible to apply several stents.[44] The iStent is inserted into

the anterior chamber through an incision in the clear cornea using a dispensing injector, which locates the implant in the trabecular meshwork after pulling the trigger. The iStent is typically inserted in the inferior nasal quadrants, which have the largest number of collector channels, bypassing the resistance within this area and directing the aqueous humor flow from the anterior chamber into the Schlemm's canal.[45,46] Early studies on the effect of iStent implantation on the corneal endothelium reported a CECL of 13.2% after combining with phacoemulsification. However, the lack of a control group impedes making conclusions regarding the effect of iStent implantation and cataract surgery alone on the ECD.[47] A retrospective study with a mean follow-up period of 18.2 months reported a CECL of 9% within 6–29 months after the iStent procedure combined with phacoemulsification. This is consistent with a reported 3.4% of CECL after KDB combined with phacoemulsification. CECL is not correlated with the postoperative follow-up duration. Another study found that iStent implantation did not significantly affect the magnitude of CV and CCT; however, it decreased the % HEX.[39] A further retrospective study reported a CECL of approximately 7.2% within one year after the phacoemulsification procedure combined with iStent implantation.[48] A Japanese study reported a CECL of only 3.6%[49] at 2 years after iStent implantation combined with phacoemulsification. Konopińska et al[50] reported that within 18–24 postoperative months, there was no significant difference in CECL between MIGS combined with surgery and phacoemulsification alone; further, iStent implantation decreased the ECD by only 2.5%.

iStent Inject

The iStent inject (Glaukos Corporation, Laguna Hills, California, USA) is a second-generation iStent model, which was approved by the FDA in 2018.[51] It involves the implantation of two stents, which are smaller than the first-generation stents. Similar to the first-generation iStent, iStent inject is made using heparin-coated biocompatible titanium. The system included an injector with two loaded stents with a central entry and four peripheral openings, which allowed aqueous humor outflow in different directions. The iStent is implanted using an *ab interno* approach in two distant parts of the trabecular meshwork, which theoretically allows a relatively more significant decrease in IOP.[52] A 1-year follow-up study of iStent inject outcomes revealed a similar CECL between cataract surgery alone (14.4%) and phaco-iStent inject combined with surgery (14.6%).[53] A mean decrease in ECD of 9.8% and 16.3% in eyes was reported where two devices and only one iStent were visible, respectively, with no significant between-group differences. There was no significant difference in CCT between before and 12 months after implantation of the iStent inject. Additionally, there was no correlation between the device position in the eye and the CECL value. Contrastingly, a 2-year follow-up study reported a CECL of 13.1% and 12.3% of phacoemulsification alone and combined with iStent inject-phaco surgery, respectively.[54] There were no significant differences in CCT and number of eyes with CECL $\geq$ 30% (9.5% and 10.4%) between phacoemulsification alone and combined with surgery. In both groups, the most significant decrease in corneal density was observed within the first 3 postoperative months (12.5% and 11.6% in the iStent inject and phacoemulsification groups, respectively). Taken together, second-generation iStents have a minimal effect on the corneal endothelium, with an effect being observed after combining iStent implantation with phacoemulsification.

MINIject Supraciliary Drainage System

A 2-year follow-up study by Ahmed et al[55,56] reported promising results with respect to the efficacy and safety of a new supraciliary drainage system. This implant targets the uveoscleral aqueous outflow, which accounts for up to 60% of the drainage system and decreases with age. The implant is made using biocompatible porous silicone material. Its dimensions are a length tube of 5 mm and a diameter of 1.1×0.6 mm. A green ring positioned at 0.5 mm from the device tip allows for accurate positioning in the anterior chamber. A mean reduction of 40.7% in IOP was reported at 24 postoperative months compared with the baseline values. The most common adverse events were anterior chamber reaction (30.8%), reduced visual acuity (30.8%), visual field defects (26.9%), IOP spikes (19.2), and lenticular opacities (19.2), with most resolving spontaneously or after cataract removal. All cases of IOP elevations resolved spontaneously. One patient developed mild, transient hypotony on postoperative day 2, which resolved within 7 days. No suprachoroidal hemorrhages were observed and no additional glaucoma surgeries were required.

Gonioscopy-Assisted Transluminal Trabeculotomy

GATT is a technique of *ab interno* trabeculotomy introduced in 2014.[57] This procedure involves paracenteses in the temporal region and in the superonasal or inferonasal quadrants. An illuminated microcatheter (iTrack, Ellex, Adelaide, Australia) is inserted through nasal paracentesis. A 1–2 mm goniotomy is performed in the nasal part of the trabecular meshwork, with a microsurgical knife under gonioscopic visualization. The microcatheter is introduced into the goniotomy-guided incision using microsurgical forceps inserted into the anterior chamber through temporal paracentesis. The catheter must reach a circumference of 360°, with its position and movement being tracked using the illuminated tip.[4]

Excimer Laser Trabeculotomy

ELT is a laser technology that partly ablates the trabecular meshwork and the inner wall of the Schlemm's canal.[3] A laser probe is inserted into the anterior chamber through a temporal or nasal incision. The laser tip was directly applied to the trabecular meshwork under gonioscopic visualization to 8–10 laser spots, with an even, 500 µm, spacing between each spot. It seeks to create small openings in the anterior part of the trabecular meshwork. ELT applies a 308 nm laser with a spot size of 200 µm and a pulse energy of 1.2 mJ/80 ns.[58]

The effect of GATT and ELT on ECD remains unclear. There is lack of any data in the literature of its influence of these devices on the cornea. Based on the surgical technique, these MIGS procedures are supposed to have a slight effect on the corneal endothelial status.

Suprachoroidal MIGS

CyPass Microstent

The CyPass supraciliary microstent (Alcon Laboratories, Fort Worth, TX) was initially introduced in 2008[59] but was withdrawn in August 2018 due to adverse effects on corneal endothelial status. These adverse effects were reported by Lass et al,[59] where a CECL of 10.1% and 20.4% at 5 years after phacoemulsification alone and combined with CyPass microstent implantation, respectively, was found. Presumably, the CECL value is influenced by the device position and the number of CyPass rings visible in the anterior chamber, which are indicative of the depth of CyPass implantation, as well as possible migration of the implant into the anterior chamber. Furthermore, the number of visible rings (more anterior CyPass placement) is positively correlated with the CECL. This could be attributed to a mechanical effect related to intermittent device-cornea touching. Moreover, there is unclear evidence regarding temporal device migration. A 5-year follow-up study reported no significant differences in terms of CV and %HEX between phacoemulsification alone and combined with CyPass implantation. After the withdrawal of CyPass, the American Society of Cataract and Refractive Surgery has recommended CECL monitoring in patients with this device implanted.[60] For patients with corneal decompensation and edema, who have at least one ring visible, repositioning or entirely removing the CyPass implant is recommended. Fili et al[61] reported that among patients who underwent CyPass removal and were treated using topical steroids and 5% sodium chloride, one patient underwent a posterior lamellar grafting procedure. Further, among patients with CyPass stent implantations affected by corneal complications, it is recommended to trim the stent until the scleral spur. Microsurgical trimming of the CyPass stent is safe and involves a small number of complications, including self-limiting bleeding, iris defects, and iridodialysis.[62] Medra et al[62] reported that 65 CyPass stents in 64 eyes have been trimmed using this method. His study confirmed, that the procedure of CyPasss shortening is associated with few complications, with a markedly reduced risk of intraoperative expulsive bleeding or postoperative fistulation.

iStent Supra

The iStent Supra is a third-generation stent that improves aqueous humor outflow through unconventional rather than conventional pathways. It is made of polyethersulfone and a colored titanium sleeve. It is comprised of a 4-mm tube with a hole at each end and is placed in the suprachoroidal space using *an ab interno* approach. It was designed to establish a new outflow pathway from the anterior chamber into the suprachoroidal space and is equipped with retention rings to ensure implantation site stability.[63] This MIGS type is not yet commercially available; therefore, there are insufficient clinical data regarding its safety and impact on the corneal endothelium.

Subconjunctival MIGS

XEN Gel Stent

The FDA approved XEN GEL Stent (Allergan INC, Dublin, Ireland) for use in 2016. The implant is made of non-resorbable soft cross-linked collagen, which has a tubular shape, is 6 mm long, and is available in the following sizes: 140, 63, or 45 µm. These stents can be implanted using both *ab interno* and *ab externo* approaches. In the *ab interno* approach, the implant is inserted into the anterior chamber through a corneal incision in the inferotemporal quadrant made using a bent 27 G needle blade. The sharp end of the implant is inserted through the trabecular meshwork and sclera into the subconjunctival space, which is approximately 2.5–3 mm posterior to the corneal limbus. This allows the connection of the anterior chamber to the subconjunctival space. Subsequently, the tube is irrigated to confirm the proper placement and formation of the filter cushion. Regarding the corneal endothelial status, a short follow-up study reported a CECL value of 2.1% at 3 months after XEN Gel Stent implantation.[64] Another 6-month follow-up study reported CECL values of 5.6%, 11.3%, and 13% in eyes with only XEN Gel Stent implantation, the XEN-phaco combined procedure, and phacoemulsification alone, respectively.[65] A comparison of CECL outcomes following combined surgery and phacoemulsification alone suggested that the cataract extraction procedure is the most important cause of CECL. Furthermore, the implantation itself had a small influence on the endothelial status. However, the 5.6% CECL value in the XEN-solo group is inconsistent with the aforementioned claim. However, 72% of patients who underwent XEN Gel Stent implantation alone had already undergone previous cataract surgery; moreover, they showed the poorest baseline corneal endothelium status. Patients in the XEN-phaco and phaco alone groups had higher baseline ECD values by approximately 300 cells/mm^2. Consequently, this may yield greater CECL in individuals with a "weaker" endothelium at baseline after cataract surgery. There were no significant differences in CCT in patients after XEN Gel implantation, combined XEN-phaco surgery, and phacoemulsification alone. A 2-year follow-up study by Gillmann et al[66] reported a similar CECL value between XEN Gel Stent surgery combined with phacoemulsification (14.3%) and phacoemulsification surgery alone (14.5%). In the combined XEN surgery group, the CECL of patients who required and did not require mitomycin-C (MMC)-enhanced needling revision was 13.1% and 15.4%, respectively. This suggested that using MMC during the revision procedure improves the endothelial safety; moreover, CECL is only caused by the direct contact between the antimetabolite and corneal endothelium. Additionally, it was suggested that the amount of MMC that penetrates the anterior chamber during needling revision is minimal and does not affect the endothelial status. Similar to the negative experience related to CyPass, which results from implant migration into the anterior chamber, XEN Gel Stent dislocation into the anterior chamber has been reported, which causes local corneal damage and a 2.1% ECD reduction within 30 days.[53] However, there was not effect on the CCT during the monthly follow-up.

PRESERFLO Microshunt

The PRESEFFLO microshunt (Santen Pharmaceutical Co. Ltd, Osaka, Japan), which is formerly known as the InnFocus microshunt, is designed to increase posterior aqueous humor outflow, which allows the formation of a perfect vesicle with walls thinner than those observed in conventional filtration surgery as well as a more posterior location.[67] Although it is implanted *ab externo*, it meets all the MIGS criteria proposed by the American Glaucoma Society and US FDA. Similar to filtration procedures, it does not require the preparation of the scleral flap. However, it only involves the formation of an intrascleral tunnel with a 27 G needle, which is used to introduce the shunt tip into the anterior chamber, while the distal end remains within the space under Tenon's capsule. A study reported no changes in the ECD and %HEX at 6 months after PRESEFFLO microshunt implantation; however, there was a significant change in the CV ($p = 0.003$).[68] A large multicenter study reported a CECL of 5.2% at 1 year after PRESERFLO Microshunt implantation. In one case, the CECL value was higher (9.4%), which was attributed to the close proximity of the microshunt to the cornea.[69,70]

Discussion

This review demonstrated that the safety of individual MIGS procedures with respect to the corneal endothelium remains unclear due to insufficient clinical data. However, MIGS treatments appear to have little effect on the ECD, do not cause corneal decompensation or edema, and do not compromise vision. Since most cases of MIGS are performed in combination with phacoemulsification, post-operative CECL may mainly result from cataract surgery itself.

The patient characteristics should be considered when analyzing clinical data regarding the impact of MIGS procedures on the corneal endothelium. This includes age, which directly influences the corneal endothelial status. Furthermore, patients with glaucoma have a significantly decreased ECD compared with healthy individuals. The influence of topical anti-glaucoma treatment on endothelial status remains unclear. However, the effect of cytostatics, including MMC, which are used during the intraoperative and postoperative periods, should be considered. Candidate eyes for MIGS that have previously removed cataracts presented with a weakened endothelium at baseline. However, further studies comparing combined surgeries with stand-alone procedures are warranted to confirm the reliability of their results, which acknowledges the numerous factors to consider when interpreting and comparing different clinical trials.

Several factors influence the surgery outcomes, including postoperative IOP and visual acuity. Moreover, it is important to ensure proper suitability of surgery. Regarding perioperative safety, patients qualified for the MIGS procedure require an adequate number of endothelial cells in the central part. It is important to ensure that the number of endothelial cells allows approximately 10% acute surgical cell loss and a subsequent gradual annual CECL of 2%, with the ECD at 72 years being ≥1000 cells/mm^2.[67]

Currently, the safety of all MIGS procedures, except for the withdrawn CyPass microstent implantation procedure, should be considered with respect to their effects on the corneal endothelium. However, most of the discussed studies only reported short-term outcomes regarding the corneal endothelium status. Further research, especially long-term follow-up outcomes, is warranted.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Kesav NP, Young CEC, Ertel MK, Seibold LK, Kahook MY. Sustained-release drug delivery systems for the treatment of glaucoma. *Int J Ophthalmol*. 2021;14(1):148–159. doi:10.18240/ijo.2021.01.21
2. Zhang X, Vadoothker S, Munir WM, Saeedi O. Ocular surface disease and glaucoma medications: a clinical approach. *Eye Contact Lens*. 2019;45(1):11–18. doi:10.1097/ICL.0000000000000544
3. Saheb H, Ahmed II. Micro-invasive glaucoma surgery: current perspectives and future directions. *Curr Opin Ophthalmol*. 2012;23(2):96–104. doi:10.1097/ICU.0b013e32834ff1e7
4. Al Habash A, Alrushoud M, Al Abdulsalam O, Al Somali AI, Aljindan M, Al Ahmadi AS. Combined gonioscopy-assisted transluminal trabeculotomy (GATT) with Ab interno canaloplasty (ABiC) in conjunction with phacoemulsification: 12-month outcomes. *Clin Ophthalmol*. 2020;14:2491–2496. doi:10.2147/OPTH.S267303
5. Richter GM, Coleman AL. Minimally invasive glaucoma surgery: current status and future prospects. *Clin Ophthalmol*. 2016;10:189–206. doi:10.2147/OPTH.S80490
6. Birnbaum FA, Neeson C, Solá-Del Valle D. Microinvasive glaucoma surgery: an evidence-based review. *Semin Ophthalmol*. 2021;36(8):772–786. doi:10.1080/08820538.2021.1903513
7. Jabłońska J, Lewczuk K, Konopińska J, Mariak Z, Rękas M. Microinvasive glaucoma surgery: a review and classification of implant-dependent procedures and techniques. *Acta Ophthalmol*. 2021;100:e327–e338.
8. Konopińska J, Lewczuk K, Jabłońska J, Mariak Z, Rękas M. Microinvasive glaucoma surgery: a review of schlemm's canal-based procedures. *Clin Ophthalmol*. 2021;15:1109–1118. doi:10.2147/OPTH.S293702
9. Toris CB, Yablonski ME, Wang YL, Camras CB. Aqueous humor dynamics in the aging human eye. *Am J Ophthalmol*. 1999;127(4):407–412. doi:10.1016/S0002-9394(98)00436-X
10. Emi K, Pederson JE, Toris CB. Hydrostatic pressure of the suprachoroidal space. *Invest Ophthalmol Vis Sci*. 1989;30(2):233–238.
11. Siegel MJ, Boling WS, Faridi OS, et al. Combined endoscopic cyclophotocoagulation and phacoemulsification versus phacoemulsification alone in the treatment of mild to moderate glaucoma. *Clin Exp Ophthalmol*. 2015;43(6):531–539. doi:10.1111/ceo.12510
12. Yook E, Vinod K, Panarelli JF. Complications of micro-invasive glaucoma surgery. *Curr Opin Ophthalmol*. 2018;29(2):147–154. doi:10.1097/ICU.0000000000000457
13. Brandão LM, Grieshaber MC. Update on minimally invasive glaucoma surgery (MIGS) and new implants. *J Ophthalmol*. 2013;2013:705915. doi:10.1155/2013/705915
14. Gołaszewska K, Konopińska J, Obuchowska I. Evaluation of the efficacy and safety of canaloplasty and iStent bypass implantation in patients with open-angle glaucoma: a review of the literature. *J Clin Med*. 2021;10(21):4881. doi:10.3390/jcm10214881
15. Dang Y, Waxman S, Wang C, Shah P, Loewen RT, Loewen NA. Intraocular pressure elevation precedes a phagocytosis decline in a model of pigmentary glaucoma. *F1000Res*. 2018;7:174. doi:10.12688/f1000research.13797.1
16. Bourne WM. Biology of the corneal endothelium in health and disease. *Eye*. 2003;17(8):912–918. doi:10.1038/sj.eye.6700559
17. Realini T, Gupta PK, Radcliffe NM, et al. The effects of glaucoma and glaucoma therapies on corneal endothelial cell density. *J Glaucoma*. 2021;30(3):209–218. doi:10.1097/IJG.0000000000001722
18. Bourne WM, Nelson LR, Hodge DO. Central corneal endothelial cell changes over a ten-year period. *Invest Ophthalmol Vis Sci*. 1997;38(3):779–782.

19. Janson BJ, Alward WL, Kwon YH, et al. Glaucoma-associated corneal endothelial cell damage: a review. *Surv Ophthalmol*. 2018;63(4):500–506. doi:10.1016/j.survophthal.2017.11.002
20. Yu ZY, Wu L, Qu B. Changes in corneal endothelial cell density in patients with primary open-angle glaucoma. *World J Clin Cases*. 2019;7(15):1978–1985. doi:10.12998/wjcc.v7.i15.1978
21. Tomaszewski BT, Zalewska R, Mariak Z. Evaluation of the endothelial cell density and the central corneal thickness in pseudoexfoliation syndrome and pseudoexfoliation glaucoma. *J Ophthalmol*. 2014;2014:123683. doi:10.1155/2014/123683
22. Sihota R, Lakshmaiah NC, Titiyal JS, Dada T, Agarwal HC. Corneal endothelial status in the subtypes of primary angle closure glaucoma. *Clin Exp Ophthalmol*. 2003;31(6):492–495. doi:10.1046/j.1442-9071.2003.00710.x
23. Baratz KH, Nau CB, Winter EJ, et al. Effects of glaucoma medications on corneal endothelium, keratocytes, and subbasal nerves among participants in the ocular hypertension treatment study. *Cornea*. 2006;25(9):1046–1052. doi:10.1097/01.ico.0000230499.07273.c5
24. Gagnon MM, Boisjoly HM, Brunette I, Charest M, Amyot M. Corneal endothelial cell density in glaucoma. *Cornea*. 1997;16(3):314–318. doi:10.1097/00003226-199705000-00010
25. Hayashi K, Hayashi H, Nakao F, Hayashi F. Risk factors for corneal endothelial injury during phacoemulsification. *J Cataract Refract Surg*. 1996;22(8):1079–1084. doi:10.1016/S0886-3350(96)80121-0
26. Fujita K, Kitagawa K, Ueta Y, Nakamura T, Miyakoshi A, Hayashi A. Short-term results of canaloplasty surgery for primary open-angle glaucoma in Japanese patients. *Case Rep Ophthalmol*. 2011;2(1):65–68. doi:10.1159/000324808
27. Sagoo P, Chan G, Larkin DF, George AJ. Inflammatory cytokines induce apoptosis of corneal endothelium through nitric oxide. *Invest Ophthalmol Vis Sci*. 2004;45(11):3964–3973. doi:10.1167/iovs.04-0439
28. Kim CS, Yim JH, Lee EK, Lee NH. Changes in corneal endothelial cell density and morphology after Ahmed glaucoma valve implantation during the first year of follow up. *Clin Experiment Ophthalmol*. 2008;36(2):142–147. doi:10.1111/j.1442-9071.2008.01683.x
29. Lee EK, Yun YJ, Lee JE, Yim JH, Kim CS. Changes in corneal endothelial cells after Ahmed glaucoma valve implantation: 2-year follow-up. *Am J Ophthalmol*. 2009;148(3):361–367. doi:10.1016/j.ajo.2009.04.016
30. Nassiri N, Nassiri N, Majdi NM, et al. Corneal endothelial cell changes after Ahmed valve and Molteno glaucoma implants. *Ophthalmic Surg Lasers Imaging*. 2011;42(5):394–399. doi:10.3928/15428877-20110812-04
31. Tan AN, Webers CA, Berendschot TT, et al. Corneal endothelial cell loss after Baerveldt glaucoma drainage device implantation in the anterior chamber. *Acta Ophthalmol*. 2017;95(1):91–96. doi:10.1111/aos.13161
32. Casini G, Loiudice P, Pellegrini M, et al. Trabeculectomy versus EX-PRESS shunt versus Ahmed valve implant: short-term effects on corneal endothelial cells. *Am J Ophthalmol*. 2015;160(6):1185–1190.e1. doi:10.1016/j.ajo.2015.08.022
33. Omatsu S, Hirooka K, Nitta E, Ukegawa K. Changes in corneal endothelial cells after trabeculectomy and EX-PRESS shunt: 2-year follow-up. *BMC Ophthalmol*. 2018;18(1):243. doi:10.1186/s12886-018-0913-0
34. Tojo N, Numata A, Hayashi A. Factors influencing the reduction in corneal endothelial cells after Ex-Press(®) surgery. *Int Ophthalmol*. 2020;40(5):1201–1208. doi:10.1007/s10792-020-01286-8
35. Arnavielle S, Lafontaine PO, Bidot S, Creuzot-Garcher C, D'Athis P, Bron AM. Corneal endothelial cell changes after trabeculectomy and deep sclerectomy. *J Glaucoma*. 2007;16(3):324–328. doi:10.1097/IJG.0b013e3180391a04
36. Polat JK, Loewen NA. Combined phacoemulsification and trabectome for treatment of glaucoma. *Surv Ophthalmol*. 2017;62(5):698–705. doi:10.1016/j.survophthal.2016.03.012
37. Kasahara M, Shoji N, Matsumura K. The influence of trabectome surgery on corneal endothelial cells. *J Glaucoma*. 2019;28(2):150–153. doi:10.1097/IJG.0000000000001128
38. Maeda M, Watanabe M, Ichikawa K. Evaluation of trabectome in open-angle glaucoma. *J Glaucoma*. 2013;22(3):205–208. doi:10.1097/IJG.0b013e3182311b92
39. Dorairaj S, Balasubramani GK. Corneal endothelial cell changes after phacoemulsification combined with excisional goniotomy with the Kahook dual blade or iStent: a prospective fellow-eye comparison. *Clin Ophthalmol*. 2020;14:4047–4053. doi:10.2147/OPTH.S263072
40. Ventura-Abreu N, García-Feijoo J, Pazos M, Biarnés M, Morales-Fernández L, Martínez-de-la-Casa JM. Twelve-month results of ab interno trabeculectomy with Kahook Dual Blade: an interventional, randomized, controlled clinical study. *Graefes Arch Clin Exp Ophthalmol*. 2021;259(9):2771–2781. doi:10.1007/s00417-021-05213-0
41. Otarola F, Virgili G, Shah A, Hu K, Bunce C, Gazzard G. Ab interno trabecular bypass surgery with Schlemm´s canal microstent (Hydrus) for open angle glaucoma. *Cochrane Database Syst Rev*. 2020;2020(3). doi:10.1002/14651858.CD012740.pub2
42. Fea AM, Consolandi G, Pignata G, et al. A comparison of endothelial cell loss in combined cataract and MIGS (Hydrus) procedure to phacoemulsification alone: 6-month results. *J Ophthalmol*. 2015;2015:769289. doi:10.1155/2015/769289
43. Ahmed IIK, Rhee DJ, Jones J, et al. Three-year findings of the HORIZON Trial: a Schlemm canal microstent for pressure reduction in primary open-angle glaucoma and cataract. *Ophthalmology*. 2021;128:857–865. doi:10.1016/j.ophtha.2020.11.004
44. Katz LJ, Erb C, Carceller GA, et al. Prospective, randomized study of one, two, or three trabecular bypass stents in open-angle glaucoma subjects on topical hypotensive medication. *Clin Ophthalmol*. 2015;9:2313–2320. doi:10.2147/OPTH.S96695
45. Saheb H, Gedde SJ, Schiffman JC, Feuer WJ. Outcomes of glaucoma reoperations in the Tube Versus Trabeculectomy (TVT) Study. *Am J Ophthalmol*. 2014;157(6):1179–1189.e2. doi:10.1016/j.ajo.2014.02.027
46. Le K, Saheb H. iStent trabecular micro-bypass stent for open-angle glaucoma. *Clin Ophthalmol*. 2014;8:1937–1945. doi:10.2147/OPTH.S45920
47. Arriola-Villalobos P, Martínez-de-la-Casa JM, Díaz-Valle D, et al. Mid-term evaluation of the new Glaukos iStent with phacoemulsification in coexistent open-angle glaucoma or ocular hypertension and cataract. *Br J Ophthalmol*. 2013;97(10):1250–1255. doi:10.1136/bjophthalmol-2012-302394
48. Takayanagi Y, Ichioka S, Ishida A, Tsutsui A, Tanito M. Fellow-eye comparison between phaco-microhook ab-interno trabeculotomy and phaco-istent trabecular micro-bypass stent. *J Clin Med*. 2021;10(10):2129. doi:10.3390/jcm10102129
49. Nitta K, Yamada Y, Morokado S, Sugiyama K. iStent trabecular micro-bypass stent implantation with cataract surgery in a Japanese glaucoma population. *Clin Ophthalmol*. 2020;14:3381–3391. doi:10.2147/OPTH.S274281
50. Konopińska J, Saeed E, Lisowski Ł, et al. Evaluation of the effect of the first generation iStent on corneal endothelial cell loss-a match case-control study. *J Clin Med*. 2021;10:19. doi:10.3390/jcm10194410
51. Al Habash A, Khan O. Outcomes of combined iStent trabecular micro-bypass and cataract surgery for the treatment of open-angle glaucoma in a Saudi population. *Clin Ophthalmol*. 2020;14:1573–1580. doi:10.2147/OPTH.S249261

52. Paletta Guedes RA, Gravina DM, Paletta Guedes VM, Chaoubah A. iStent inject (Second-generation Trabecular Microbypass) versus nonpenetrating deep sclerectomy in association with phacoemulsification for the surgical treatment of open-angle glaucoma and cataracts: 1-year results. *J Glaucoma*. 2020;29(10):905–911. doi:10.1097/IJG.0000000000001576
53. Gillmann K, Mansouri K, Ambresin A, Bravetti GE, Mermoud A. A prospective analysis of iStent inject microstent implantation: surgical outcomes, endothelial cell density, and device position at 12 months. *J Glaucoma*. 2020;29(8):639–647. doi:10.1097/IJG.0000000000001546
54. Samuelson TW, Sarkisian SR Jr, Lubeck DM, et al. Prospective, randomized, controlled pivotal trial of an Ab Interno implanted trabecular microbypass in primary open-angle glaucoma and cataract: two-year results. *Ophthalmology*. 2019;126(6):811–821. doi:10.1016/j.ophtha.2019.03.006
55. Denis P, Hirneiß C, Durr GM, et al. Two-year outcomes of the MINIject drainage system for uncontrolled glaucoma from the STAR-I first-in-human trial. *Br J Ophthalmol*. 2022;106(1):65–70. doi:10.1136/bjophthalmol-2020-316888
56. Denis P, Hirneiß C, Reddy KP, et al. A first-in-human study of the efficacy and safety of MINIject in patients with medically uncontrolled open-angle glaucoma (STAR-I). *Ophthalmol Glaucoma*. 2019;2(5):290–297. doi:10.1016/j.ogla.2019.06.001
57. Grover DS, Godfrey DG, Smith O, Feuer WJ, Montes de Oca I, Fellman RL. Gonioscopy-assisted transluminal trabeculotomy, ab interno trabeculotomy: technique report and preliminary results. *Ophthalmology*. 2014;121(4):855–861. doi:10.1016/j.ophtha.2013.11.001
58. Durr GM, Töteberg-Harms M, Lewis R, Fea A, Marolo P, Ahmed IIK. Current review of excimer laser trabeculostomy. *Eye Vis*. 2020;7:24. doi:10.1186/s40662-020-00190-7
59. Lass JH, Benetz BA, He J, et al. Corneal endothelial cell loss and morphometric changes 5 years after phacoemulsification with or without cypass micro-stent. *Am J Ophthalmol*. 2019;208:211–218. doi:10.1016/j.ajo.2019.07.016
60. FDA. Available from: https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/alcon-announces-voluntary-global-market-withdrawal-cypass-micro-stent-surgical-glaucoma. Accessed May 22, 2022.
61. Fili S, Seddig S, Vastardis I, Perdikakis G, Wölfelschneider P, Kohlhaas M. Explantation of the CyPass implant in a case series of patients with corneal decompensation. *Ophthalmologe*. 2021;118(1):42–49. doi:10.1007/s00347-020-01106-5
62. Medra A, Schwanengel M, Weber A, Brinkmann CK. Microsurgical trimming of the CyPass stent: surgical procedure of the Neubrandenburg Eye Clinic. *Ophthalmologe*. 2020;117(12):1241–1246. doi:10.1007/s00347-020-01247-7
63. Myers JS, Masood I, Hornbeak DM, et al. Prospective evaluation of two iStent® trabecular stents, one iStent Supra® Suprachoroidal Stent, and postoperative prostaglandin in refractory glaucoma: 4-year outcomes. *Adv Ther*. 2018;35(3):395–407. doi:10.1007/s12325-018-0666-4
64. Olgun A, Duzgun E, Yildiz AM, Atmaca F, Yildiz AA, Sendul SY. XEN Gel Stent versus trabeculectomy: short-term effects on corneal endothelial cells. *Eur J Ophthalmol*. 2020;31:346–353.
65. Sacchi M, Agnifili L, Brescia L, et al. Structural imaging of conjunctival filtering blebs in XEN gel implantation and trabeculectomy: a confocal and anterior segment optical coherence tomography study. *Graefes Arch Clin Exp Ophthalmol*. 2020;258(8):1763–1770. doi:10.1007/s00417-020-04671-2
66. Gillmann K, Bravetti GE, Mermoud A, Rao HL, Mansouri K. XEN gel stent in pseudoexfoliative glaucoma: 2-year results of a prospective evaluation. *J Glaucoma*. 2019;28(8):676–684. doi:10.1097/IJG.0000000000001295
67. Sadruddin O, Pinchuk L, Angeles R, Palmberg P. Ab externo implantation of the MicroShunt, a poly (styrene-block-isobutylene-block-styrene) surgical device for the treatment of primary open-angle glaucoma: a review. *Eye Vis*. 2019;6:36. doi:10.1186/s40662-019-0162-1
68. Pillunat KR, Herber R, Haase MA, Jamke M, Jasper CS, Pillunat LE. PRESERFLO™ MicroShunt versus trabeculectomy: first results on efficacy and safety. *Acta Ophthalmol*. 2021;100:e779–e790. doi:10.1111/aos.14968
69. Baker ND, Barnebey HS, Moster MR, et al. Ab-Externo MicroShunt versus trabeculectomy in primary open-angle glaucoma: one-year results from a 2-year randomized, multicenter study. *Ophthalmology*. 2021;128(12):1710–1721. doi:10.1016/j.ophtha.2021.05.023
70. American National Standard Institute. American national standard for ophthalmics-implantable glaucoma devices (standard No. Z80.27-2014); 2019. Available from: https://webstore.ansi.org/Standard/VC%20(ASC%20Z80)/ANSIZ80272014. Accessed May 19, 2022.