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REVIEW/UPDATE

Standalone interventional glaucoma: evolution from the combination-cataract paradigm

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One of the most impactful recent developments in the glaucoma community has been the concept of interventional glaucoma. In brief, this paradigm shift involves proactive rather than reactive intervention to address glaucoma earlier in the disease process, including in both standalone and combination-cataract settings. By intervening earlier with minimally invasive surgical, laser, or drug-delivery treatments instead of prolonged topical medications, interventional glaucoma aims to take the burden of medication compliance off the patient. It also allows for standalone surgical interventions rather than letting cataract surgery dictate the glaucoma treatment plan. This interventional mindset has been made possible by the increasing diversity and availability of effective minimally invasive treatment options. With these options as a springboard, it is time to reevaluate and advance the traditional glaucoma treatment paradigm.

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The past decade has ushered in a substantial shift in the treatment paradigm for glaucoma. One of the most disruptive technological advances has been the introduction of microinvasive glaucoma surgery or MIGS. These surgeries are commonly characterized by a microinvasive (typically ab interno) approach, minimal tissue trauma, rapid recovery, high-safety profile, and scalable efficacy based on disease severity.[1] Traditional filtering surgeries, such as trabeculectomy and tube shunts, have the benefit of dramatically lowering intraocular pressure (IOP), but when these surgeries result in prolonged hypotony, corneal decompensation, bleb leaks, or infection, they can be detrimental.[2–5] One of the advantages of MIGS has been a far lower incidence of complications while restoring IOPs to a more physiologic level. This improved risk–benefit ratio has fueled surgeons' increasing use of MIGS at earlier stages of the disease.[6,7] In addition, many new procedural pharmaceuticals—such as the bimatoprost intracameral implant (Durysta, Allergan, Inc.) and the sustained-release iDose TR travoprost intraocular implant (Glaukos Corp.)—are designed to be used in all stages of glaucoma severity and ocular hypertension.[8,9] This flexibility may allow for earlier, more proactive interventions and better 24-hour IOP control in comparison with eyedrops.[10–12]

Over the past decade, MIGS has increasingly bridged the chasm that formerly existed between the 2 ends of the traditional treatment spectrum: topical medications and laser procedures on one end, and higher-risk filtration surgeries on the other. In addition, modified bleb-based surgeries with implantation of devices such as the XEN Gel Stent, Ex-PRESS, and PreserFlo MicroShunt have emerged that have sought to lessen some of the complications of traditional filtering surgery.[13,14] Regarding prevalence, starting from a negligible portion of glaucoma surgeries at the time of its U.S. release in 2012, the iStent trabecular micro-bypass (Glaukos Corp.) MIGS device rose to account for 43.7% of all glaucoma surgeries, MIGS or otherwise, in the United States by 2017.[6] As shown in Figure 1, MIGS now comprises the majority of all glaucoma surgeries in the United States.[6] These rising rates seem to reflect the field's broader recognition of the benefit of using MIGS at earlier stages in the disease because the MIGS era has provided more opportunity for IOP reduction and stability with a decrease in medication burden. Indeed, in areas of the United States with higher adoption of MIGS, there are lower rates of trabeculectomy.[7]

Historically, the traditional treatment algorithm has been a stepwise reactive approach of drops, laser, and end-stage filtering surgery. For drops, a topical prostaglandin is often used first in treating glaucoma, followed by a second or third drop if the IOP is not at goal or if there is progression.

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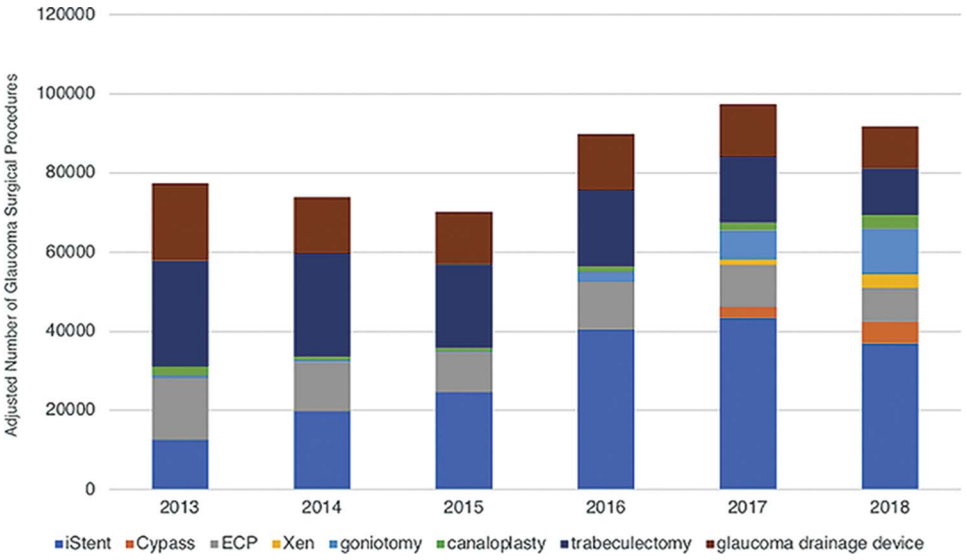

Figure 1. Composition of glaucoma surgical procedures in the United States from 2013 to 2018. Reprinted with permission from Elsevier from Yang SA, et al.[6] All permission requests for this figure should be made to the copyright holder.

This approach relies on patient compliance, while watching and waiting for further disease progression before considering laser therapy or filtering surgery, the latter of which is invasive and can have substantial complications. Owing to the higher risks of incisional filtering glaucoma surgeries, this reactive approach may have called for filtering surgery only when the disease state was severe, or when it could be combined with another intraocular procedure such as cataract surgery. This reactive approach has several drawbacks that fundamentally limit its appropriateness for a chronic, progressive, irreversible, and vision-threatening disease such as glaucoma.

By contrast, the interventional glaucoma treatment paradigm advocates earlier procedural intervention regardless of lens status, is fundamentally *proactive*, and allows safer options because less invasive solutions have become available. Compared with eyedrops, interventional glaucoma aims to reduce and steadily maintain IOP targets, delay or avoid higher-risk surgery, and decrease reliance on patient adherence and compliance. Secondarily, an interventional mindset resets the burden on patients by decreasing medication load.

Standalone surgery goes hand-in-hand with an interventional, proactive approach; in fact, the first U.S. Food and Drug Administration (FDA)–approved trabecular micro-bypass device (iStent) was developed with the intention to treat glaucoma independently of disease state or lens status, but ultimately the regulatory pathway associated with combination-cataract surgery in the United States proved to be more viable for bringing these first-generation devices to market with the FDA. Thus, it was not lack of clinical efficacy, but rather practical and regulatory issues, that initially tied many MIGS procedures to be performed at the time of cataract surgery. Many subsequent MIGS devices have followed the same legacy combination-cataract model.

Given this traditional predisposition toward—and comfort with—combination-cataract surgery, it is important to note that the average age of cataract surgery is decreasing, with the mean age estimated at 62.5 years in a broad population-based study in Australia; this suggests that many patients may be opting for proactive cataract surgery before they have serious vision loss.[15] In contrast to this trend toward earlier cataract surgery, glaucoma surgery has remained more reactive in nature and often has been considered only when topical medications have failed, when the IOP goal is above range, and/or when a visual field change is detected. This has meant that a large segment of the glaucoma population has been unable to benefit from earlier procedural intervention unless their cataract surgery coincided with the time a glaucoma procedure was needed or considered. Thus, by tying glaucoma intervention to cataract surgery, doctors may be limiting patients' treatment options to an unnecessarily narrow window. Rather than delaying intervention until a cataract develops, we can consider addressing glaucoma before irreversible damage occurs.

When evaluating glaucoma procedures either with or without cataract surgery, it is important to remember that cataract surgery alone is known to reduce IOP. However, the effect in treated glaucoma patients is typically modest: less than 2 mm Hg on average, or a reduction vs baseline of 16.5% 3 years after cataract extraction, as shown in the Ocular Hypertension Treatment Study.[16–19] In addition, evidence has shown that the reduction in IOP may be more significant at 1 year after cataract surgery and that, subsequently, IOP tends to return to baseline levels with time.[16,20–22]

Given that phacoemulsification cataract surgery lowers IOP, it is worthwhile to evaluate some of the MIGS pivotal studies that compare device + phacoemulsification vs phacoemulsification alone. In the pivotal trials for both Hydrus microstent and iStent *inject* trabecular micro-bypass, the treatment group (Hydrus or iStent *inject* with phacoemulsification) had higher proportions of eyes with IOP ≤18 mm Hg, IOP reduction ≥20%, and eyes medication-free than their respective phacoemulsification

alone groups.[23,24] In addition to these pivotal trials, a number of other studies have demonstrated the independent IOP-lowering and/or medication-lowering effect of glaucoma procedures, as separate from cataract extraction, and the longer duration of such effect than that expected after cataract extraction.[25–38]

In the past, when the entirety of the glaucoma treatment spectrum consisted of either medications or invasive surgery, the traditional reactive treatment approach was logical, acceptable, and the best we could do at the time. However, with the increasing diversity and availability of microinvasive surgical interventions, as presaged by Saheb et al. a decade ago, we have already reached a tipping point of what should be considered an appropriate treatment algorithm for our patients.[1] Indeed, for both patients' benefit and relevance in our own field, it behooves us to reexamine formerly held treatment patterns. To paraphrase Rear Admiral Grace Hopper, the most dangerous phrase is "we've always done it this way."

There is a wealth of robust evidence supporting the shift to an interventional—and, where appropriate—standalone approach to glaucoma, provided that safe and effective minimally invasive surgical options exist. Topical medications, although challenged as first-line therapy by the Laser in Glaucoma and Ocular Hypertension (LiGHT) trial, typically still remain the first-line intervention in early-diagnosed or newly diagnosed glaucoma.[39,40] Medications can be effective in lowering IOP, and we now have preservative-free options that lessen side effects; however, we would be remiss to ignore the realities of noncompliance that limit medications' real-world utility. Even very effective medications are rendered useless if they are applied improperly, inconsistently, or not at all. Rigorous studies of medication adherence, including those who provide free medication and assistive technology to boost adherence, have reported that only a minority of patients apply their medications consistently or properly.[41–43] An article by Nordstrom et al., for example, reported that >90% of patients are nonadherent with topical medications and approximately 50% purposely discontinue their topical medication(s) within 6 months.[42] In addition, adherence is known to decrease dramatically when more than 1 medication is prescribed or when dosing frequency is increased.[44,45] This is consequential considering that an estimated 40% to 75% of patients with glaucoma take 2 or more medications.[46,47] Nonadherence, in turn, is significantly associated with glaucomatous vision loss.[48,49] By contrast, surgical intervention provides a more constant foundation of IOP control that does not rely on patient compliance, understanding, manual dexterity, or caregiver assistance.[10,12] This independence from patient adherence helps decrease the risk of glaucoma progression.[48,50,51] In addition, selective laser trabeculoplasty (SLT) and procedural pharmaceuticals such as Durysta and iDose TR are designed for use in all severities of glaucoma and ocular hypertension, possibly facilitating earlier intervention and avoidance of adding topical medication.

Another major limitation to the conventional approach of a topical medication-first treatment algorithm is that patients with glaucoma are often progressing under this paradigm. A large longitudinal study in Olmsted County showed that over 20 years, there was a 13.5% unilateral and 4.3% bilateral rate of progression to blindness.[52] Studies by Chen et al., Hattenhauer et al., and Kwon et al. found similar results.[53–55] One possible reason for continued disease progression and blindness, aside from nonadherence to prescribed medical therapy, is that medications do not necessarily attenuate IOP fluctuations, including both diurnal and nocturnal variability.[51,56] IOP fluctuations, in turn, increase the risk of disease progression and optic nerve damage.[57–60] By contrast, patients with glaucoma undergoing a filtering or MIGS intervention have reduced IOP fluctuations than patients on medications alone.[10–12] As a result, surgical intervention has been shown to preserve vision better than medications.[61,62] These findings were corroborated in a recent comprehensive literature review and meta-analysis which showed that visual field progression after trabecular micro-bypass surgery was lower than that expected in medically treated patients with glaucoma.[63]

In addition, it is important to note that any therapy in the treatment algorithm—from topical medications and laser trabeculoplasty to later-stage invasive filtering surgery—may be governed by the proverbial law of diminishing returns. The chronic use of topical medication can result in a plateau-like effect, with medication efficacy flattening or even diminishing over time.[64] Thus, it is not surprising that additional medications are needed in the aforementioned 40% to 75% of patients, although they are known to produce diminishing benefit with each addition. A study by Patel et al. corroborated a shorter-lasting benefit and higher health-related costs with each additional medication in a given patient's glaucoma treatment regimen.[65] As a result, questions have been raised about whether the addition of a third or fourth medication is effective at all.[66]

The interventional mindset and the findings in the LiGHT trial have afforded the option of SLT as first-line therapy. The 6-year findings of the trial showed lower VF progression, higher eyedrop-free IOP control, and lower trabeculectomy rates in the SLT arm than in the topical medication arm.[39] However, a key understanding is that SLT also may be subject to the same law of diminishing returns. SLT wanes in effectiveness over time, with success rates decreasing from 45% to 87% at 1 year to 18% to 62% at 3 years and 25% at 5 years.[67–70] Patients may have repeat SLT because of waning efficacy, as was necessary in 44.5% of patients not taking medications in the LiGHT trial, or they may be placed on medications, as was necessary in 81.1% of eyes by 1 year in a Brazilian study of SLT vs medications.[71] However, repeat SLT may have lower success than initial SLT and harbors the same inherent issue of waning effectiveness, while topical medications have the considerable limitations that were detailed previously.[72] More time and data are needed to discern whether newly developed technologies such as direct SLT may be able to circumvent some of these limitations.

At the invasive extreme of the treatment spectrum, 30.7% of filtering surgeries fail by 3 years and 46.9% fail by 5 years, and repeat filtering surgeries have lower success rates than

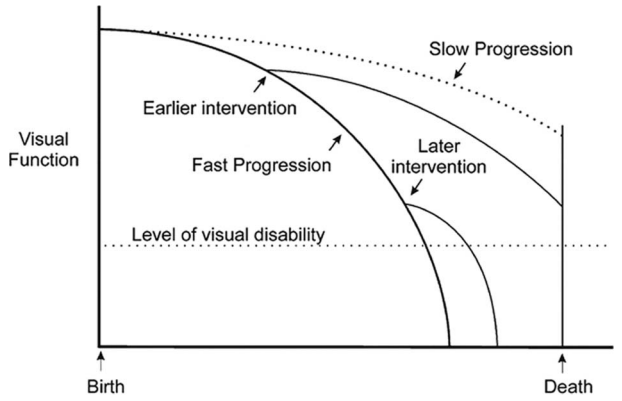

Figure 2. Effect on visual disability of patients with glaucoma as a function of time of intervention and rate of progression. Reprinted with permission from Elsevier from Caprioli J. The importance of rates in glaucoma. Am J Ophthalmol 2008;145(2):191–192. All permission requests for this figure should be made to the copyright holder.

initial filtering surgery.[5,73,74] They are associated with substantial short-term and long-term risks, many of which are cumulative over the lifetime of the patient.[3–5] By contrast, studies have shown that earlier and more proactive intervention (ie, not watching and waiting until filtration surgery is needed) may contribute to not simply a delay in further surgery, but rather a shifting of the disease trajectory.[75,76] That is, earlier intervention helps slow the rate of disease progression such that visual disability may be delayed or prevented (Figure 2).[75]

Regarding any of these therapies, it is important to note that glaucoma treatment is a continuum, with no single therapy being a panacea for all patients. Treatments have limitations, and there are no one-size-fits-all solutions. An interventional treatment paradigm does not sidestep these shortcomings but rather tries to minimize them by considering procedural interventions earlier in the patient's journey. For many patients, this could mean doing SLT, a MIGS procedure, or a procedural pharmaceutical implant while using medication as a bridge or adjunct therapy (rather than first-line treatment).

The medication literature is replete with evidence of side effects that can lead one to question whether medications should really be considered a "conservative" intervention. These sequelae include but are not limited to damage to the corneal and conjunctival surface, pathologic cellular changes due to preservatives, hyperemia, eyelid and iris hyperpigmentation, periorbital fat atrophy, systemic reactions (including fatalities), costs, increased risk of later surgical failure, and significantly diminished quality of life.[77–92] Indeed, a recent study reasserted that glaucoma treatment poses a considerable burden on patients, independent from the burden of the disease itself.[93]

Considering the limitations of the traditional polarized topical medication-or-filtering surgery treatment paradigm, we are overdue to closely examine the minimally invasive procedural interventions that have made possible an entire spectrum of treatment options. To date, angle-directed MIGS surgeries in the United States have generally been comprised of either implant-free canal-based procedures (Kahook Dual Blade, trabectome, gonioscopy-assisted transluminal trabeculotomy, ab interno canaloplasty, OMNI, and ABiC) or trabecular bypass procedures (iStent, iStent *inject*, iStent infinite, and Hydrus). The former involve opening the Schlemm canal through either viscodilation or goniotomy of the trabecular meshwork; the latter provide a patent pathway for aqueous fluid to egress through the diseased trabecular meshwork, in some cases with a scaffolding component as part of the mechanism of action (Hydrus). In addition to patient-specific factors, the selection of a particular MIGS surgery in the United States has been influenced by FDA indication (standalone or combined with cataract surgery), disease severity (mild, moderate, and severe), and safety profile.

Before 2022 in the United States, canal-based, implant-free MIGSs, such as goniotomy and canaloplasty, have been some of the only MIGS options available to surgeons in standalone settings (not only combined-cataract cases) and in a variety of disease severities (not just mild or moderate disease). These surgeries involve opening the Schlemm canal through either viscodilation or goniotomy of the trabecular meshwork. They have been shown to reduce IOP and medications when used in standalone procedures or in combination with cataract or other MIGS surgeries. However, concerns about safety events such as hyphema, cyclodialysis, and IOP spikes have limited their use.[94]

Trabecular bypass surgeries have been widely used and approved for standalone use outside the United States, indicating a realization of the potential value of standalone trabecular bypass procedures. In mid-2022, standalone trabecular bypass also became possible in the United States, when the FDA approved the iStent infinite for those who failed prior surgical and medical therapy. The device contains 3 stents implanted into 3 trabecular meshwork sites, accessing up to three-quadrants of aqueous outflow. The prospective, multicenter, pivotal trial showed that over three-fourths met the responder endpoint of a ≥20% mean diurnal IOP reduction from baseline on the same or fewer medications, with a good safety profile.[95] Notably, the patients represented all stages of glaucoma severity, from mild to severe, and included a subset of patients who had failed maximum-tolerated medical therapy (rather than failed prior surgery). As a result, the results might be generalizable to a broader segment of the glaucoma population beyond the study population.

Over 50 scientific publications have demonstrated the safety and efficacy of trabecular micro-bypass in standalone usage. These devices have been shown to have comparable efficacy with each other, and, in the case of iStent and iStent *inject*, they have similar general and corneal endothelial safety as cataract surgery alone.[96,97] Of particular relevance are 2 studies which have specifically analyzed the viability of standalone trabecular micro-bypass as an alternative to the traditional glaucoma treatment paradigm: either as first-line intervention, instead of medication in newly diagnosed patients, or instead of trabeculectomy or tube shunt in advanced patients. Fechtner et al. reported the results of a 5-year prospective randomized clinical study comparing topical prostaglandin vs standalone

implantation of 2 first-generation trabecular micro-bypass stents in newly diagnosed treatment-naïve patients with glaucoma.[98] The study showed similar IOP reductions in the stent and prostaglandin groups, with higher treatment success and lower need for supplemental glaucoma treatments in the stent group. At the more advanced end of the treatment spectrum, Paletta Guedes et al. compared standalone implantation of 2 to 3 trabecular micro-bypass stents vs traditional trabeculectomy in eyes with moderate to severe glaucoma.[99] The study found that the multistent group experienced clinically and statistically significant IOP and medication reductions with higher safety-adjusted treatment success rates than the trabeculectomy group. Together these studies indicate realistic viability of minimally invasive glaucoma surgery to treat both earlier and later-stage patients in the glaucoma treatment spectrum. Further new technologies—such as excimer laser trabeculoplasty (Elios), femtosecond laser trabeculotomy (Vialase), and supraciliary stents (iSTAR)—are also on the horizon, and may add even more versatility and diversity to the options available to doctors to treat their patients with glaucoma.

CONCLUSIONS

Despite technological advancements, topical medications often dominate glaucoma treatment as the initial step in management, while procedural interventions are often reserved for the time of cataract surgery, at least in the United States, due to initial regulatory indications. Before the advent of MIGS, and due to the significant risks of surgical filtration procedures, it may have been reasonable to treat with increasing numbers of medications and defer surgical intervention until late in the disease. However, as laser, MIGS, and sustained drug delivery procedures have evolved, diversified, and improved over time, and with the emergence of sound published clinical evidence, there are increasing segments of the glaucoma population that would benefit from surgical intervention instead of topical medication as first-line intervention. In this context, the traditional polarized treatment algorithm is due for reevaluation and advancement. Indeed, we hope that the evidence and clinical expert opinions we have summarized demonstrate that the field of glaucoma has evolved. To remain relevant and provide the highest standard of care to our patients, it is essential that MIGS, laser procedures, and sustained drug delivery be widely covered, accepted, used, and further advanced by our glaucoma community. To realize the level of acceptance these interventions merit, we need to start appreciating their value as standalone surgeries. These procedures should not be relegated to a secondary role in relation to cataract surgery. Instead, they represent a vital option for patients who deserve better than overmedication with undereffective drops and as an alternative to riskier filtering surgeries. Widespread acceptance and implementation of laser, MIGS, and sustained drug delivery procedures is long overdue.

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71.–99. References 71–99 are listed in Supplemental Data File 1 (http://links.lww.com/JRS/B220).

Disclosures: *J.M. Micheletti: ACE Vision Group—C, E; Alcon Laboratories, Inc.—C, R, L; Allergan, Inc. (AbbVie)—C, R; Avellino—C; Bausch & Lomb, Inc.—C; BVI—C; Centricity Vision—C; Diamatrix—C, P; Elios—C; Glaukos Corp.—C, L; Johnson & Johnson Vision—C, R; Lenstec—C, R, L; New World Medical, Inc.—C, L; NOVA Eye—C; Rxsight, Inc.—C; Samsara—C; STAAR—C, R, L; Synopic—C, E; Tarsus—C; Visus Therapeutics—C; Carl Zeiss Meditec AG—C, L. M. Brink: Allergan, Inc. (Abbvie): Consultant; Alcon Pharmaceutical: Consultant; Alcon Surgical: Consultant; Bausch & Lomb, Inc.: Consultant; Dompe: Consultant; Glaukos Corp.: Consultant; New World Medical, Inc.: Consultant; Sight Sciences: Consultant, Speaker; Tarsus: Consultant. J.W. Brubaker: Alcon Laboratories, Inc.: R, C, S; Allergan, Inc. (Abbvie): R, C, S; Equinox: R, C; Glaukos Corp.: R, C; Iridex: S, C; iStar: R; New World Medical, Inc.: C; Nicox: R; Santen: R, S; Twenty/Twenty Therapeutics: R. D. Ristvedt: Allergan, Inc.: consultant, speaker; Glaukos Corp.: consultant, speaker; RxSight: consultant, speaker; Sight sciences: consultant, speaker. S.R. Sarkisian [C = consultant/advisor, E = employee, L = lecture fees, O = equity owner, P = patents/royalty, S = grant support]: Aerie Pharmaceuticals, Inc.—L; Alcon Laboratories, Inc.—C, L, S; Allergan, Inc. (Abbvie)—C, L, S; Allysta Pharmaceuticals—S; Bausch & Lomb, Inc.—C, L; Beaver-Visitec International—C; Carl Zeiss Meditec USA, Inc.—C; Elios—S; Glaukos Corp.—C, S; iCare USA, Inc.—C; iStar Medical—C, S; Karena Products, Inc.—C; MST—C; Novartis Pharma—C; Ocular Science—C, O, S; Ocular Therapeutix—S; Santen, Inc.—C; Sight Sciences, Inc.—C, O, S; TearLab Corp.—C.*

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