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# Prioritizing Patient Safety and the Role of Early Interventional Surgery in Glaucoma Management

## Selected presentations from the EGS meeting




L. JAY KATZ, MD
LAURA CRAWLEY, BSC (HONS), MB CHB (HONS), MRCP, FRCOPHTH
PROF. ANTOINE LABBÉ
IMRAN MASOOD, BSC, MB CHB, MRCS(ED) FRCOPHTH

At the 2023 meeting of the European Glaucoma Society, Glaukos Corporation invited a panel of experts to discuss the latest developments in the use of minimally-invasive glaucoma surgery (MIGS), including the iStent *inject*® W trabecular micro-bypass (Glaukos Corp.). Read the summaries of those presentations and use each QR code to watch the recordings.

# Shifting the Standard of Glaucoma Care

Why early surgical intervention is better than medications.

**BY L. JAY KATZ, MD**

For the past century, we've been relying on topical glaucoma medications as the first-line treatment of a disease that can lead to blindness. The standard of care for glaucoma that most of us were taught was to use topical medications first, exhaust them, then move on to interventions. Next came laser trabeculoplasty, and then filtering surgeries, like trabeculectomy and tube shunts, as a last resort. **Now, new diagnostic and therapeutic options are giving us good reasons to reevaluate our protocols.** Over the years, more and more studies have revealed the shortcomings of topical glaucoma medications, which include issues of toxicity, compliance, adherence, and even efficacy.

## THE CASE FOR CHANGING THE TREATMENT PARADIGM

### Toxicity and Compliance

Stacking topical glaucoma drops, which has historically been the standard of care, is fraught with problems of toxicity and compliance. Documented side effects include hyperemia, preorbital fat atrophy, ocular surface disease, and iris hypochromia.[1] Medication stacking often instigates dry eye disease (DED),[2,3] as Figure 1 illustrates. In turn, **these symptoms may contribute to medication noncompliance and nonadherence.**[4,5]

Prescription medication nonadherence is an issue in and of itself and likely contributes to the disease's progression. In a retrospective cohort study of health insurance claims data, Nordstrom et al found that **almost 50% of those who filled a topical glaucoma prescription discontinued the therapy within 6 months.**[1] Prescription renewals for the various drug categories in glaucoma over a period of several years decreased dramatically in every drug class.[6] Should we be taking the burden of adherence out of patients' hands?

### Efficacy of IOP Control

Equally important is the question of how effectively these topical pharmaceuticals control IOP. Is it stabilized for 24 hours, 7 days a week? Recent data indicate that **the practice of medication stacking is not very effective in lowering IOP after the initial drop**[7] **(Figure 2)**, or in preventing blindness. Neelakantan et al found that the addition of a third and fourth glaucoma medication produced **a relatively poor cumulative probability of success, including safety outcomes.**[8] In the United States, Malihi et al conducted a longitudinal study to determine the trend toward blindness in patients with

| Number of drops | Incidence of dry eye disease among 61 glaucoma patients[2] | Incidence of dry eye disease among 19,665 glaucoma patients[3] |
|---|---|---|
| 1 | 11% | 51% |
| 2 | 39% | 55% |
| 3+ | 40% | 60% |

Courtesy of J. Paul Singh, MD.

Figure 1. Studies show a direct correlation between the number of glaucoma medications used and the incidence and severity of dry eye disease.[2,3] (Data adapted from Rossi et al, *Eur J Ophthlamol*, 2009; and Erb et al, *Graefes Arch Clin Exp Ophthalmol*, 2008.)

Courtesy of Iqbal "Ike" K. Ahmed, MD

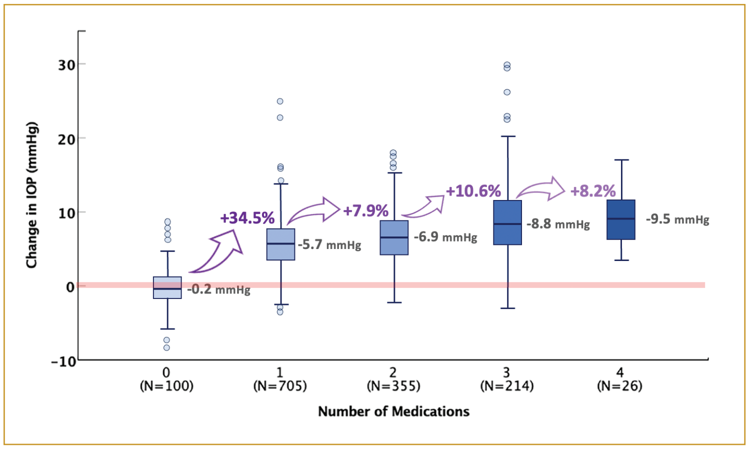


Figure 2. The first glaucoma medication is often the most impactful in reducing IOP. Subsequent medications have less effect. (Adapted from: Johnson TV et al. *Am J Ophthalmol*. 2020.[7])

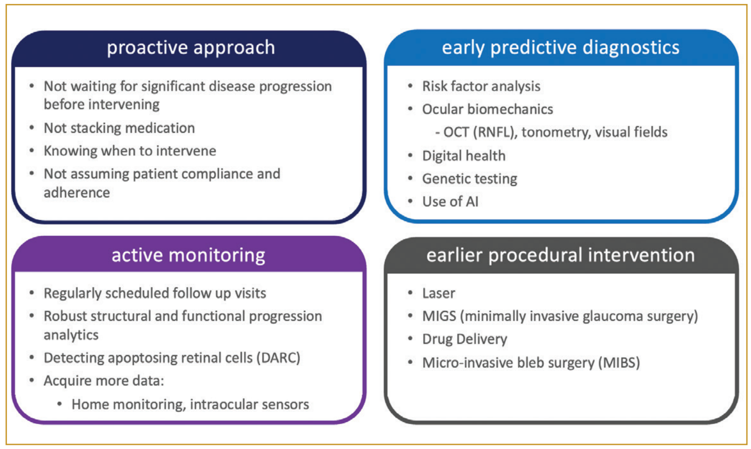


Figure 3. The differentiators of interventional glaucoma, as outlined by Iqbal "Ike" K. Ahmed, MD, of the John A. Moran Eye Center in Utah, USA.

open-angle glaucoma between 1965 and 2009. **Despite treatment with topical glaucoma medications, patients' probability of disease progression leading to blindness in at least 1 eye was 13.5%, and the average time to blindness was 4.8 years.[9]**

In Europe, Peters et al conducted a retrospective study of patients who received glaucoma treatment for 20 years. By the conclusion of the study, more than one-third of the patients were blind in one eye, and 13% were blind in both eyes.[10] I consider these data an indictment against our standard treatment paradigm. Together, these findings suggest that **we should change our approach to both evaluating and treating glaucoma**.

## A New Model: Interventional Glaucoma Care

Some of our glaucoma colleagues, such as Iqbal "Ike" Ahmed, MD, in the United States, have been leading change in our field, especially in the surgical management of glaucoma. Dr. Ahmed describes **interventional glaucoma as a proactive approach to treating the disease**, in which clinicians regularly screen for glaucoma, actively monitor patients' disease, and institute procedural interventions earlier in the treatment paradigm, **with the goal of keeping patients' vision stable over the long term** whilst considering topical medications as supplemental only (Figure 3).

A new era of early predictive diagnostics is emerging, in which technology will enable the detection of glaucoma at a very early stage and actively monitor the disease's progression. No longer should we wait for a noticeable decline in vision; now, we can intervene quickly to adequately control a patient's glaucoma.

We are already seeing the tip of the iceberg of interventional glaucoma with the introduction of laser trabeculoplasty and procedural pharmaceuticals, which are increasingly being adopted as first-line therapies for newly diagnosed open-angle glaucoma patients.[11] Minimally invasive glaucoma surgery (MIGS) is increasingly introduced at fairly early stages, especially in combination with cataract surgery, with encouraging results.[12] Additionally, filtering surgery with stents like XEN® Gel Stent (AbbVie/Allergan) and the PRESERFLO™ Ab-Externo Miroshunt (Santen) can provide IOP reduction with less risk and more standardization than trabeculectomy and tube shunts.

## CONCLUSION

**Well-run clinical trials have shown the safety, efficacy, and cost savings of interventional alternatives to topical pharmaceutical glaucoma management.** Our clinicians and researchers will continue to amass scientific evidence favoring the use of procedural pharmaceuticals, MIGS, trabeculectomies, and other modalities for maintaining consistent IOP control. I foresee increased adoption of the interventional mindset to treat glaucoma more proactively, rather than waiting for the disease's progression to force our hands. ■

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**L. JAY KATZ, MD**
■ Chief Medical Officer and Glaucoma Specialist, Glaukos Corporation
■ jkatz@glaukos.com

# iStent *inject*® W

A safe and proven technology for earlier intervention.

BY LAURA CRAWLEY, BSC (HONS), MB CHB (HONS), MRCP, FRCOPHTH

Performing cataract surgery in a patient who has glaucoma or who is taking IOP-lowering medication is a very common clinical scenario. In the United Kingdom, we've adopted combined procedures at a fairly significant rate, and we now have enough data to answer the question of whether patients gain benefit from the simultaneous placement of an iStent *inject*® W (Glaukos Corp.) or other trabecular bypass stent versus doing cataract surgery alone. Due to these volumes, I think we can now say there is a new gold standard of glaucoma management in which we consider surgical IOP control, if medically appropriate, in eyes requiring cataract surgery.

## COMBINED CATARACT AND MIGS PROCEDURES: NO LONGER A QUESTION OF BENEFIT

**From my own experience and patients' outcomes, when I seek the safest and most effective options for lowering IOP that won't negate other interventions the patient might need in the future, the iStent *inject*® W (Glaukos Corp.) fits into that category of treatment nicely.** For example, the pivotal study for the iStent *inject*®, published in 2019, was a prospective, multicenter, randomized, controlled trial of 505 total patients who were randomized 3:1 to receive either phacoemulsification and the iStent *inject*® (n=387), or phacoemulsification alone (n=118). Patient follow-up was performed over 2 years, with annual washouts. The study met its effectiveness endpoints: (primary) a reduction of ≥ 20% in unmedicated diurnal IOP and (secondary) a mean reduction in unmedicated diurnal IOP (Figure 1).[1] Furthermore, **the treatment group's safety profile was favorable and similar to that of the control group throughout the 2-year follow-up.**

In contrast, the effect of phacoemulsification alone on open-angle glaucoma is likely attenuated from 2 years on.[2] Meaning, **although cataract surgery alone may lower IOP initially, the effect is not necessarily permanent**.

In a meta-analysis of 13 studies (778 eyes) of iStent implantation alone out to 5 years, Healey et al found that the iStent provided well-sustained reduction in IOP, as well as reduced medication usage.[3] Reducing medication usage is important, not only because of the issues of toxicity and compliance, but across the UK, we've seen real challenges to the supply chain of some of the most commonly used drops. **Healey et al found a 60% reduction in medication dependence**, which is the average of what we see across iStent trials. In turn, removing this insult to the ocular surface would likely push scores on the Ocular Surface Disease Index much more towards the range of normal and mild.

For those patients who've been on the traditional pathway of glaucoma diagnosis, (topical medication then surgery), **we want to maximize the chance of surgical success should they need filtration later on.** Again, in the clinical trials with the longest-term follow-up of patients receiving an iStent implant, the device reduced patients' medication burden, more so than other factors.[4-7]

## QUALITY-OF-LIFE MEASUREMENTS WITH ISTENT

Some of the key takeaways from this year's EGS plenary session were new goals for designing future clinical trials in glaucoma. It was agreed that outcomes should target at least a 20% reduction in medications for patients, if not complete elimination.

Because it was the first MIGS device brought to market, the **iStent *inject*® is the only drainage device that has pivotal trial data showing significant durable improvements in vision-related quality-of-life measurements.[8]** The device also has subjective patient data on metrics like general vision, ocular pain, and driving. But what's most exciting, although relatively new, are functional measures.

A meta-analysis conducted by Gillmann et al produced evidence that the **iStent slows the rate of functional vision loss (Figure 2).[9]** That's interesting; we've not really seen this outcome until very recently, and

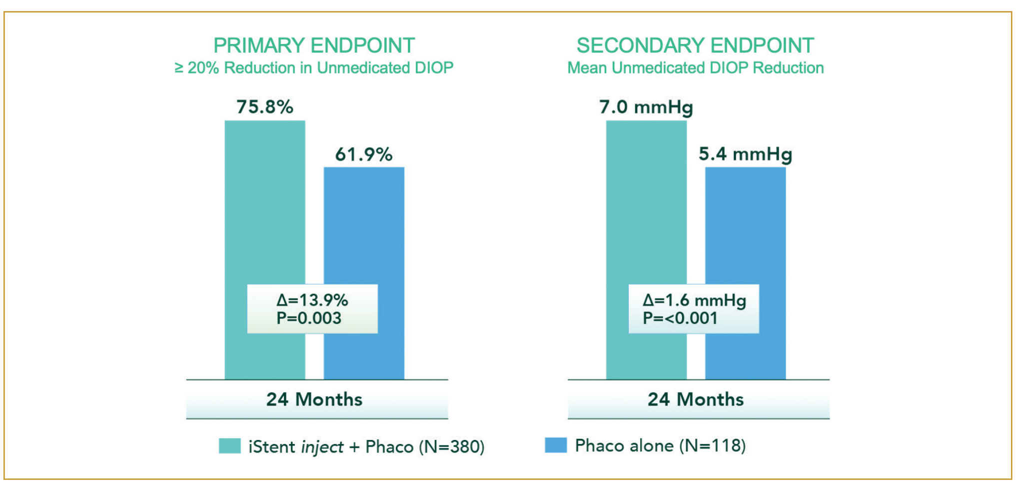


Figure 1. The pivotal study for the iStent *inject*® met its primary and secondary endpoints.

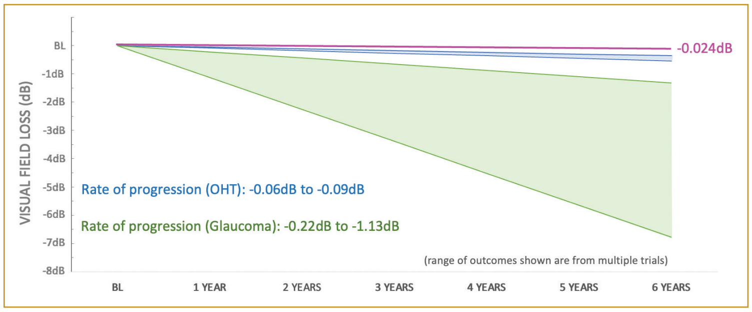


Figure 2. Researchers compared the observed visual field mean deviation progression following implantation of iStent technologies (pink line) with the rates of progression reported in the literature for ocular hypertension (blue lines) and glaucoma (green lines). (Data adapted from Gillmann K, et al. *BMJ Open Ophthalmology*. 2024.[9])

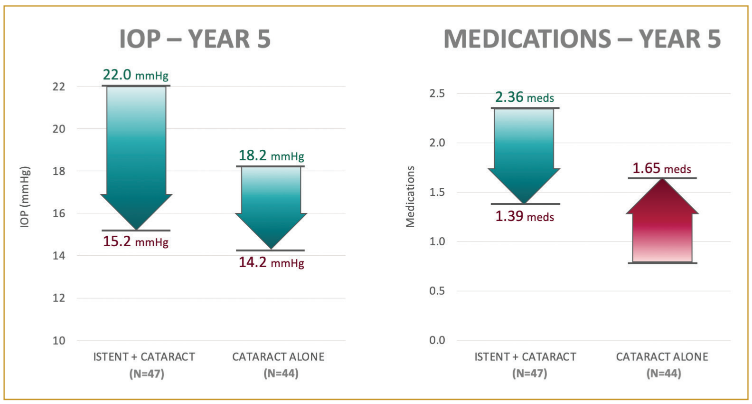


Figure 3. The author and her colleagues reviewed their 5-year results on IOP and medication usage in patients who underwent cataract surgery with the first-generation iStent (n=47) versus cataract surgery alone (n=44). Patients who had received the iStent had a greater reduction in IOP and required fewer medications at 5 years.

it warrants further research and debate. Still, it helps us give patients more information about what might happen if their IOP control is suboptimal, and how we can influence it.

My colleagues and I at Imperial College reviewed our 5-year results in an observational, retrospective, single-center, longitudinal cohort study of 47 patients who received the first-generation iStent at the time of cataract surgery. Our control group was 44 patients who had undergone cataract surgery alone. We found that IOP was reduced in both groups immediately after surgery, but the cataract-alone patients needed increasing medications over 5 years of follow-up to maintain their target IOPs (Figure 3). Those who received the first-generation iStent had a lower medication burden at 5 years (Figure 3).

Perhaps more exciting were the data from our visual field analysis: **those who had the iStent experienced a stabilization of their visual field**—we didn't see further significant loss or further reduction in the mean deviation. In contrast, the visual fields of those who underwent cataract surgery alone deteriorated (Figure 4). These data reflect previous reports that even patients who receive regular follow-up care can lose their visual field function over time. And again, even though our patients tell us that they take the drops every day, we know from a multitude of

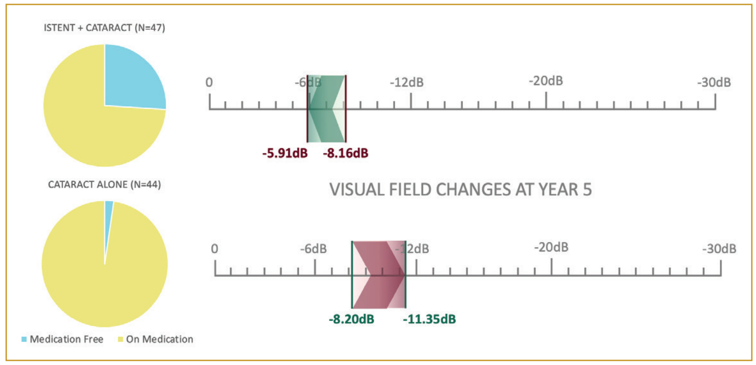


Figure 4. An observational, longitudinal, 5-year outcome for the change in visual field mean deviation before and after cataract surgery combined with the first-generation iStent (n=47) versus cataract surgery alone (n=44). The two groups were matched for age, visual field mean deviation, and glaucoma diagnosis. (Glaucoma Unit, Imperial College Healthcare, NHS Trust, unpublished data.)

evidence that they don't. So, **removing that patient-dependent factor should translate into longer-term visual field stabilization**. In our study, 26% of patients were medication-free at 5 years.

## CONCLUSION

In summary, I think **the safety and efficacy of the iStent *inject*® W has been proven in both randomized control trials and in the real-world setting**. I believe this device offers not only significant benefits for our patients, but for us surgeons, as well as for the healthcare system at large and the financial model within which we have to operate. The iStent *inject*® W procedure is incredibly elegant and safe, and I think it should be among our first considerations for cataract surgery patients with high IOP, controlled or not. It feels like a missed opportunity if we don't offer a secondary procedure that does not have an impact on the cataract surgical procedure but **can potentially change the patient's quality of life and/or their treatment outcome.** ■

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**LAURA CRAWLEY, BSC (HONS), MB CHB (HONS), MRCP, FRCOPHTH**
- Imperial College Healthcare NHS Trust, London
- Private practice at Clinica London and The London Clinic
- drlauracrawley@gmail.com
- Financial disclosures: Speaker (Glaukos Corporation)

# The Cure Should Not Do Harm

Is it the end of the road for topical glaucoma medications?

**BY PROF. ANTOINE LABBÉ**

Because scientists still do not know the exact pathophysiology of glaucoma, current pharmaceutical treatments are designed to lower and maintain IOP within a narrow target range to slow the disease's progression. We have a variety of topical eye drops for lowering IOP (fixed combinations, preservative-free formulas, etc.), some of which we can combine for specific effects. These drops are generally effective at lowering IOP by 15% to 35%.[1]

Yet, IOP-lowering medications have certain drawbacks. Foremost, we know that many patients do not comply with their drop regimen. In fact, data from the United States show that **patients only use 30% to 70% of their prescribed glaucoma eye drops.**[2] In France, Nordmann et al used an electronic device called the Travalert® (Alcon) to measure the rate of glaucoma medication compliance in patients, which was 60% in those who were aware that their compliance was being monitored.[3] Again in the United States, dispensing records of glaucoma medications in two community retail pharmacies showed that **the overall proportion of days covered was only 57% over 12 months, and the medication possession ratio was 71%.**[4] **If patients are only purchasing half the drops they are prescribed, that's a very big issue.** Results from the Nordmann et al study mirrored this finding; when we compared the doctors' estimations with the data from the electronic system, there was a large gap between what patients were using and what doctors thought they were using. Additionally, Okeke et al found that **many patients will take their eye drops as prescribed 5 days before their next consultation, and then their use declines over the following month.**[5] We also know that, as we increase the number of eye drops we prescribe patients, we increase the risk of noncompliance.[2]

## REASONS FOR NONCOMPLIANCE

Why do patients stop using their medications? There are several reasons. Older patients often have difficulties instilling eye drops, especially if they have disabilities. Many simply forget, but there are also patients who misuse their eye drops. I remember one very nice patient who came to see me for the first time. When I asked how they used their eye drops, they told me that they put a drop in their coffee every morning. Then, I asked a member of my family who has glaucoma, "Please show me how you put in your eye drops?" She touched the bottle's tip to her eyeball. Because she could feel the sensation, she thought she was getting the drops in her eyes. Do you think this misunderstanding is rare? It is not rare. This was my own family member!

If we combine the number of patients who don't use their eye drops routinely with the number of those who miss their eyes, then we see there is potentially a large population of patients whose IOP is going unmanaged. Unfortunately, **nonadherence to glaucoma medication can lead to blindness in this population**.

## PREVALENCE OF TOXICITY WITH DROPS

As clinicians, we see a high prevalence of signs of ocular surface toxicity in our glaucoma patients (Figure 1). We know that **the more drops patients have to use, the more ocular irritation they experience**. More than half of patients who receive pharmaceutical treatment for glaucoma have some degree of ocular surface disease, with one-third of these individuals showing signs of severe ocular surface disease.[6] Baudouin et al showed a direct correlation between the number and frequency of topical drops patients were using and the severity of their ocular surface disease.[6] **More than two-thirds of patients who were using three glaucoma medications showed some degree of ocular surface disease.**

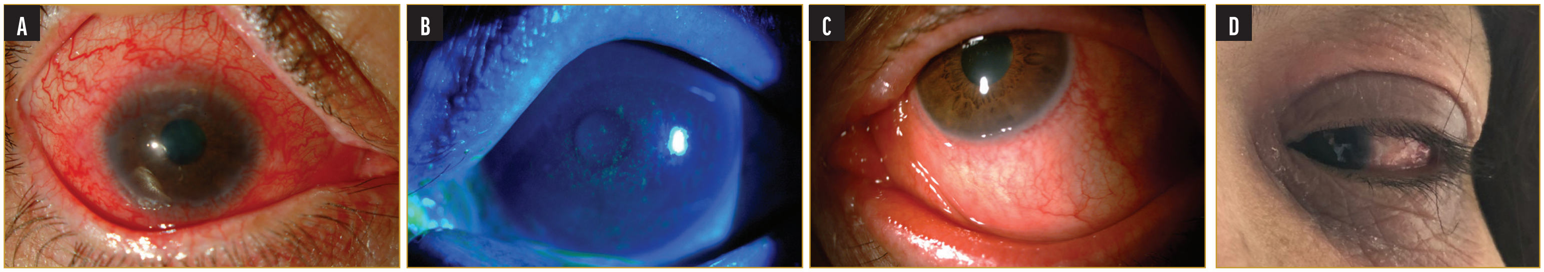


Figure 1. Obvious signs of medication toxicity in glaucomatous eyes: severe ocular surface inflammation (A), toxic keratitis (B), toxic blepharitis (C), and palpebral eczema (D).

## THERAPEUTIC MANAGEMENT

My colleagues and I conducted a departmental study of the reasons why we would change a patient's glaucoma medication.[7] For more than one-third of our patients, the reason we switched their medication was not efficacy, but because of adverse effects to the ocular surface from the eyedrops. If we can't find a glaucoma drop that is comfortable for patients and does not inflame the ocular surface, then we must perform filtering surgery. However, **filtering surgery is much more likely to fail in eyes that have received many eye drops** versus eyes that have not received eye drops previously. Baudouin et al published an interesting study in 2021 about the vicious cycle of inflammation in glaucoma treatments.[8] **In the early stages of glaucoma, there is damage to the trabecular meshwork that increases IOP.** So, we prescribe eye drops to decrease the IOP, but these drops may induce inflammation and ocular surface disease. We know that this inflammation can target the trabecular meshwork and raise IOP. **Over time, the efficacy of the glaucoma drops decreases, and the inflammation increases the eye's outflow resistance, thereby contributing to uncontrolled IOP.** When we can no longer control the IOP with medication, we do surgery, but **the success rate of the surgery is compromised by the damage done to the ocular surface by the drops.** There is a spiral to blindness due to pharmaceutical-induced inflammation and toxicity. So, maybe we should think differently.

## SUMMARY

In short, we have many kinds of glaucoma medications that are effective at controlling IOP, but these drops have several limitations, from noncompliance, to misuse, to toxicity. Therefore, **it may be time to rethink our conventional glaucoma therapy and consider a new treatment algorithm**. Perhaps we should use glaucoma drops as a supplemental treatment for glaucoma, because we have other options today. ■


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**ANTOINE LABBÉ, MD**
- Department of Ophthalmology, Ambroise Paré Hospital (AP-HP), Boulogne-Billancourt, France
- Department of Ophthalmology, IHU FOReSIGHT, Quinze-Vingts National Ophthalmology Hospital, Paris, France
- Paris-Saclay University, Vision Institute, Paris, France
- dr.antoinelabbe@gmail.com
- Financial disclosures: Speaker (Glaukos Corporation, Alcon, Thea, Horus Pharma, Santen, Baush + Lomb, Elios Vision)


# With MIGS, Efficacy and Safety Are Paramount

There are important considerations for early glaucoma interventions.

**BY IMRAN MASOOD, BSC, MB CHB, MRCS(ED) FRCOPHTH**

We glaucoma surgeons have a plethora of options for managing IOP in glaucoma patients—we can approach the canal, we can enter the suprachoroidal space, or we can create blebs or use lasers. For me, a paper published by Saheb and Ahmed in 2012 set the benchmark for **our goals with MIGS: an ab interno microincision, minimally traumatic, with at least modest efficacy, a favorable safety profile, and rapid recovery.**[1] I believe there are important considerations of safety and efficacy when we choose a device to achieve these goals.

## IOP REDUCTION

Recent studies have shown a similar performance in terms of IOP control between the iStent *inject*® (Glaukos Corp.) and the Hydrus Microstent (Alcon). In its 2-year pivotal trial versus cataract surgery, the iStent *inject*® met its primary outcome measure (a reduction in unmedicated diurnal IOP from baseline of ≥20% and change in unmedicated diurnal IOP from baseline in month 24) in 75.8% of patients.[2] In the 2020 COMPARE study between the iStent and the Hydrus Microstent, 80% of the participants who received the Hydrus achieved the primary outcome of an IOP of ≤18 mmHg and no topical glaucoma medications at 12 months.[3]

## SAFETY

Yet, the abovementioned were in vitro studies. Although supporting data are not

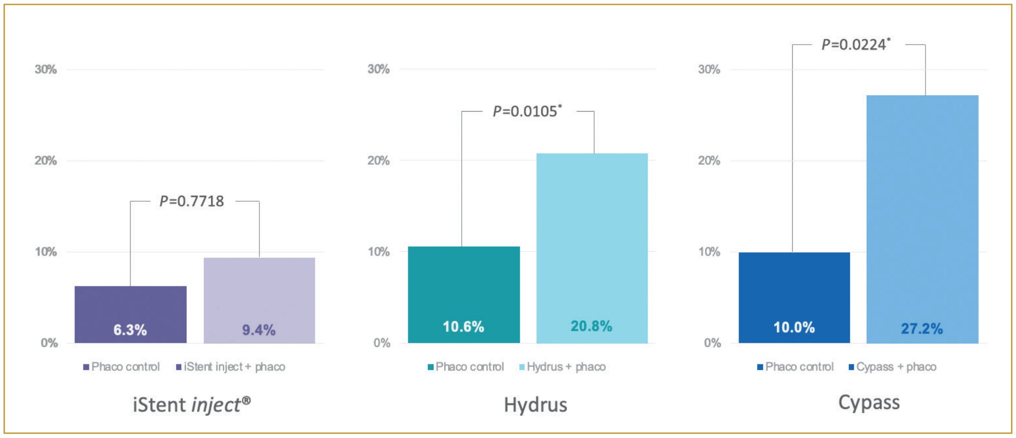


Figure. Evidence from pivotal trials of 3 MIGS devices showing the proportion of patients experiencing ≥20% endothelial cell loss at 5 years (Data adapted from Ahmed IIK et al, JCRS 2024).[8]

available, **in my practice, I have not seen the clinical benefit of implanting such a large device (the 8-mm Hydrus)**. In a contralateral eye study between either the iStent *inject*® or the iStent *inject*® W (both from Glaukos Corp.) versus Hydrus, Schultz et al found no difference in efficacy, but the Hydrus device had two postoperative adverse events (one device dislocation and one malposition).[4]

Safety is very important with all the MIGS procedures. If I am operating on patients with mild disease and my aim is to reduce their glaucoma medication therapy, then I prefer a procedure with a low rate of complications. Rates of **secondary surgical interventions** in recent MIGS studies are as follows: 10.4% in the ROMEO study[5] with the OMNI Surgical System (Sight Sciences); 7.5% for the Hydrus device and **5.4% for iStent *inject*® in Holmes et al**[6]; and 25.5% in an 8-year follow-up study[7] of combined phacoemulsification and excimer laser trabeculotomy.

Ahmed et al performed a post-hoc analysis to compare the corneal **endothelial safety over 5 years of three MIGS devices**: the iStent *inject*®, the Hydrus Microstent, and the CyPass Micro-Stent (Alcon).[8] Although the CyPass has since been withdrawn from the market, in this study, **the Hydrus impacted endothelial cell count significantly compared to the iStent *inject*® (Figure).**

In all their trials, **the iStent devices have shown an overall safety profile fairly similar to that of cataract surgery alone.** In my experience evaluating patients' outcomes, iStent devices target the site of pathology and promote a rapid recovery of vision.

## SUMMARY

Glaucoma surgery is a highly complex, decision-orientated discipline that requires an intimate understanding of the disease process—it is very important to identify where the patient is in their individual disease journey. Then, we have to select the right procedure at the right time. All of these canal-based procedures have their own indications, but **in terms of safety, I don't think any device outperforms the iStent *inject*® W.** ■

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**IMRAN MASOOD, BSC, MB CHB, MRCS(ED) FRCOPHTH**
- Consultant Ophthalmic Surgeon, Birmingham and Midland Eye Centre
- Assistant Professor, University of Nottingham
- Senior Clinical Research fellow, University of Birmingham
- imranmasood777@gmail.com
- Financial disclosures: Speaker (Glaukos Corporation)