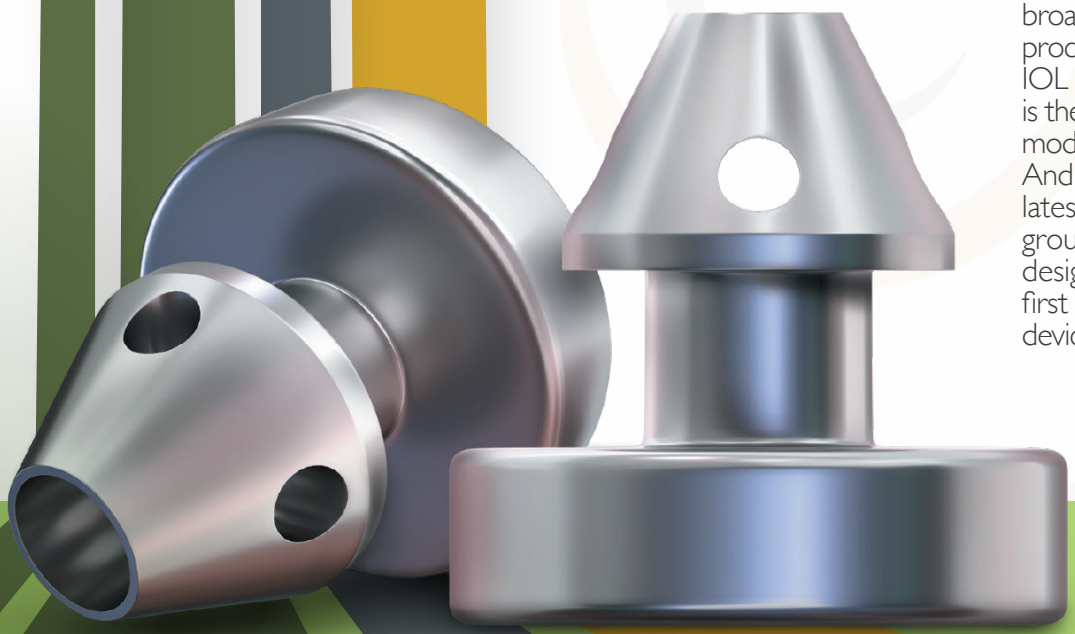
GLAUCOMA MANAGEMENT: INFINITELY IMPROVED

Glaukos founded the MIGS category 20 years ago with the first generation iStent. Continuous innovation since then has resulted in a device portfolio that has revolutionized glaucoma management. With two decades of studies behind it, the iStent platform has the longest-term body of evidence of any MIGS procedure: its safety and efficacy are evident in 200+ peer-reviewed publications – setting the device apart from others.

Given the short learning curve of the iStent *inject*® W and its broad compatibility with other procedures – including advanced IOL implantation – this device is the first choice for mild-to-moderate glaucoma management. And now, iStent infinite, the latest manifestation of Glaukos' ground-breaking technology, is designed to provide surgeons the first standalone, non-ablative MIGS device for patients in need.



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A Sponsored Supplement From
the Ophthalmologist

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When should we use iStent technologies?

Historically, glaucoma treatment would have begun with the safest approaches: topical medication or laser intervention. If these did not control disease, the only remaining options were either trabeculectomy or tube shunt surgery. But most glaucoma patients are not good candidates for such relatively aggressive procedures; typically, they have mild-to-moderate disease (1), and therefore require low-risk interventions. Twenty years ago, Glaukos recognized this need – and in addressing it, founded the entire field of micro-invasive glaucoma surgery (MIGS). These low-trauma, ab-interno approaches are associated with high safety and rapid recovery in mild-to-moderate glaucoma management. But when exactly should we use them?

Thomas Samuelson suggests bearing two principles in mind (2). Firstly, since mild-to-moderate disease is often asymptomatic, maintaining an acceptable risk/benefit ratio implies low-trauma interventions. Secondly, where the patient also requires cataract surgery, we should remember that phacoemulsification alone has an IOP impact. However, post-phaco IOP reduction in treated glaucoma patients is typically modest: less than 2 mmHg on average (3, 4, 5) or a reduction of 16.5 percent three years after cataract extraction, as shown in the Ocular Hypertension Treatment Study (OHTS) (6). In addition, evidence has shown that the reduction in IOP may be more significant at one year after cataract surgery and that, subsequently, IOP tends to return to baseline levels with time (5, 7, 8, 9). It therefore makes sense to avoid interventions which risk losing the IOP benefits conferred by phacoemulsification alone.

Given these principles, which MIGS approaches are likely to be of benefit while "doing no harm?" Samuelson (2) does the math: "The iStent *inject*® W – with a total diameter (two iStent *inject* W implants) of 720 microns compared to the Schlemm's canal length of 36 mm – leaves 98 percent of the canal untouched." In other words, this MIGS intervention manipulates a mere 2 percent of the angle. The iStent *inject* W risk-benefit ratio therefore is likely to be favorable, especially when combined with the IOP-lowering effect of phacoemulsification. Accordingly, Samuelson chooses iStent *inject* W for mild-to-moderate cases: **"Most patients do well with this approach, and it means we can save stripping out the meshwork as a 5-10-year option, if they progress."**

Similarly, Mark Gallardo asserts that, when combining a glaucoma procedure with cataract surgery in mild-to-moderate

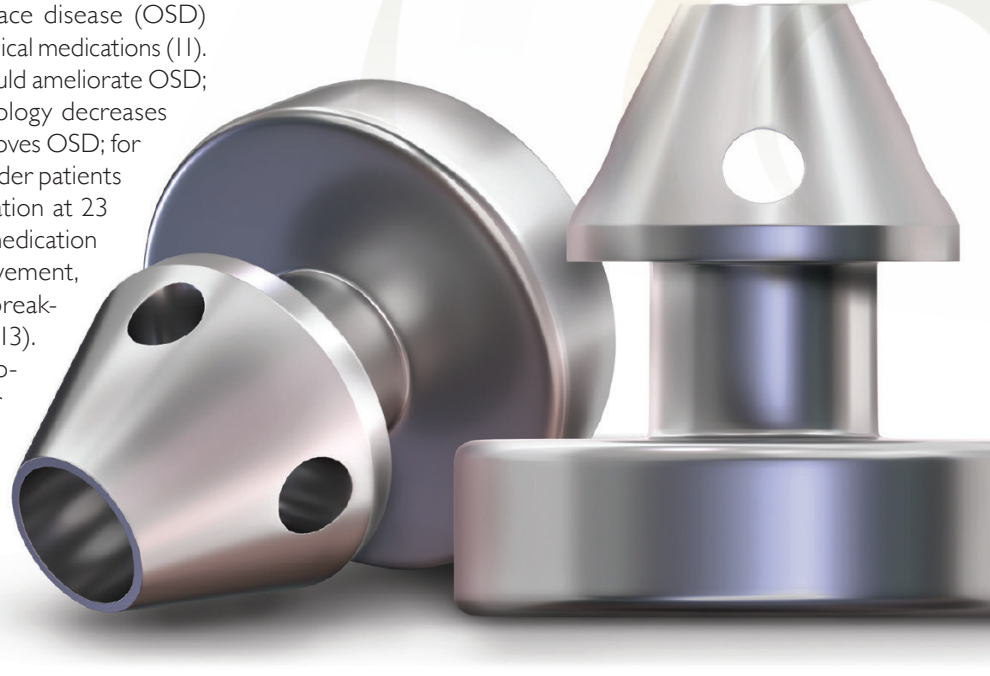
patients, we should choose a procedure that doesn't increase risk above that of the cataract surgery itself (10). Christophe Baudouin concurs, and notes that, in his personal experience, the iStent *inject*® safety profile is similar to standalone cataract surgery – unsurprising, he says, as it is implanted via the same incision as required for cataract surgery, and has none of the bleb-associated issues that occur with filtration surgery. Baudouin adds that iStent *inject* W attractiveness is partly related to its mechanism of action (2): "Stenting the trabecular meshwork, where outflow resistance is located, restores and maintains natural physiological outflow."

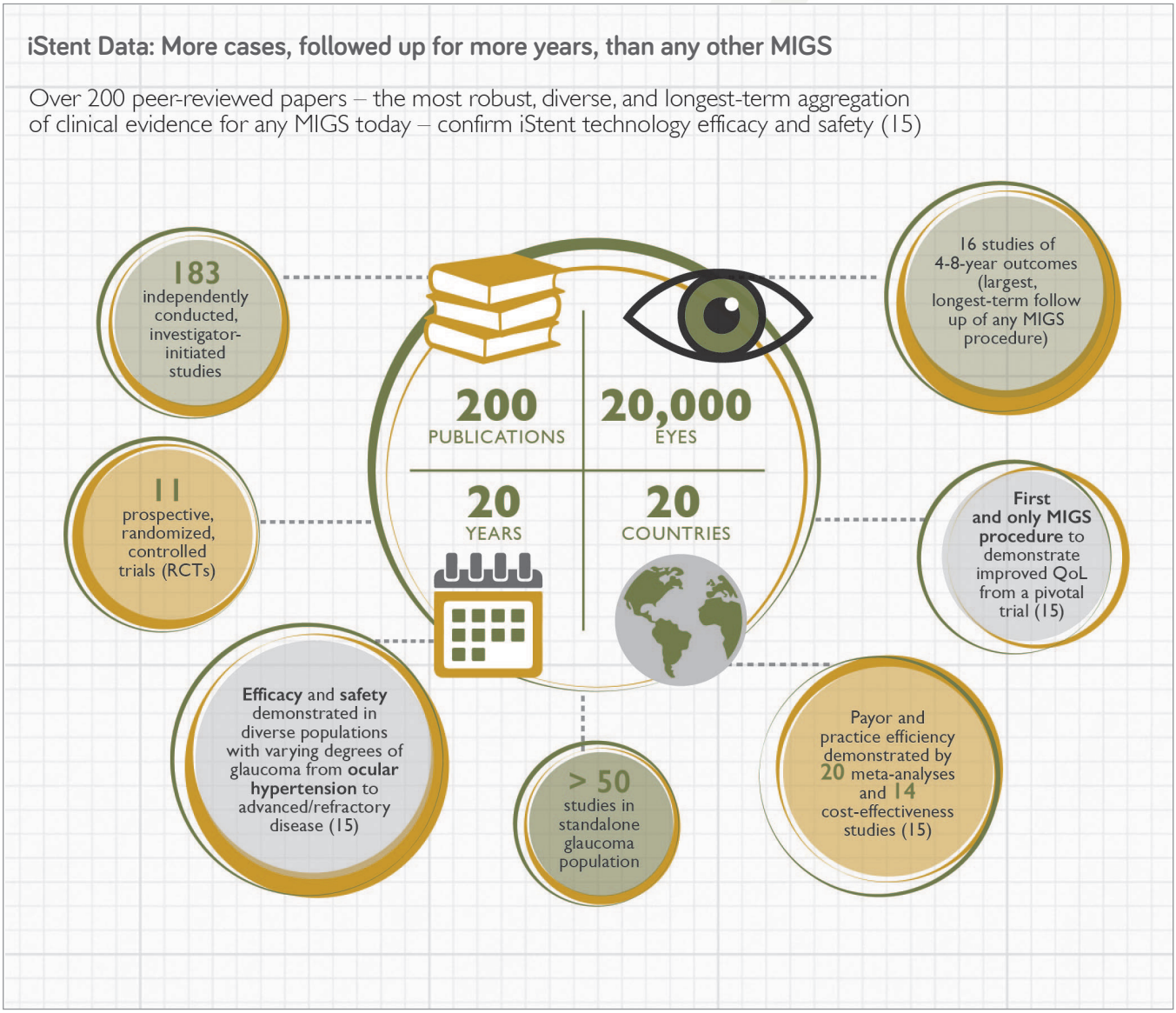
Gallardo reminds us that no procedure works all the time for every patient, and advocates always planning for the next step. In this context, he notes the advantages of the iStent *inject* W small footprint in the eye (2): "It leaves the option of future non-filtration surgery on the outflow system, if necessary." The iStent *inject* W broad compatibility with other procedures extends to premium IOL implantation: Baudouin points out that the iStent *inject* procedure is refractively neutral, and results in patient comfort and visual acuity outcomes equivalent to those normally observed in cataract surgery. Gallardo (10) confirms this: "The iStent *inject* is astigmatically neutral – it doesn't change curvature or alter corneal astigmatism." And Deborah Ristvedt notes that premium IOL patients typically wish to resume normal activity as soon as possible; it therefore makes sense, she says, to pair toric or presbyopia-correcting IOL implantation with a MIGS device that is minimally disruptive to vision, and that does not add to the risk profile of cataract surgery alone (10). "The combination speaks for itself," she says.

Baudouin reminds us that ocular surface disease (OSD) severity is correlated with the number of topical medications (11). Reducing medication burden therefore should ameliorate OSD; indeed, studies indicate that iStent technology decreases topical medication needs and thereby improves OSD; for example, 84 percent of iStent *inject* responder patients were totally free of anti-glaucoma medication at 23 months after surgery (12) and post-iStent medication reduction is associated with OSD improvement, including a 49 percent increase in tear break-up time and reduced corneal damage (13). Baudouin concludes that trabecular micro-bypass surgery offers a new option for management of eyedrop-associated OSD in glaucoma patients, thereby improving their quality of life.

Gallardo (2) also emphasizes that clinical decisions should be informed by the need to minimize medication burden. "Eye-drops are caustic, and their benzalkonium chloride (BAK) component damages trabecular column endothelial cells, thereby reducing the effective filtration area of the trabecular meshwork." By employing angle-based procedures, however, we may reduce or completely eliminate the medication burden, and Gallardo notes that his MIGS experience since 2013 indicates that iStent technology significantly reduces the number of medications required to maintain disease control: **"For patients with controlled disease on one or two, sometimes three, medications, I now opt for phacoemulsification combined with iStent inject W."**

"To safely optimize outflow, the iStent inject W is my go-to device for mild-to-moderate glaucoma in combination with cataract surgery."
Deborah Ristvedt





What about patients with uncontrolled glaucoma of mild to moderate severity? Gallardo (2) is clear: "I still opt for iStent *inject* W because I'm very confident it will reduce IOP to the target range." He cites his own data (14) indicating that iStent *inject* not only reduced medication burden in patients with uncontrolled glaucoma, but also reduced average IOP by ~30 percent.

In summary, the iStent *inject* W safety, ease-of-use, reliability and predictability in terms of reduction of pressures and medications make it a natural choice for mild-to-moderate glaucoma patients with cataracts, including those opting for premium IOLs.

Outcome data – there's no substitute for reality

MIGS procedures have not always been as broadly accepted as they are today – Gallardo (2) remembers an unfounded "lack of belief" when the first iStent was approved in 2012. He suggests that this might have been due to some forgetting that clinical trials do not perfectly represent reality: "In real life, surgeons can use the device on many patients one after another, enabling them to rapidly move along the learning curve; in clinical trials, inclusion/exclusion criteria force much more sporadic use of the investigational device." Real-world data, then, will provide

Spotlight on real-world data

1. STRATIFIED ANALYSIS UNDERSCORES ISTENT INJECT® UTILITY ACROSS A RANGE OF PRE-OPERATIVE TREATMENT BURDENS

I. Paul Singh and colleagues (20) examined effectiveness outcomes stratified by pre-operative disease burden in a post-hoc analysis of the iStent *inject*® pivotal trial: iStent *inject*® plus phaco (INJ) versus cataract surgery alone (CS).

Percentage of eyes achieving >=20 percent reduction in unmedicated DIOP

	Low-DIOP	Mid-DIOP	High-DIOP
INJ	75.4%	77.1%	74.4%
CS	64.5%	63.6%	33.3%
	Low-med	Mid-med	High-med
INJ	76.8%	70.8%	79.7%
CS	69%	63.3%	29.4%

CONCLUSIONS: PROPORTION OF CS EYES ACHIEVING ENDPOINT DIMINISHED WITH INCREASING BASELINE IOP BUT STAYED CONSTANT IN INJ EYES, SUGGESTING ISTENT INJECT® HAS POTENTIAL UTILITY ACROSS THE SPECTRUM OF PRE-OPERATIVE TREATMENT BURDEN (INCLUDING CHALLENGING CASES)

The iStent *inject*® treatment over control (cataract surgery alone) advantage was higher (not lower, as is sometimes assumed) in eyes with higher preoperative IOP and higher preoperative medication levels

2. FIVE-YEAR FOLLOW-UP HIGHLIGHTS IMPACT OF ISTENT INJECT-PHACOEMULSIFICATION COMBINATION: SAFE AND DURABLE REDUCTION OF IOP AND TOPICAL MEDICATION

Karsten Klabe summarizes his iStent inject® experience (21):

Mean pre-operative IOP (with medication): **18.5 mmHg**; mean baseline medications: **1.47** (range 0-4)

Retrospective review: **164 eyes**; 03 patients; mean age 75.4 y; 82 percent POAG; 18 percent pseudoexfoliation glaucoma

Follow-up: Of **164 implants**, 157 followed to 24 months; 129 to 26 months; 85 to 48 months; and 61 to 60 months

Results: Mean IOP decreased to **16 mmHg** (1 month), **15.5 mmHg** (6 months); stable thereafter

Mean medication range 0.17 to 0.23; no patients took more than two medications during follow-up, no evidence of increase over time

Over the 5-year follow-up, only **4.3 percent eyes** required a second procedure (Xen stent, Preserflo microshunt, SLT, cyclophotocoagulation).

Conclusions: Implanted patients rarely need **further intervention for glaucoma**; most can become medication-free. Combining iStent inject® with cataract surgery ameliorates adherence issues and **OSD potential** associated with glaucoma medication.

Efficacy by patient ethnicity				
Device	Ethnicity (reference)	Timeframe (months)	IOP Reduction (mmHg)	Medication reduction (%)
iStent	Korean (23)	6	1.3	64
iStent *inject*	Brazilian (24)	12	3.1	94
iStent	African American (22)	12	2.4	42
iStent	Japanese (25)	24	2.9	81
iStent	Hispanic (14)	36	6	45

Table 1. Summary of studies demonstrating iStent efficacy across diverse populations.

Efficacy by glaucoma type			
	Mean post-op IOP (mmHg)	Mean IOP reduction (mmHg)	Medication reduction (%)
Normal tension glaucoma: 1 year, iStent *inject* (26)	12.32	3.5	70
Pigmentary glaucoma: 3 years, iStent (27)	14.68	4.82	21
PXG: 5 years, iStent (28)	15.3	4.5	25

Table 2. Summary of studies demonstrating iStent efficacy across diverse glaucoma types.

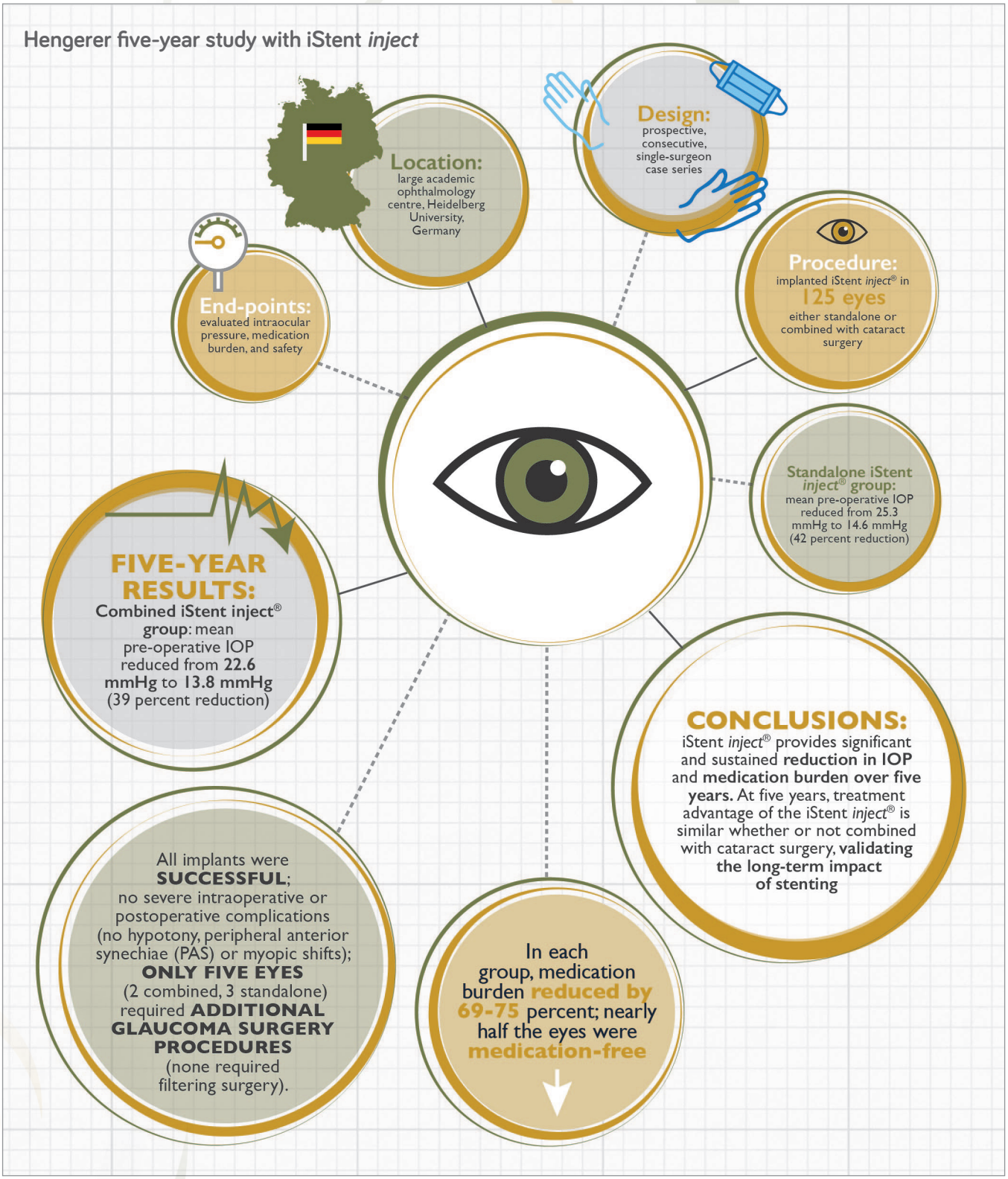
the most accurate picture of iStent technologies' safety and efficacy; what do such studies tell us?

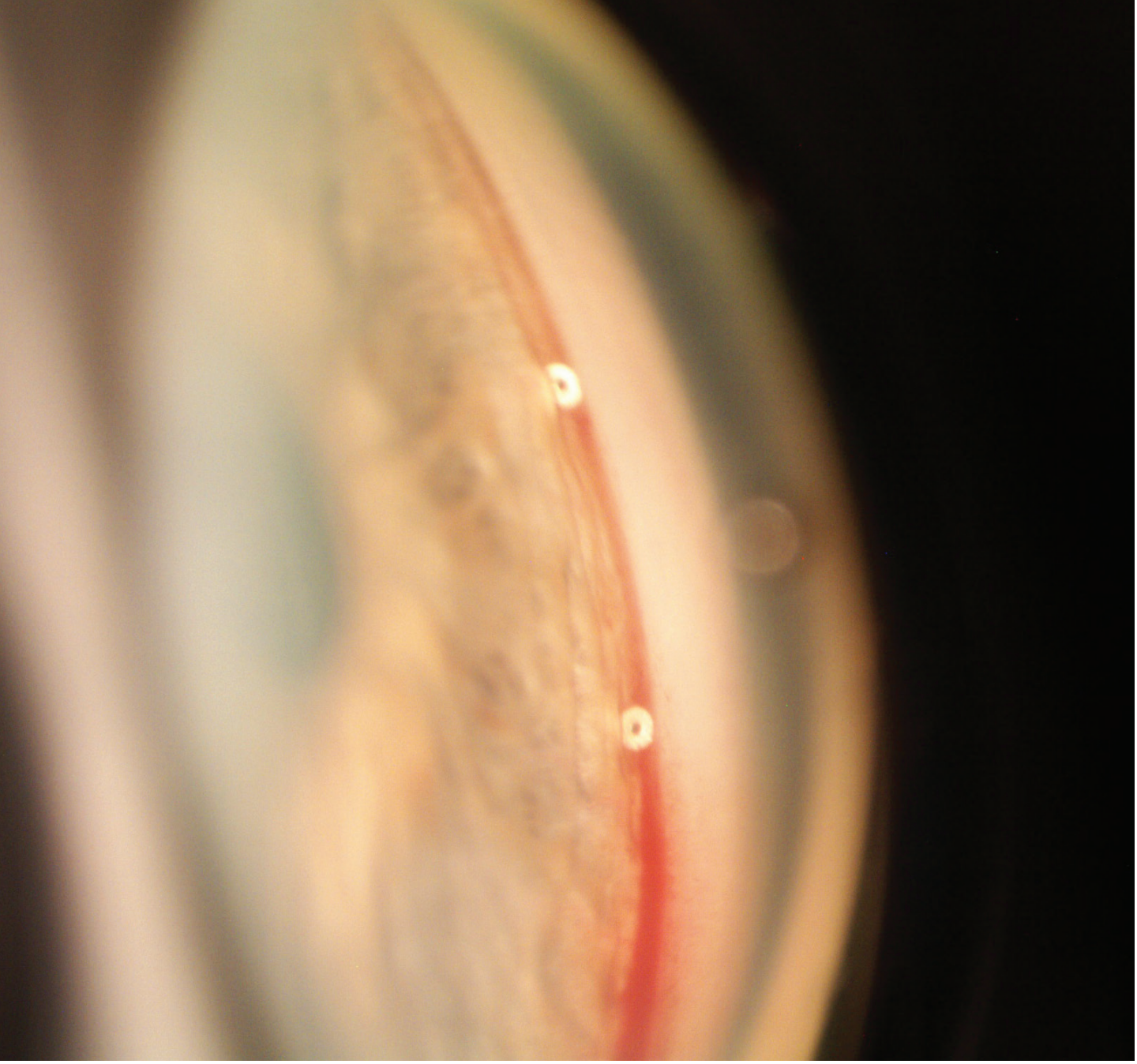
Weight of data

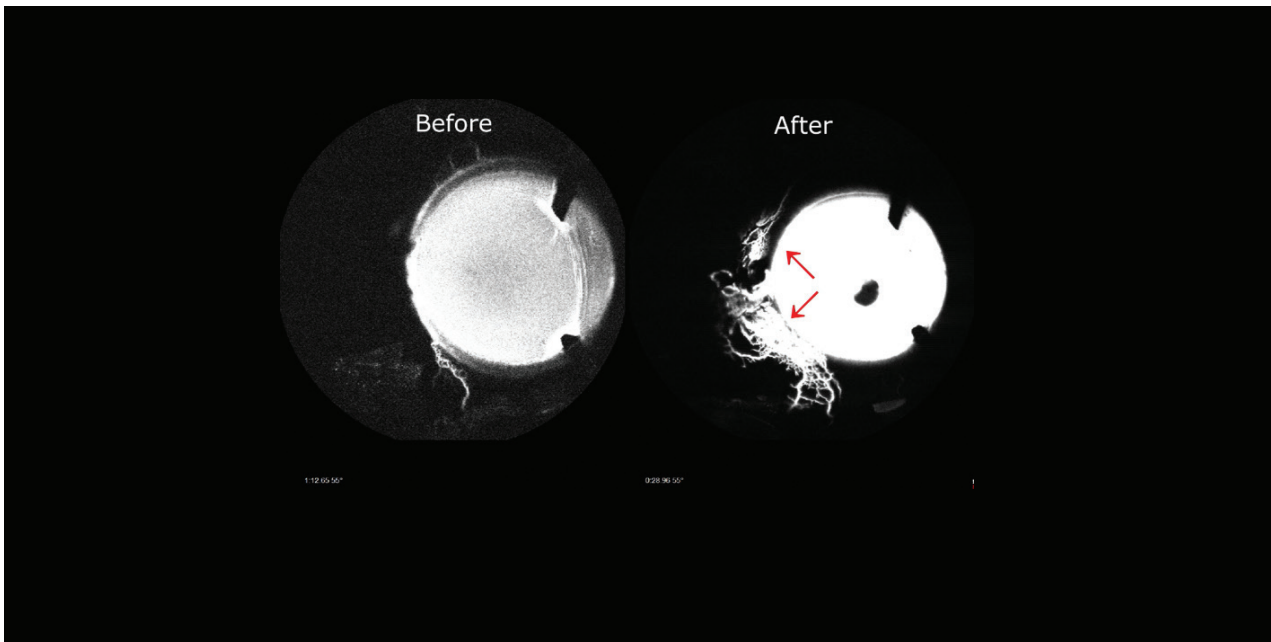
First of all, it is clear that the peer-reviewed data-set for iStent technologies are more robust, more diverse and covers a longer time period than the data for any other MIGS procedure (see sidebar and box below). To date, there are more than 200 peer-reviewed publications, and one million+ iStent procedures have been performed (15), including multiple five-, six-, seven- and eight-year real-world studies. This body of work provides convincing evidence of iStent technologies safety and efficacy across a wide range of mild-to-moderate glaucoma patients, demonstrating that iStent significantly reduces IOP, decreases patient reliance on glaucoma medication, optimizes the natural aqueous outflow and delays progression to secondary surgical intervention compared to cataract surgery alone (2).

Leon Herndon provides more detail on this 20-year data-set. By way of example, he cites a 505-patient trial (12) which showed that iStent *inject* together with phacoemulsification reduced IOP levels (unmedicated patients) by 20 percent or more compared to phacoemulsification alone (mean reduction of 7 mmHg versus mean reduction of 5.4 mmHg). Furthermore, **this study reported a 31 percent reduction in medication-free IOP (baseline ~25 mmHg, versus ~17 mmHg at month 24), and the lowest mean post-operative**

Hengerer five-year study with iStent *inject*







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IOP of any MIGS pivotal trial. Furthermore, says Herndon (2) there are no fewer than 16 studies reporting four-to-eight-year follow-up iStent technology data. By way of example, he cites four independent, real-world studies that clearly demonstrate the long-term benefits of iStent devices.

Firstly, a five-year study of 65 eyes reported a mean post-operative IOP of 13.6 mmHg (mean IOP reduction of 9 mmHg, and 69 percent medication reduction) (16). Secondly, a six-year study of 411 eyes reported a mean post-operative IOP of 14.9 mmHg (mean IOP reduction 3.9 mmHg, and 21 percent medication reduction) (17). Thirdly, a seven-year study of 19 eyes demonstrated a mean post-operative IOP of 16.4 mmHg (mean IOP reduction of 4.9 mmHg, and 27 percent medication reduction) (18). And fourthly, an eight-year study of 62 eyes showed a mean post-operative IOP of 14.2 mmHg (mean IOP reduction of 5 mmHg, and 18 percent medication reduction) (19). The take-home message, says Herndon, is that the iStent technologies consistently maintain IOP in the low to mid-teens over periods of several years.

Meta-analysis of 13 studies

Systematic review and meta-analysis of four randomized controlled trials and nine non-randomized single-arm studies (778 eyes)

iStent implantation was associated with: weighted mean IOP reduction of:

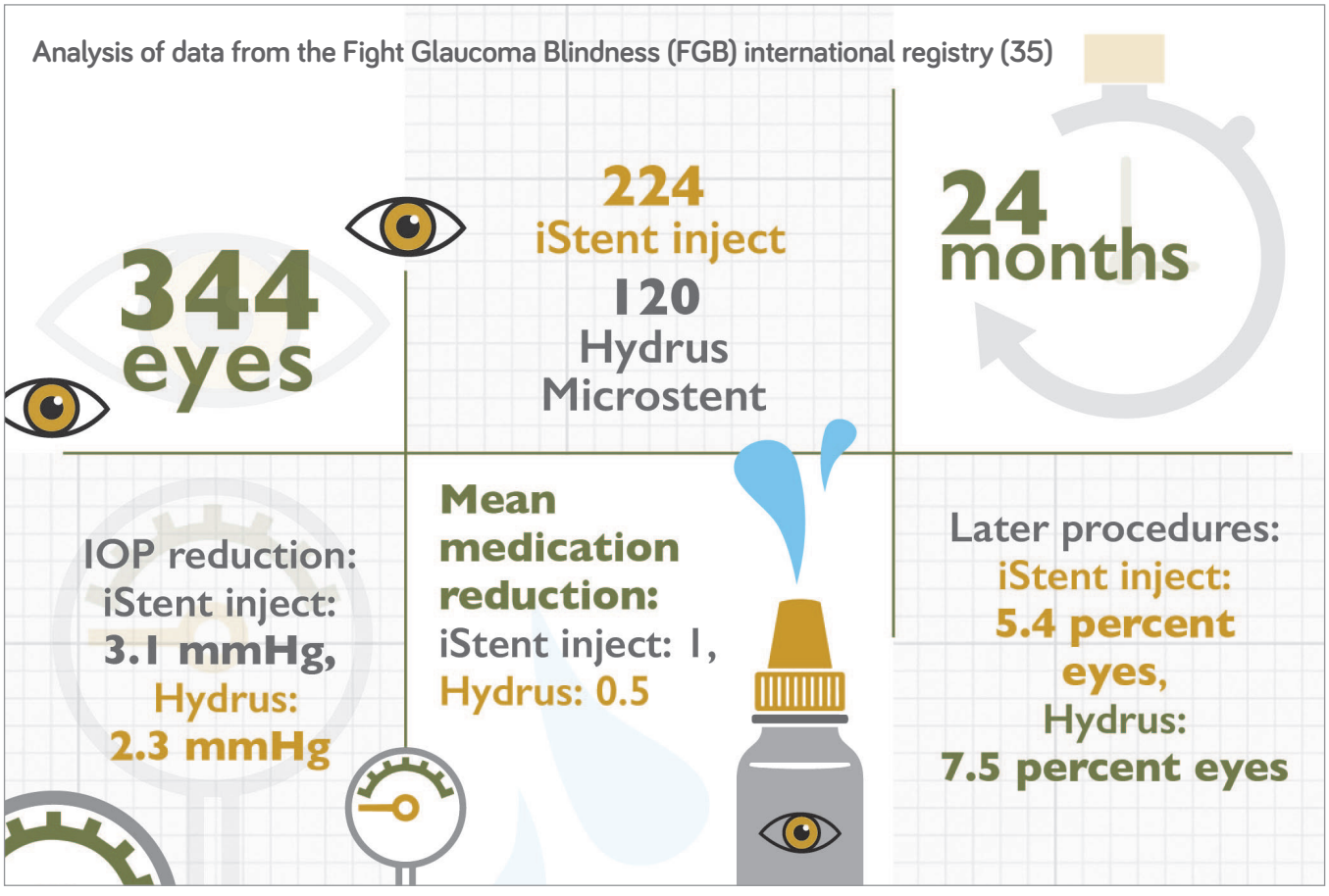
- **31 percent at 6-12 months;**
- **30 percent at 36-48 months;**
- **33 percent at 60 months.**

Pooled weighted mean IOP reduction across all studies: 7 mmHg at 6-12 months

- **6.6 mmHg at 36-60 months.**

Medication burden reduced by

- **1.2 medications at 36-60 months.**



Diversity of study populations

Herndon also draws attention to the broad range of ethnicities and glaucoma subtypes covered by iStent technology data: "We have the most diverse set of clinical data for any MIGS." For example, Herndon's own data (22), a 12 month, 89 eye study in African Americans with open-angle glaucoma, showed that first generation iStent implantation was associated with stable IOP and medication reduction (mean IOP reduced from ~18 mmHg to ~16 mmHg; mean medication burden reduced from 1.9 to 1.1). This study also showed that eyes that had undergone prior SLT achieved smaller reductions of IOP than eyes with no SLT history, but that the IOPs at year 1, and medication reduction, did not significantly differ between the two groups. **The conclusion we can draw from numerous studies around the world, says Herndon, is that iStent technology facilitates IOP reduction (up to 6 mmHg) and significant medication reduction (up to 94 percent), regardless of population or glaucoma type** (Table 1, Table 2).

Independent investigations

Herndon also emphasises the number of independent, non-sponsored studies of real-world outcomes. One investigation (29) compared iStent *inject* with Hydrus and Kahook Dual Blade approaches. This showed a mean IOP change of 10.6 percent for iStent *inject* eyes versus 4.3 percent in Hydrus eyes and 7.7 percent in Kahook Dual Blade eyes. **Reductions in medication burden were ~60 percent (iStent), 0 percent (Hydrus) and ~30 percent (Kahook).** respectively. Another study (30) compared iStent *inject* with Kahook Dual Blade at 12 months and reported a mean IOP change of ~35 percent in iStent *inject* eyes compared to ~20 percent in Kahook Dual Blade eyes (medication reductions: 62 percent for iStent *inject* eyes and 39 percent for Kahook eyes).

Data up-to-date: iStent *inject* W

Fritz Hengerer also attests to the real-world utility of iStent *inject*, and can provide data for the latest model: iStent *inject* W. The *inject* W builds on the micro-invasive, tissue-sparing performance of iStent *inject*, but has the added advantages of more predictable implantation, courtesy of the wider flange on the iStent *inject* W. The iStent *inject* W also benefits from an improved injector; key features include a tri-bevelled trocar tip for reduced tissue tethering; a splayed trocar to improve the delivery mechanism; and new collet tines behind the first stent for improved safety. "The device is very light and easy to handle," says Hengerer.

Hengerer points to his five-year data (see box below) focusing on the impact of iStent *inject* either standalone or combined with phacoemulsification, in eyes with a wide range of pathologies and surgical histories. **The five-year results are outstanding: mean IOP reduction of over 40 percent and medication reduction of over 70 percent. Importantly, many patients ended up entirely medication-free, despite relatively high initial medication burdens;** as Hengerer says: "This result makes patients and surgeons very happy – reducing the medication-associated dry eye burden is extremely important." Overall, Hengerer's five-year data support the use of iStent technology in the broad range of patients typically seen in a large practice – a conclusion endorsed by Liang (see sidebar below).

Finally, many years of collected iStent data may be summarised by a recent systematic review (32) which evaluated the independent effect of iStent and iStent *inject* without cataract surgery. This meta-analysis indicates that iStent technologies are of clear and sustained benefit with regard to reduction of both IOP and medication burden (see sidebar below).

Putting it all together – how to integrate iStent technologies into your practice

Clearly, there is overwhelming real-world evidence that mild-to-moderate glaucoma patients have benefited enormously from iStent technology; but how should a busy practice go about adopting this trabecular micro-bypass system?

First steps: education and anatomy

Ristvedt suggests that we might begin by educating referring doctors on the benefits of using iStent technologies to surgically intervene at a relatively early stage of glaucoma. For Samuelson (2), the first practical step for surgeons contemplating the iStent technologies is to ensure they understand intraoperative gonioscopy and the anatomy of the angle. Similarly, Gallardo advises surgeons new to the iStent technologies to ensure they understand the aqueous pump and outflow system, in particular by reference to Murray Johnstone's work. Herndon also agrees that anatomical knowledge is critical: "Residents and fellows should be familiar with what they're looking at." He recognizes that acquiring anatomical expertise can be time-consuming, but reminds us that synthetic models are available to assist with education.

Training tips

Herndon's top tip for beginners also relates to visualisation: "When first implanting iStent devices, novices may wish to use trypan blue to stain the trabecular meshwork." Ristvedt also has a pearl: "Schedule all the iStent technology implantations one after the other, so that you do the procedure repeatedly –- this helps you acquire the necessary muscle-memory more quickly." Gallardo (2) recommends learning by observing trabecular micro-bypass experts at work. Alternatively, he says, new surgeons can take advantage of support offered by the manufacturer, including access to KOLs who will talk through difficult cases or post-operative management issues: "Glaukos will also help you with on-site reps and demonstration devices – they are there for you." For his part, Singh notes the importance of learning how much viscoelastic to put in the eye, how much pressure to use with the gonioprism and what type of gonioprism to use.

"Fifteen years ago, we would not have considered performing glaucoma surgery on a one-medication patient with mild, stable disease – the risk-benefit profile of trabeculectomy didn't make sense in that indication."
Mark Gallardo

Set up for success

The consensus view is that new surgeons must, above all, ensure that they position the patient and microscope optimally. For example, Samuelson emphasizes the importance of 'getting a good view', while Herndon states that novices must turn the patient's head sufficiently to achieve a good en-face view of the angle. Ristvedt also emphasizes the importance of visualization: "Correct set-up is key to viewing the trabecular meshwork and angle – you need a head-on view, not a view from above." She therefore recommends that learners begin by tilting the microscope and the head of the patient, in order to ensure they can visualize the trabecular meshwork: "That will set you up for success!" Singh also agrees: "Anyone starting with iStent technologies should know that obtaining the best perpendicular en-face view eliminates much of the difficulty of MIGs."

Is the iStent straightforward to adopt?

Klabe (21) notes that the iStent technology procedures have a short learning curve and, given that they require minimal additional settings and instruments, are straightforward to integrate into normal practice: "When combined with phacoemulsification, the glaucoma portion of the procedure can be done either prior to or after cataract surgery according to surgeon preference." And Ristvedt believes that adoption has become more elegant with iStent *inject* W: "With iStent *inject*, there was a slight risk that by pressing too hard you could bury the device in the Schlemm's canal – that risk is much reduced with the *inject* W." Liang (31) agrees: "The injector system works very well; we no longer have to worry so much about the amount of pressure to apply"

Nathan Radcliffe (Medical Director, New York Eye Surgery Centre, USA) concurs (see sidebar below): "In patients undergoing refractive cataract surgery, I select a MIGS technology that does not disrupt refractive outcomes – in this context, the iStent *inject* W has been a great addition to my practice" (33).

Any other tips?

Ristvedt notes the importance of communicating with patients when integrating iStent *inject* W into a practice: "I tell them that alongside cataract surgery I will be working in the angle to optimise the natural outflow pathway." Particularly important, she says, is to emphasize the likely reduction in eyedrops, consequent decrease in OSD and ultimate improvement in quality of life – alongside a lower likelihood of invasive surgery in the future.

Samuelson recommends training surgeons on how to avoid atypical responses to the procedure: "For example, you can get pressure spikes if you withdraw medication too quickly – I always tell my staff to cut medications by one or two drops at a time, almost never three or four at a time." He also recommends training doctors in methods of defusing patient anxiety should such atypical events occur.

A future of infinite promise

Certainly, the surgical treatment of glaucoma has progressed extraordinarily over the last twenty years – but what does the future hold? More of the same, but better, it seems: Glaukos has already taken the iStent through three generations, yet continues to innovate. And now the company will offer us the iStent infinite®

– essentially a combination of three iStent *inject* W implants. "Just as two stents are better than one, so three stents are better than two," asserts Gallardo, **"because you are creating more outflow channels while still sparing tissue."** This is important, because not all collector channels are equivalent. For example, Alex Huang reminds us of aqueous angiography data showing that outflow is not equal around the 360 degrees of the limbus, but exists as a segmental arrangement of areas of higher and lower flow, which themselves are dynamic (pulsatile). Outflow thus varies over time and space within a single eye, from one eye to another in a given patient, and from one patient's eyes to another's. Placing stents in a given region of the eye therefore may have different impacts according to whether or not the stents rescue flow in a low-flow region or reinforce flow in a high flow region. It's not yet clear, says Huang, whether the best approach is to stent high or low-flow areas; but it's certain that having more stents per procedure gives you more options, including targeting both low and high-flow areas.

It is also relevant, says Singh, that most collector channels – specifically high-flow collector systems – are located in the nasal and inferior nasal quadrants. "In my experience, and according to the data I have seen, **placing two stents two clock hours apart in the nasal angle will access sufficient distal channels to reduce pressure significantly in the majority of our patients.**" It is a misconception, then, that we need to access high numbers of collector channels: "The canal can only handle a certain amount of flow – the outflow system vessels become smaller and smaller distally, and flow is limited by the smallest vessel in that chain," says Singh.

How is the iStent infinite performing so far? Gallardo (32) cites recent pivotal clinical trial data: "The iStent infinite showed wonderful one-year efficacy as a stand-alone procedure in tough to treat glaucoma patients." This means, he continues, that surgeons will have an option to non-ablatively manage the angle with a standalone procedure. Singh agrees: "It's an exciting system; the injector has been advanced, and the study shows that the device can achieve a 30 percent or greater reduction in IOP in 50 percent of patients, alongside a 13 percent reduction in topical medication." Furthermore, says Singh, these results were achieved in a challenging patient population with a history of prior glaucoma surgery: **"It takes a remarkable system to reopen the conventional outflow pathway in these patients – iStent infinite has shown to be that remarkable system."** Finally, Blake Williamson notes that Glaukos' continual investment in R&D is also paying dividends outside the iStent platform (10): non-stent products include devices for goniotomy (iAccess), visco delivery (iPRIME)and sustained drug delivery (iDose, which is designed to have long-term effect in reducing IOP).

The new iAccess Trabecular Trephine, has features to perform a goniotomy procedure while sparing up to 95% more natural anatomy than conventional goniotomy approaches. iAccess is performed via an ab interno approach using a gonioscope lens. iAccess employs a blade, or trephine, to precisely incise the trabecular meshwork and excise 220-µm circular cores of tissue across an unlimited number of clock hours. The device is unrestricted in the ability to create numerous incisions, thereby creating an extensive opening to Schlemm's canal and allowing aqueous to flow from the anterior chamber.

Hydrus Versus iStent *inject*

A recent study of the Hydrus and iStent inject pivotal trials (34) reports that Hydrus-implanted eyes exhibited levels of substantial endothelial cell loss (ECL) more than double those of iStent inject (14.2 percent versus 6.7 percent, at three years post-surgery when compared to baseline). For both devices, control groups appeared identical (10 percent of eyes had substantial ECL), indicating that it is valid to compare the respective study populations for Hydrus and iStent *inject*.

Conclusions

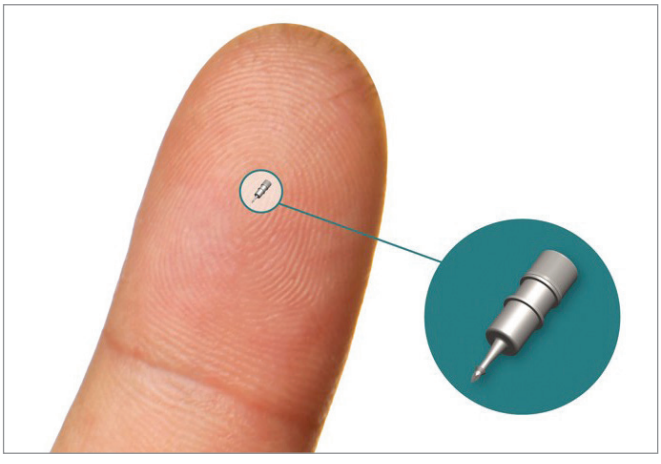
The purpose of MIGS procedures is to safely lower IOP in order to inhibit glaucoma progression – particularly with regard to visual field loss. To what extent have they risen to this challenge? Gallardo is clear: "Fifteen years ago, we would not have considered performing glaucoma surgery on a one-medication patient with mild, stable disease – the risk-benefit profile of trabeculectomy didn't make sense in that indication." But iStent technologies have changed that calculation; indeed, they have been demonstrating protection against visual field loss since 2011. And now their safety and efficacy mean they can be offered to almost every patient on glaucoma medication who requires cataract surgery. Singh agrees: "The iStent

inject W is a fantastic way to start with MIGS procedures, because of its high safety profile." He adds that a significant benefit of the iStent *inject* W is its impact on medication burden: "In mild-to-moderate patients on multiple medications, iStent technologies can reduce their burden by one or two drops, sometimes all three." Even if the IOP remains similar, says Singh, a reduction in medication means the procedure is worthwhile.

Furthermore, the iStent platform is backed up by 20 years of data, including not just clinical trials but real-world studies and meta-analyses. Together, these cover more patients, from more diverse populations, over longer time periods, than any other MIGS procedure; they also demonstrate that iStent technologies are of benefit in a broad range of patients, not just those deemed eligible for clinical trials. In brief, iStent technologies have more than 200 peer-reviewed publications, a body of work which represents the most robust, diverse, and longest-term aggregation of clinical evidence for any MIGS today. Importantly, the data show not just impressive efficacy, but also demonstrate that the iStent technologies are the safest of any MIGS device.

Importantly, it is clear that the iStent *inject* W is straightforward to adopt and integrate into a modern practice by virtue of its short learning curve, high levels of safety and broad compatibility with other procedures, including multifocal IOLs. Similarly, the iStent *inject* W is so non-traumatic and interferes with so little of the angle that it does not preclude future surgical interventions, should they become necessary in future years.

Finally, the continuous investment and innovation by Glaukos has resulted in a growing portfolio of advanced technologies for glaucoma management. Glaukos reinvests ~30 percent of its revenue back into R&D; its goal is to provide ophthalmologists with products to effectively treat any glaucoma patient they may see. Several of these new technologies will launch in the coming months, thereby broadening treatment options for patients around the world. In particular, the latest iStent iteration, the iStent infinite, promises to build on and improve upon the success of iStent *inject* W. Having established MIGS as a viable approach, Glaukos is now turning it into the standard of advanced care.



Important Safety Information

INDICATION FOR USE

The iStent® Trabecular Micro-Bypass Stent (Models GTS100R and GTS100L) is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.

CONTRAINDICATIONS

The iStent® is contraindicated in eyes with primary or secondary angle closure glaucoma, including neovascular glaucoma, as well as in patients with retrobulbar tumor, thyroid eye disease, Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure.

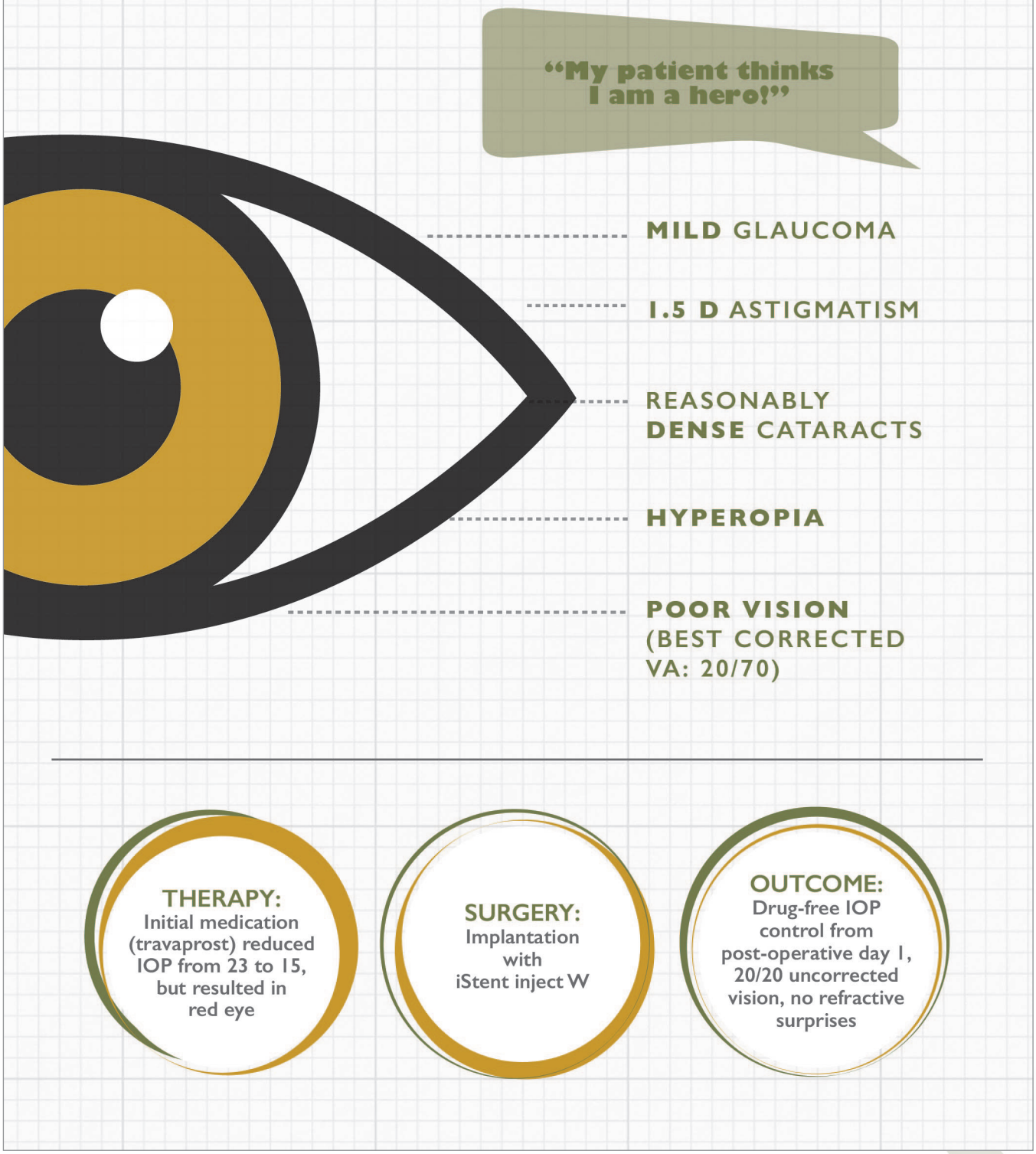
WARNINGS

Gonioscopy should be performed prior to surgery to exclude PAS, rubeosis, and other angle abnormalities or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. The iStent® is MR-Conditional meaning that the device is safe for use in a specified MR environment under specified conditions, please see label for details.

PRECAUTIONS

The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. The safety and effectiveness of the iStent® has not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, chronic inflammation, or an abnormal anterior segment, in pseudophakic patients with glaucoma, in patients with pseudoexfoliative glaucoma, pigmentary, and uveitic glaucoma, in patients with unmedicated IOP less than 22 mmHg or greater than 36 mmHg after washout of medications, or in patients with prior glaucoma surgery of any type including argon laser trabeculoplasty, for implantation of more than a single stent, after complications during cataract surgery,

Expanding patient satisfaction through MIGS (Nathan Radcliffe) (33)



and when implantation has been without concomitant cataract surgery with IOL implantation for visually significant cataract.

ADVERSE EVENTS

The most common post-operative adverse events reported in the randomized pivotal trial included early post-operative corneal edema (8%), BCVA loss of = 1 line at or after the 3 month visit (7%), posterior capsular opacification (6%), stent obstruction (4%) early post-operative anterior chamber cells (3%), and early post-operative corneal abrasion (3%). Please refer to Directions for Use for additional adverse event information.

CAUTION

Federal law restricts this device to sale by, or on the order of, a physician. Please reference the Directions for Use labeling for a complete list of contraindications, warnings, precautions, and adverse events.

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