ESCRS
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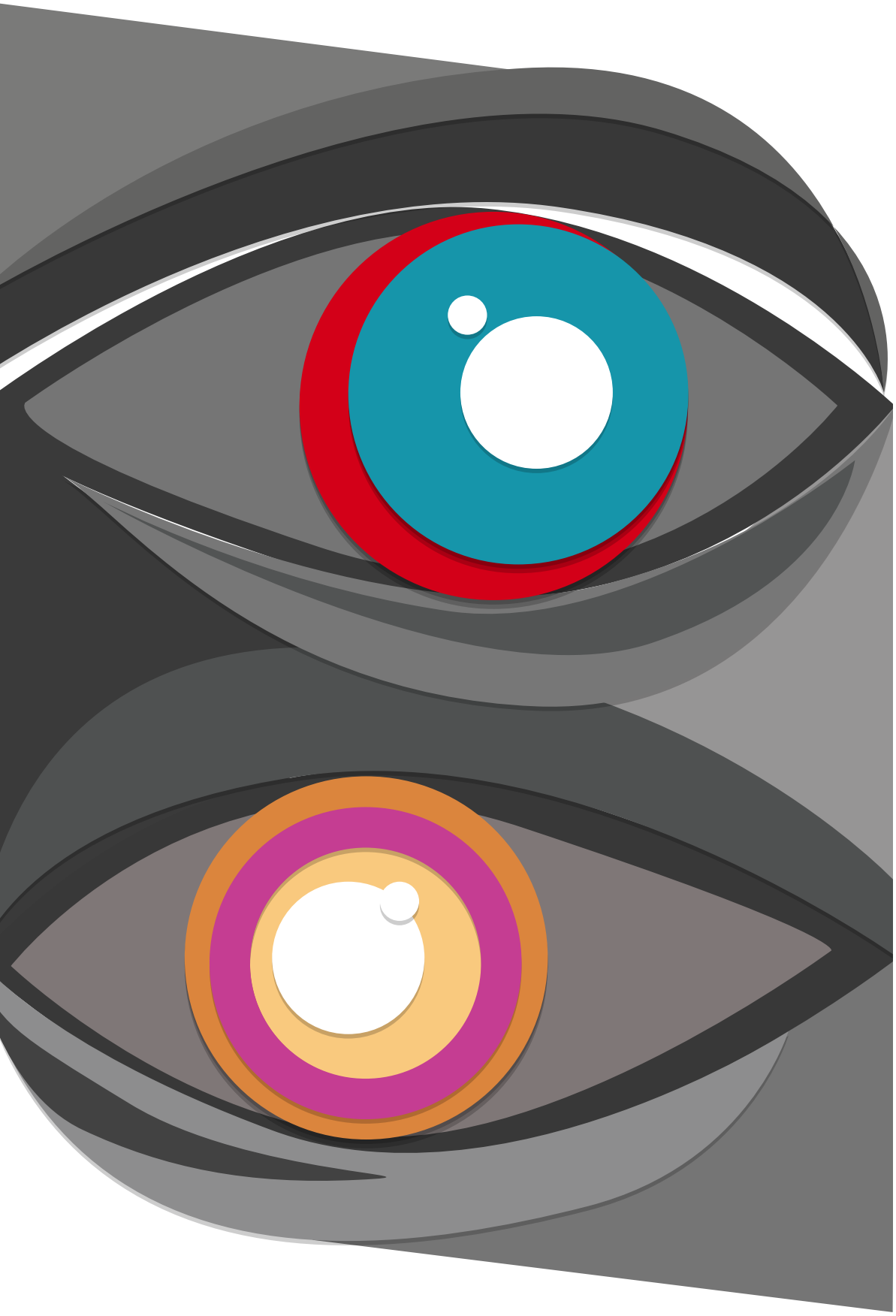
Optimising the latest Medical Therapies

& Modern MIGS for the Glaucoma Cataract Patient



ESCRS
Education Forum

ESCRS Clinical Trends Survey Provides Insight into Medical Therapies and Use of MIGS

Roberto Bellucci, MD

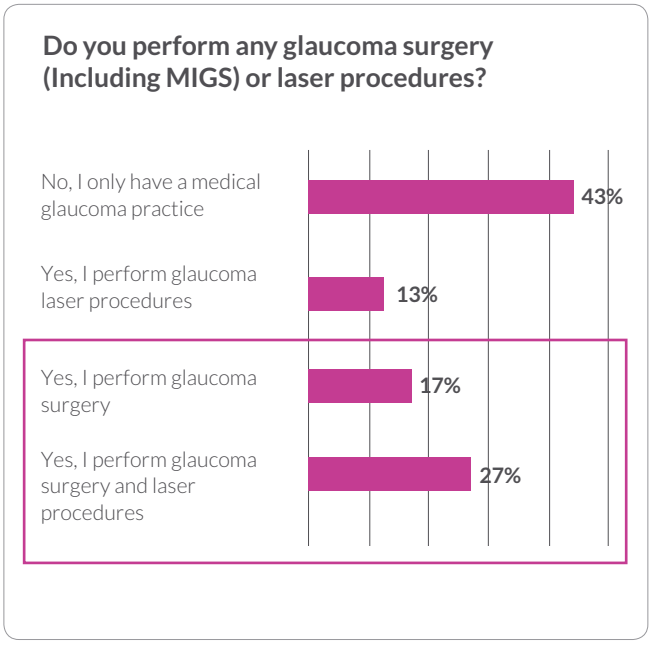
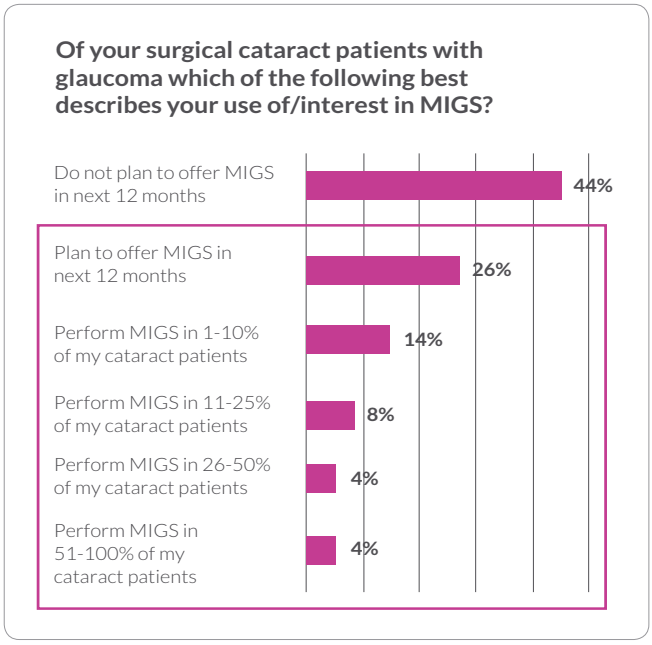


Figure 1. Results from the ESCRS 2018 Clinical Trends Survey show that 44% of delegates perform glaucoma surgery procedures.



56% of survey respondents are currently using or plan to incorporate minimally invasive glaucoma surgery (MIGS) in the next 12 months.

The 2018 European Society of Cataract & Refractive Surgeons (ESCRS) Clinical Trends Survey asked 155 questions to over 1,200 delegates in order to address practice patterns and obstacles in improving clinical outcomes. The ESCRS Survey provides the basis for educational programming in line with the survey responders' interests. The result is a new type of educational programming, an evidence-based series, including tactics such as live events and digital education. Highlighted survey topics included cataract surgery, postoperative medications, compliance, glaucoma, and the use of minimally invasive glaucoma surgery (MIGS).

Results of the ESCRS Survey provide information about the current state of ophthalmologists' expertise and also highlight desired areas of focus.[1] Patients with glaucoma comprise a significant portion of ESCRS delegates' patients. Over 96% of delegates see glaucoma patients: 29% reported seeing between 10 and 30 patients per month and 27% perform glaucoma surgery and laser procedures. In addition to seeing a majority of patients with glaucoma, survey respondents share concern for patient compliance when they are prescribed one or more topical glaucoma medications. In fact, 2018 ESCRS survey respondents believe that a third of patients who are prescribed one or more topical medications are not compliant.

MIGS is a fairly recent development in the treatment of glaucoma. This approach can decrease intraocular pressure in the cataract patient and decrease the need for one or more topical glaucoma medications, thus increasing patient compliance. The majority of ESCRS delegates know about MIGS but believe less than 10% of their cataract patients with glaucoma to be candidates for MIGS. Glaucoma surgery and laser procedures are performed by 44% of ESCRS delegates, with 62% initiating laser intervention after use of one or more medications, and 56% are using or planning to use MIGS in the next year (Figure 1).

Based on the 2018 ESCRS Clinical Trends Survey, there exists a strong interest in MIGS, yet the confidence and understanding required to perform the surgery needs be improved. Addressing these concerns through improving understanding of new developments in glaucoma treatment and MIGS procedures will continue to be a focus of ESCRS.

> **"The ESCRS Survey provides the basis for educational programming in line with the survey responders' interest**

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The Benefits of Early Intervention for the Glaucoma Patient

Philippe Denis, MD, PhD

Glaucoma, usually caused by a buildup of pressure in the eye, can lead to damage of the optic nerve and even blindness if left untreated. Methods for treating glaucoma include eye drops, laser procedures, and surgery. However, surgical intervention is often used late in the patient's disease progression. As an ophthalmologist and researcher in the field, I believe that earlier surgical intervention for glaucoma can provide patients with substantial long-term benefit.

The decision to treat a glaucoma patient surgically is not an easy choice and not one to be taken lightly. The most critical part of deciding if a patient is suited for surgery is to remember that each patient is unique, yet there are three factors that can be considered during this process.

First, an assessment of the rate of glaucoma disease progression is necessary. Glaucoma typically progresses slowly and silently, but approximately 5% of glaucoma patients are fast progressors, defined as having a mean defect loss of at least -2dB per year. The ability to separate fast progressors from slow progressors helps us to promote and propose an appropriately aggressive treatment for those with the highest risk for visual disability. For these fast progressors, early intervention is critical with early surgery providing more benefits than later surgery. Disease progression in patients may also occur because of a late diagnosis, insufficient intraocular pressure (IOP) lowering or fluctuations, a lack of patient compliance/adherence/attendance, or insufficient monitoring of progression at regular intervals. The ability to separate fast versus slow progressors is critical to proposing a more aggressive treatment for the patient with the highest risk of visual disability (Figure 2).

Second, it is important to avoid ocular surface toxicity. Ocular surface toxicity is a common comorbidity in patients with glaucoma due to the prevalence of topical eye drops. Monotherapy with eye drops may be successful; however, many patients require two or even three topical medications to reduce IOP. A high prevalence of ocular surface diseases has been reported among patients with glaucoma, and the severity of symptoms has been positively correlated to the number of topical antiglaucoma medications. The added treatments may provide progressively lower levels of efficacy, thus forcing patients and physicians to question the cost to benefit ratio of adding more topical medications to a patient's disease management protocol. Glaucoma filtering surgery is a good way to avoid ocular surface toxicity. Often, early surgical intervention prevents the need for one or more topical medications, alleviating signs and symptoms of ocular surface toxicity.

Lastly, one must note that early intervention may help avoid the progression of glaucoma to causing severe visual impairment, including blindness. This benefit is most seen in naïve patients compared to those who are previously medicated or who use preservatives.

The benefits of early surgical intervention lie in lowering intraocular pressure. Results of the Advanced Glaucoma Intervention Study suggest that lower pressure is associated with better visual field protection, with post hoc analysis of this dataset suggesting that achieving IOP of 12mm mean or less than 18mm Mercury to stop progression.[2] When comparing surgical intervention to eye drops for the lowering of IOP, the

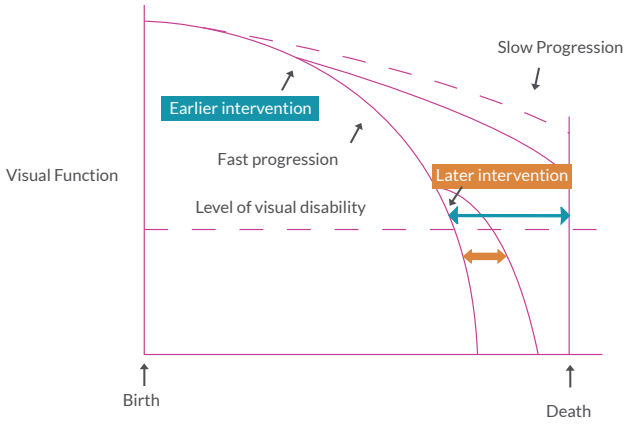

Figure 2. The effect of timing of the intervention on rate of progression shows that fast progressors benefit more from early, rather than late surgical intervention.

Collaborative Initial Glaucoma Treatment Study showed that in an eight-year follow-up, the surgically treated group had lower IOP levels (15mmHg versus 18mmHg), but presented with similar visual field progression rates.[3] Interestingly, the benefit for mean lower IOP was seen more strongly for patients with advanced cases who were originally treated with surgery. An added benefit for these patients included elimination or attenuation of extreme fluctuation or variability in IOP (e.g. less change in IOP from sitting to supine positions).

Glaucoma is, in most cases, a slow and symptomatic disease with a very late visual loss. Thus, early intervention is key. There are typically two approaches for treating glaucoma. The conservative approach is to treat modest increases in IOP conservatively with topical medication and only once it progresses, to escalate therapy. The more aggressive approach is to treat the patient early by assessing the risk of progression and, if there is high risk, to proceed to surgical intervention in order to take the patient out of risk of blindness. I would recommend the latter: don't waste time observing disease progression but be aggressive in treating it.

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New Developments in Glaucoma Medical Therapy and Improving Patient Compliance

Simonetta Morselli, MD

Eye drops are among the common methods of treating glaucoma, caused by a buildup of pressure in the eye (intraocular pressure). This topical medication may seem easy to use, yet patients often incorrectly apply these drops, potentially neutralising the effect of the drug. Improvements in patient adherence and compliance in the use of drops is key for increased efficacy of current medications. Potential advances in pairing of medications, such as fixed combination therapy, as well as new types of medication and innovations in drug delivery provide patients additional treatment options to decrease intraocular pressure and allow the management of glaucoma.

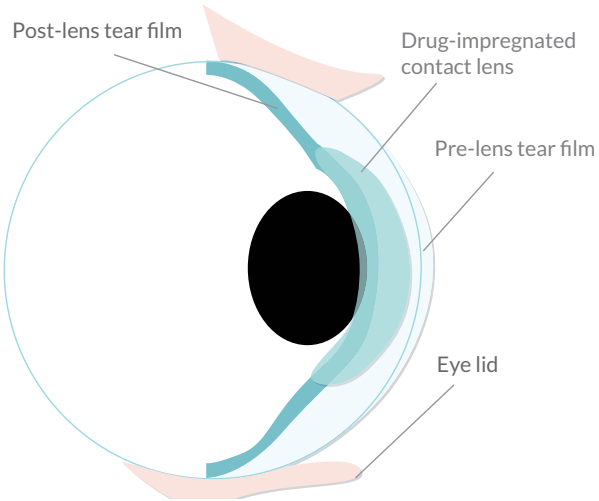

Figure 3. The contact lens is a device that can release medication for slow long-term release. Various methods include the soak and release method, an imprinted medicated contact lens, or polymeric nanoparticle release.

Topical eye drops are highly effective in decreasing intraocular pressure (IOP); however, they must be used in an appropriate manner. Survey results suggest that 80% of patients are not able to apply the eye drops correctly, resulting in neutralisation of the effects of the drug.[1] Decreasing the number of required drops and the instillation time results in higher patient compliance rates. While monotherapy with topical IOP-lowering medication is the current first line treatment for glaucoma, future directions lead toward fixed combination therapy. This EU-approved therapy uses two medications in a single bottle, theoretically increasing patient compliance, adherence, and simplifying the overall medication regimen. Often, prostaglandin analogues (PGAs, the most effective class for reducing IOP) are combined with other commonly used classes in one bottle, e.g. PGA + timolol.

Perhaps, however, instead of increasing the number of medications per bottle, we should question the medication itself. Studies suggest that after the first two years of medication, more than 75% of patients need two or more eyedrops to achieve their target pressure.[2] And, after five years, 49% of patients need two or more eyedrops to reach a 20% reduction of IOP.[3] Such data encourages research on new classes of medication or those with alternate mechanisms of action.

Two highly researched medications are nitric oxide emerging PGAs and ROCK inhibitors. The mechanism of action for nitric oxide donating PGAs allows for relaxation of the trabecular meshwork and scleral channel, with safety and precautions similar to well-known prostaglandins.[4] In fact, less than 1% of patients discontinue the medication due to adverse events.[4] ROCK inhibitors, currently only approved in the US, are a new class of drugs that lower IOP by targeting the trabecular outflow pathway.[5] They relax the trabecular meshwork resulting in increased trabecular outflow.[6] In a fixed-dose combination, once daily netarsudil-latanoprost resulted in reductions of IOP through three months and ocular adverse events in 5% of patients.[7]

Medications can also be placed in particular devices that allow for long-term release of the drug directly to the eye. These medications can be implanted as plugs, microparticles or shields in various locations, such as the canaliculus, anterior chamber, subconjunctival space and/or ocular surface. Innovative research in long-term drug delivery uses various devices in different stages of clinical testing. One device is already regularly used by many patients: the contact lens. A contact lens can be modified to release medication through the soak-and-release method, imprinting of medication or polymeric nanoparticle release (Figure 3).[8]

Other devices may be less commonly known by patients or physicians, but research involving their use is on the rise (Figure 4). Ocular inserts, made of a silicon matrix on inner polypropylene ring, are used to release bimatoprost and suggest positive results in decreasing IOP. Yet, the device runs the risk of dislodgement.[9] Research involving punctum plugs with travoporst in a polyethylene glycol hydrogel have shown elution with a 42% retention rate at 30 days.[10] Results from a Phase I/II clinical trial of bimatoprost sustained release implants show elution up to four-to-six months.[11] Lastly, a titanium slow release device for bimatoprost, showed elution up to four-to-six months with no intraoperative adverse events, yet with the possibility of infections or rescue in the case of an adverse reaction.[12] These devices seem to provide limitless potential in innovative thinking. While there are certain benefits to advancing medicine through the use of drug release devices, limitations and side-effects should be considered as these devices continue to move through development and testing.

Technology and innovation have the power to advance current treatment of glaucoma and set the stage for future medical development. New drug classes, such as nitric oxide emerging PGAs and ROCK inhibitors, may improve efficacy with complimentary mechanisms of action. Sustained release delivery methods and novel devices, including but not limited to ocular inserts, punctum plugs, and sustained release implants, may help to overcome poor patient compliance. These advances can help patients lower their IOP to see life fully, especially when used in conjunction with other techniques, such as minimally invasive glaucoma surgery.

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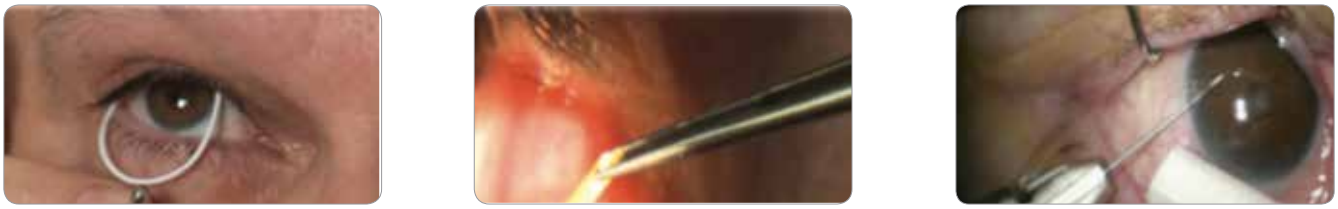

Figure 4. Devices are being studied in various stages of development and testing for slow release of medications. Examples include ocular inserts (left), punctum plugs (middle) and sustained release implants (right).

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The Use of MIGS in the Mild-to-Moderate Glaucoma Patient

By Christophe Baudouin, MD, PhD, FARVO

Use of minimally invasive glaucoma surgery (MIGS) for the mild-to-moderate glaucoma patient is on the rise. While the majority of American surgeons prefer to use phacoemulsification cataract surgery alone to treat glaucoma (40%), combination techniques such as phacoemulsification with MIGS are used with increasing prevalence and preference (22%).[1] Personally, I find MIGS beneficial for decreasing intraocular pressure in the glaucoma patient, but we must be considerate of potential benefits alongside the risks.

Filtration surgery, or trabeculectomy, is a common form of surgery used to reduce intraocular pressure (IOP) in the glaucoma patient. This surgery creates an alternative path for fluid to leave the eye through openings, thus decreasing intraocular pressure. This method can be associated to cataract surgery and has various pros: surgeons can perform double procedures, there is no compliance issue, and no or reduced risk of postoperative IOP spike. However, there also exist cons: higher risk of complications, longer visual recovery and creation of blebs that may be less effective or result in its own set of bleb-related issues (Figure 5). One method to address the issue of bleb-related complications is to use MIGS.

Advanced MIGS techniques can generally be classified by two criteria: ab-interno versus ab-externo and bleb versus bleb-less. The first category (ab-interno vs. ab-externo) includes examples such as ab interno trabeculotomy, trabectome, trabecular micro-bypass injection, intracanalicular scaffolding, suprachoroidal microstent, stent supra and subconjunctival tube ab interno. Examples of the second category (bleb vs. bleb-less) include canaloplasty, stegmann canal expander, subconjunctival microshunt ab externo, suprachoroidal microshunt and suprachoroidal shunt. I will focus on a few technologies in this article.

In mild cases of glaucoma, it is much better to propose the surgery that will be the least aggressive. One such surgery is to open the trabecular meshwork with ab interno surgery. This method emphasises that glaucoma is not a disease of Schlemm's canal–it is a disease of access to Schlemm's canal. Thus, simply bypassing the trabecular meshwork to open it will allow release of the aqueous humour in Schlemm's canal and decrease the IOP for the patient. Another method is to use stents (Figure 6).

Stents bypass the trabecular meshwork with a tube and allow the aqueous humour to diffuse through Schlemm's canal. Use of a

scaffold microstent also allows surgeons to cross the trabecular meshwork. In these methods, complications are generally low, and studies have shown reliable results in decreasing intraocular pressure and the number of medications needed after surgery.[2-3]

Another approach to decreasing IOP is using suprachoroidal drainage implants, which allow for access and IOP decrease through the uveoscleral pathway. It is important to recognise that with such new technology comes the promise of new potential advances. However, also with new technology comes the unknown. One cautionary tale is the use of a novel MIGS technique involving a supraciliary microstent, where immediate results post-surgery were quite impressive, yet results at four and five years post-procedure showed low endothelial cell density.[4] In this emerging field of MIGS, surgeons must not only consider short-term advances but also mid- and long-term potential complications. We must be certain that we are aware of side effects.

The second criteria for defining MIGS techniques is the presence of blebs. Blebs are formed intentionally for treatment of glaucoma in order to facilitate the circulation of the aqueous humour and decrease intraocular pressure. One technique is the subconjunctival drainage, where a small tube is inserted inside the eye with minimal manipulation at the subconjunctional level. Another example for subconjunctival drainage is the use of an ab externo microshunt for drainage in a more posterior fashion.

Surgeons treating a patient with glaucoma have a variety of tools and techniques at their disposal, such as cataract alone, cataract plus MIGS with no bleb, and/or cataract plus MIGS with bleb. While the choice of which method to use is based on each surgeon's personal preference and the patient's needs, I do have my own set of personal recommendations. Please note that these recommendations do not fit all patients. In light of the new MIGS technologies, my personal recommendation for patients with severe glaucoma progression is filtration surgery with phacoemulsification. My personal preference for treatment of patients with mild glaucoma is cataract surgery with one medication. And for all other intermediate cases, I would propose an ab interno strategy of phacoemulsification with MIGS. Ultimately, however, the choice is yours.

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Figure 5. Bleb-related complications can impair the eye of the patient and make it difficult to suggest alternate surgeries. Four examples of bleb-related complications are shown.

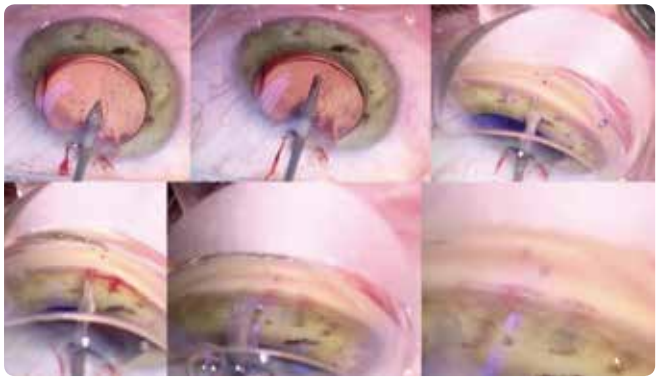

Figure 6. MIGS can be performed using stents or tubes to bypass the trabecular meshwork and allow increased access to Schlemm's canal. A series of steps (top to bottom, left to right) for MIGS using a stent is shown.

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The Use of MIGS in Patients with More Advanced Glaucoma

By Boris Malyugin, MD, PhD

Cataract surgery can effectively lower intraocular pressure (IOP) in patients with mild-to-moderate glaucoma, but for those with advanced glaucoma, other procedures are necessary. One such case study is a 72-year-old patient with advanced glaucoma, who received maximal medication therapy (i.e. three topical eye drops) but still had poor IOP control and measures of visual acuity. This advanced glaucoma patient would be an excellent candidate for a combination subconjunctival minimally invasive glaucoma surgery (MIGS) with cataract surgery.

In patients with advanced glaucoma and cataract, more aggressive treatment than simply accessing Schlemm's canal is needed. Some procedures to consider are the suprachoroidal or subconjunctival approach, as these procedures have the potential

to limit the number of eye drops needed by the patient thus improving compliance. Furthermore, these methods allow ophthalmologists to avoid traditional filtration surgery. My suggested approach would be combining subconjunctival MIGS with cataract surgery.

Use of MIGS with these significantly less invasive approaches allow for reduction of intraocular pressure with less risk, shorter operating times, and rapid recovery. Many devices exist, such as stents and shunts (Figure 7). Various stents can be used as part of MIGS to create a permanent channel through the sclera for aqueous humor to flow into the subconjunctival space. Advantages of such an ab-interno approach include the creation of bleb without dissection of the conjunctiva, thus decreasing the risk of scarring.

Studies using stents for glaucoma treatment have shown positive results with MIGS on 65 patients with advanced refractory glaucoma.[1,2] These patients needed further IOP reduction despite use of the maximum tolerated medications and failed previous refractive filtering or cilio-ablative procedures. Results showed a reduction of IOP by 20% within one year post procedure and a decrease in the number of medications from 3.5 to 1.7 medications. While there were no intraoperative complications, 32% of patients did require postoperative management in the form of bleb needling. Thus, while use of this stent in MIGS allows for decrease in IOP, there may be additional procedures needed.

The Apex Phase IV study also evaluated the use of a subconjunctival gelatin stent implant as the primary surgical intervention for reducing IOP in medically uncontrolled moderate primary open-angle glaucoma.[3] This prospective, non-randomised, open-label, multi-centre, two-year study showed positive results using MIGS in 202 eyes with decreases in IOP maintained postoperatively long term (mean reduction in IOP -6.5 ± 5.3 at 1-year and -6.2 ± 4.9 at 2-years post procedure). These results showed a stable procedure with long-term results. Furthermore, in the rare case where there was a decrease in the long-term efficacy, surgeons still have the choice to re-enter the eye and perform bleb needling which allows for long-term IOP stability. These two studies, and others, emphasise the use of subconjunctival MIGS for advanced glaucoma patients.

> **“ To the best of my knowledge, these procedures can and should be best used for patients with advanced glaucoma as an alternative to trabeculectomy**

Certain shunts are considered a more aggressive approach than stents due to opening of the conjunctiva for best results. The shunt works by draining aqueous from the anterior chamber to the scleral surface. In an observational study of 34 eyes that had failed tolerated glaucoma medication with 14 using a microshunt alone and nine with cataract surgery, IOP was reduced with minor compilations that resolved spontaneously.[4] The results suggested a high success rate with IOP decrease maintained through-three year follow up. Surgeons were able to perform the surgery with minimal scarring; however, if that did occur, additional management by filtering bleb is recommended.

There are many devices that can be used with MIGS for the advanced glaucoma patient. The decision to use these approaches is secondary to determining if the patient is a good candidate. And, of course, this decision is unique to the ophthalmologist. My recommendations are that combined surgery is good for advanced glaucoma patients with cataract who are on maximum medications that is progressing, while standalone surgery might be considered good for patients with well controlled advanced glaucoma. Although the technology may provide positive results, the choice of using it is up to the individual surgeon. In all honesty, debate still exists as to whether or not subconjunctival procedures involving aqueous drainage procedures are even considered MIGS!

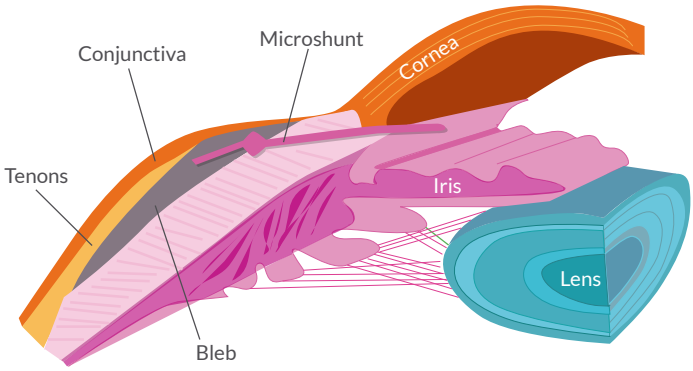

Figure 7. MIGS may be used in association with shunts and stents to allow for decrease of IOP in the advanced glaucoma patient.

Overall, MIGS procedures are highly effective in lowering IOP for the advanced glaucoma patient. They are able to do so with low operating time, low risk of complications and long-term results. While there are risks of losing effect due to scarring, this can be managed by needling and Mitomycin-C. To the best of my knowledge, these procedures can and should be best used for patients with advanced glaucoma as an alternative to trabeculectomy.

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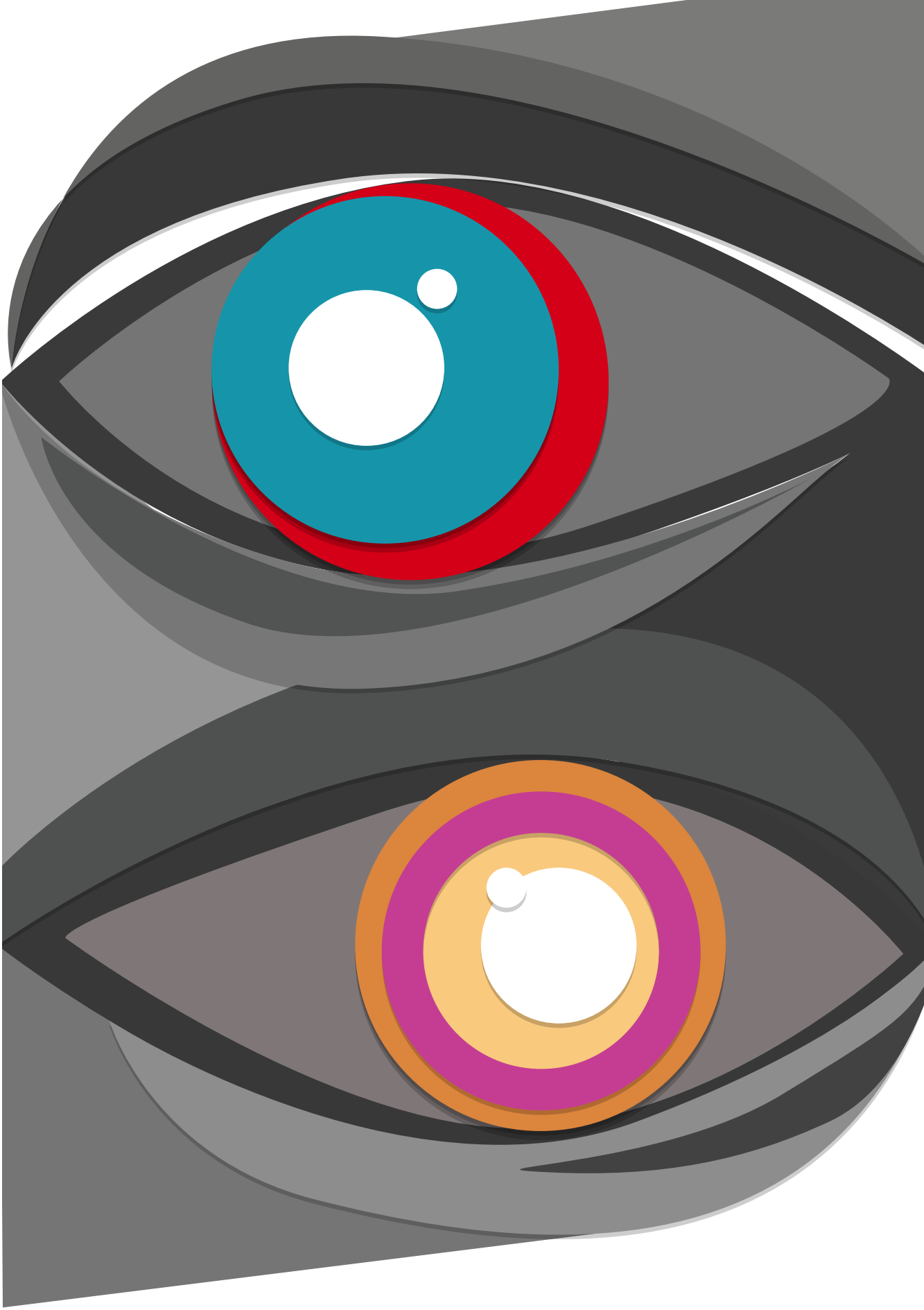

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