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Minimally Invasive Glaucoma Surgery: Where Is the Evidence?

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Purpose: The last decade has witnessed an unprecedented growth in glaucoma treatment options through the introduction of minimally invasive glaucoma surgeries (MIGS). The aim of the present review is to provide an understanding of the currently available MIGS and to examine what data are currently available to guide treatment choice.

Design: Meta-analysis and systematic review of randomized and non-randomized control trials.

Methods: Out of 2567 articles identified, a total of 77 articles were retained for analysis, including 28 comparative studies and 12 randomized control trials. Overall, 7570 eyes were included. When data permitted, the weighted mean difference in intraocular pressure reduction was calculated for comparison purposes.

Results: Weighted mean intraocular pressure reductions from all analyzed studies were: 15.3% (iStent), 29.1% (iStent inject), 36.2% (ab interno canaloplasty), 34.4% (Hydrus), 36.5% (gonioscopically-assisted transluminal trabeculotomy), 24.0% (trabectome), 25.1% (Kahook dual blade), 30.2% (Cypass), 38.8% (XEN), and 50.0% (Preserflo).

Conclusions: One of the advantages of the heterogenous range of available MIGS options is the chance to tailor therapy in an individualized manner. However, high-quality data are required to make this choice more than an educated guess. Overall, this review confirms the efficiency of assessed MIGS compared with standalone phacoemulsification, but it highlights that only few studies compare different MIGS techniques and even fewer assess MIGS against criterion standard treatments. Current evidence, while non-negligible, is mostly limited to heterogenous non-randomized studies and uncontrolled retrospective comparisons, with few quality randomized control trials. We suggest that future research should be comparative and include relevant comparators, standardized to report key outcome features, long-term to assess sustainability and late complications, and ideally randomized.

Key Words: comparison, glaucoma, MIGS, meta-analysis, review

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Glaucoma is a progressive optic neuropathy and a leading cause of blindness worldwide. Indeed, with a forecasted rise in excess of 45% from 2020, it has been estimated that >110 million people would suffer from glaucoma by 2040.[1] To face the increasing burden of glaucoma, the landscape of glaucoma management has changed radically over the last decade. Although the 1990s were the decade of glaucoma drainage devices and novel topical therapeutic agents, and innovations slowed down in the 2000s, the second decade of the millennium witnessed an unprecedented growth in treatment options through the introduction and integration of minimally invasive glaucoma surgeries (MIGS).

Traditionally, when topical pharmaceutical therapies and laser treatments failed, the only alternative was filtering surgery. Since the 1980s, filtering surgeries have benefited from the development of antimetabolites and evolved into highly effective procedures, with reported relative intraocular pressure (IOP) reductions as high as 50%.[2] However, this evolution was associated with an increase in severe adverse events such as chronic hypotony, bleb leak, or endophthalmitis, with a rate of late complications in excess of 30% in some reports.[3] MIGS were designed to bridge the gap between medical or laser therapies and more invasive filtering surgeries in mild-to-moderate glaucoma. By essence, MIGS are meant to have an extremely favorable safety profile ensuring prompt postoperative recovery, so should achieve reliable IOP reduction, albeit more modest than that of traditional filtering surgery.[4] Through the array of available techniques, MIGS have not only provided clinicians with a wider range of therapeutic options, but they have also enabled them to adjust their therapies more finely which may have contributed a more patient-centric decision-making process. But such a large armamentarium to choose from can be overwhelming, especially in the absence of evidence-based criteria.

The aim of the present review is to provide an understanding of the currently available classes of MIGS and, through a meta-analysis and the authors' commentaries on the recent literature, look into what data are currently available to influence and guide treatment choice.

METHODS

The meta-analysis presented in this article adheres to the Preferred Items for Systematic Reviews and Meta-Analyses guidelines. Electronic databases of medical literature were searched using specific keywords referring to each study of MIGS, including current and previous tradenames, alternative designations, and surgical techniques. The following MIGS were included in the search: Trabectome (NeoMedix Corporation, Tustin, USA), Excimer Laser Trabeculotomy, Kahook Dual Blade (New World Medical, Rancho Cucamonga, USA), Gonioscopy-Assisted Transiluminal Trabeculotomy, Ab Interno Canaloplasty (iTrack, Ellex Medical Lasers, Adelaid, Australia), Hydrus Microstent

(Ivantis Inc, Irvine, USA), High Frequency Deep Sclerotomy (HFDS, Oertli Instrumente AG, Berneck, Switzerland), iStent Trabecular Micro-bypass (Glaukos, San Clemente, USA), iStent inject (Glaukos), CyPass Supraciliary Micro-Stent (Alcon, Geneva, Switzerland), Trans-scleral Cyclophotocoagulation, Endo-Cyclophotocoagulation, Preserflo (Santen, Osaka, Japan), and XEN Gel Stent (Allergan, Irvine, USA). Keyword search identified 2567 peer-reviewed articles, among which 394 duplicates were excluded.

Only articles that were available in English were considered. Nonclinical studies, case reports, studies with a follow-up duration <6 months, studies with retention rates <20%, and studies consisting exclusively of pediatric patients (younger than 18 years), or of patients with secondary or narrow-angle glaucoma were excluded. A total of 77 articles were retained for analysis [trabeculotomy (n = 28); canaloplasty (n = 5); Hydrus (n = 7); HFDS (n = 2); trabecular micro-bypasses (n = 26); CyPass (n = 2); Preserflo (n = 1); XEN (n = 6)], among which 12 were randomized control trials (RCTs). Overall, 7570 eyes were included.

The following data were collected: study design, number of eyes enrolled, follow-up duration, surgical technique, percentage of IOP reduction, percentage of antiglaucoma medication reduction, complication rates, main complications, and elicited risk factors. In all comparative studies (n = 28), absolute IOP reduction and standard deviation were collected for both groups. When these were available, they were used to calculate the weighted mean difference and 95% confidence interval using the following formula: $(M_1 - M_2) \pm 1.96 \times s_{(M1\ -\ M2)}$ where M_1 and M_2 are the mean IOP reductions, and $s_{(M1\ -\ M2)}$ is the standard error calculated as $\sqrt{[(s^2_p/n_1) + (s^2_p/n_2)]}$. All calculations were performed using a commercially available software (MedCalc v.19.1.7, MedCalc Software, Ostend, Belgium).

REVIEW

Approaches

MIGS can generally be classified based on their physiological mechanisms and anatomical sites of action. Said mechanisms can focus on: Schlemm canal, suprachoroidal space, subconjunctival space, and ciliary body. Each class of MIGS presents its own advantages and limitations, and several techniques or devices usually come under each heading, representing technical or dimensional variations. The main classes of MIGS and mechanisms of actions are illustrated in Figure 1 and Figure 2.

Schlemm Canal: Trabecular Meshwork Bypass and Schlemm Canal Dilatation

Physiologically, the trabecular or conventional pathway accounts for the largest part of aqueous humor outflow. Aqueous humor drains through the trabecular meshwork into Schlemm canal, before reaching a wide network of vessels through the collector channels. In primary open-angle glaucoma, however, trabecular meshwork outflow resistance increases, possibly in response to extracellular matrix changes, the etiology of which is still mostly known.[5,6] Furthermore, in the early 1960s, Grant showed how ab interno 360 degree removal of the trabecular meshwork resulted in a 75% reduction of the total resistance in enucleated eyes at an IOP of 25 mm Hg.[7,8] Bypassing a site of increased outflow resistance (often considered the primary site of resistance) and enhancing the main physiological outflow pathway are 2 of the principles underlying the rationale of trabecular meshwork bypass or ablation. This class of MIGS aims to reduce outflow resistance and IOP by facilitating aqueous drainage into Schlemm canal either by bypassing the trabecular meshwork via some stent devices, or by merely removing all or a portion of the trabecular meshwork. Several variations of stent devices and trabecular meshwork ablation techniques exist.

However, recent studies have suggested that, contrary to the common misconception that the main site of glaucoma resistance lies within the juxtacanalicular trabeculum, the IOP elevation observed in primary open-angle glaucoma is more accurately caused by a combination of 3 equally determinant factors: loss of permeability of the entire thickness of the trabecular meshwork, collapse of Schlemm canal, and downstream resistance, notably with the closing of collector channel entrances.[9–11] This was further supported by the finding that Schlemm canal dilatation was positively correlated with the magnitude of IOP reduction.[12] It was, therefore, theorized that Schlemm canal's increased volume is associated with the stretching of its walls, which in turn causes the opening of pressure-dependent collector channels, leading to aqueous outflow.[13] Based on these observations, another subcategory of MIGS specifically targets Schlemm canal, with the aim of restoring a healthy Schlemm canal function and opening closed collecting channels. Two approaches were used to produce Schlemm canal dilatation: the mechanical dilatation using a temporary or resorbable medium, and the use of a permanent implantable scaffold.

Despite theoretically different approaches, these 2 subcategories of MIGS are, in effect, physiologically related. Indeed, although the latter group directly targets Schlemm canal to cause its dilatation with aqueous humor and restore distal outflow capacity, studies have shown that the former group, although merely bypassing the trabecular meshwork, produces a similar effect. Indeed, it was reported that the magnitude of IOP reduction after trabecular meshwork bypass implantation was directly correlated to the dilatation of Schlemm's canal.[14] Furthermore, aqueous angiography techniques have shown that, beyond their effects on Schlemm canal, trabecular bypass devices could increase collector channel outflow.[15] Both of these approaches, however, suffer the same limitation in that they do not address any resistance that may be distal to the collector channels' openings. Therefore, the IOP achieved will always be dependent on distal outflow capacity and episcleral venous pressure, resulting in a floor effect in IOP reduction.

This raises the question of the importance of targeting collector channels with MIGS. Although it has been reported that trabeculotomies performed in the nasal hemisphere, where the concentration of collector channels is denser, increases outflow more than trabeculotomies performed in the temporal hemisphere,[16] more recent research suggests a more nuanced reality. Indeed, Huang et al[17] have shown that targeting an area deprived of collector channel outflow could recruit new, previously closed, channels. In the absence of a dedicated comparative study, the question remains controversial and most MIGS procedures continue to be performed superonasally, both for practical reasons and to target more collector channels.

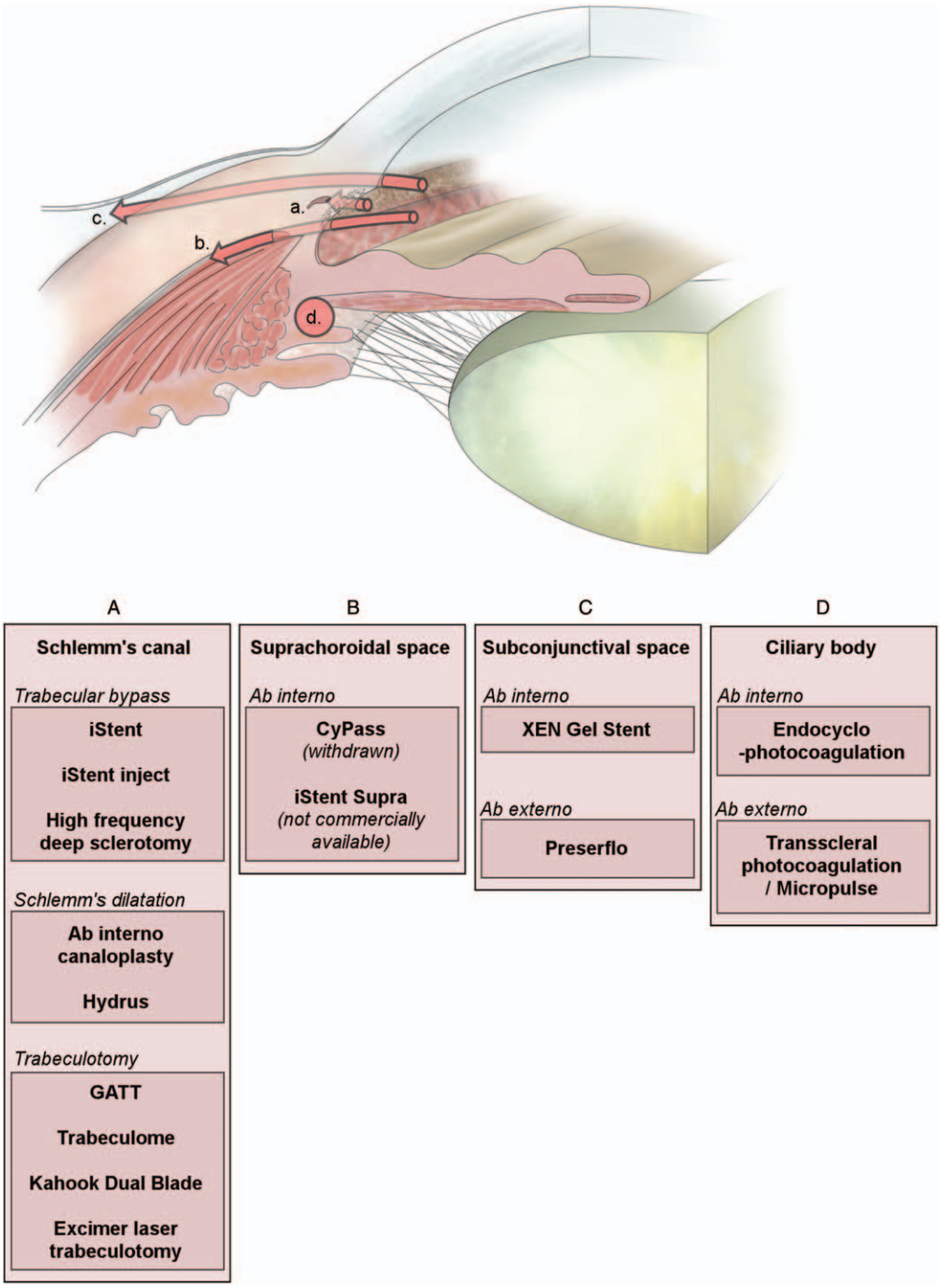

FIGURE 1. Illustration of different anatomical and technical approaches of minimally invasive glaucoma surgeries. GATT indicates gonioscopy-assisted transluminal trabeculotomy.

Suprachoroidal Space: Suprachoroidal Shunts

The physiological proportion of aqueous humor draining through the suprachoroidal space is subject to debate due to the lack of techniques available to measure uveoscleral flow, but estimates range between 4% and 60%.[18,19] It is, however, accepted that aging is responsible for a mark reduction in uveoscleral outflow.[20] This outflow pathway is produced by a combination of relative ciliary body permeability, which is believed to be the site of main resistance in the uveoscleral pathway,[21] and the existence of a hydrostatic pressure gradient through the anterior chamber, the supraciliary space, and the suprachoroidal space.[22] Such a negative gradient is believed to be produced by the rapid absorption of aqueous from the suprachoroidal space into the large and dense choroidal vasculature.[23,24] Another characteristic of the uveoscleral pathway is that it is relatively pressure-independent, and was shown to have a constant effect between 4 and 35 mm Hg.[25]

These last 2 characteristics suggest that exploiting uveoscleral pathway may theoretically provide remedy some of the conventional pathway: the risk of distal resistance and the floor effect. However, devices targeting this pathway can be expected to have a whole different risk profile to trabecular bypass devices. Indeed, the potentially greater outflow capacity of this approach could, in theory, be associated with higher risks of hypotony and

FIGURE 2. Illustration of a selection of minimally-invasive glaucoma surgery procedures. From top left to bottom right: iStent, iStent inject, Hydrus Microstent, iTrack, trabectome, TRAB 360, Kahook Dual Blade, CyPass Micro-stent, iStent Supra, XEN 45, PreserFlo, MicroPulse G6 cyclophotocoagulation.

choroidal detachment, especially in patients with a long history of prostaglandin therapy. Although the cases are too rare to warrant for a prospective study, there has been anecdotal cases suggesting that patients who were chronically treated with prostaglandins may be at a higher risk of developing choroidal pathologies.[26–29] This may be related to the effect of prostaglandins, reducing collagens within the uveoscleral pathway.[30] Furthermore, from a practical point of view, the suprachoroidal space may be less readily accessible and visualizable by a surgeon than the trabeculum.

Although there are no commercially available MIGS relying on suprachoroidal drainage, some new devices are under development and sound clinical data are available on a previously commercialized device. Therefore, we will discuss the case of this device, some characteristics of which may be comparable with future devices of the same category.

Subconjunctival Space: Subconjunctival Filtration

Contrary to the trabecular and the uveoscleral approaches, subconjunctival filtration does not seek to enhance or increase a physiological pathway. Instead, it relies on the creation of an artificial canal between the anterior chamber and the subconjunctival space, typically through a stent. This process results in an iatrogenic filtration bleb from which aqueous humor diffuses into the surrounding subconjunctival tissue and is eventually reabsorbed into subconjunctival capillaries.[31]

The idea of subconjunctival filtration is not new. Indeed, it stems from the anterior sclerectomy technique designed by De Wecker in 1858.[32,33] Although modern-day trabeculectomies and deep sclerectomies have considerably refined the technique, the use of the subconjunctival pathway remains. Like trabeculectomy, the success of subconjunctival MIGS procedure depends on the persistence of a healthy filtering bleb. Therefore, these MIGS share many similarities with filtering surgeries, in terms of risks and advantages. One of the main advantages of subconjunctival filtration is precisely that it does not impact any of the physiological outflow pathways, and as such, preserves any remaining physiological filtration. Another significant advantage of these techniques is that they do not rely on episcleral venous pressure or suprachoroidal pressure gradients to achieve filtration. Instead, their filtration capacity is only dependent on the outflow resistances of the stent and the subconjunctival space. Therefore, they

can potentially achieve lower IOPs than physiological approaches.

The outflow resistance of the subconjunctival space, however, is very much patient-dependent and can be difficult to predict. A significant factor recognized to influence resistance is conjunctival scarring and fibrosis, which has been linked to a significant proportion of failures after filtering surgery.[34] The pathophysiology of fibrosis is complex, but growth factors and cytokines expressed in inflammatory cells are clear culprits.[35] This is particularly problematic in glaucoma patients when inflammation is exacerbated through 4 mechanisms: the predisposition of patients to conjunctival fibrosis through long-term use of topical prostaglandins or toxic preservative, both of which were associated with local inflammation[36,37]; the surgical procedure itself is a clear source of inflammation; subconjunctival flow, by itself, constitutes a persistent mechanical stress to local tissue, which was shown to translate into pro-inflammatory biochemical signals[38–40]; and the mere presence of aqueous humor in the subconjunctival space, where it is not naturally present, was shown to promote tissue fibrosis. Some components, particularly transforming growth factor-beta, and endothelial growth factor-A, present at increased levels in the aqueous humor of glaucoma patients are believed to be responsible.[41,42] Although both endothelial growth factor antagonists and Rho-kinase inhibitors were suspected to be beneficial in the context of bleb surgery, they have so far failed to demonstrate clear superiority or to translate into clinical practice,[43,44] and, to date, the clinical recommendations with regards to inflammation mediation are the preoperative washout from proinflammatory topical medications and the prolonged postoperative use of topical steroids. This point, however, remains the major impediment to sustainable subconjunctival filtration and the control of inflammation in glaucoma has become a clear focus of research. With this regard, MIGS may have a role to play in reducing the amount of inflammation caused by subconjunctival procedures.

Further risks common to all bleb-creating procedures include bleb dystesthesia, bleb leaks, blebitis, and bleb-related endophthalmitis. These complications can be common and some authors have reported rates of bleb interventions in excess of 50% after XEN implantations.[45] Hypotony is another inherent risk of having a low floor effect, but this risk can theoretically be mediated by the adjustment of devices' internal dimensions to create specific levels of outflow resistance.[46] Finally, contrary to traditional filtration surgery, prospective studies and occasional case reports have highlighted a risk of stent displacement and occlusion, which are inherent to the placement of an artificial stent.[47,48]

Ciliary Body: Reduction of Aqueous Humor Production

The ciliary body is site of aqueous production. Reducing aqueous humor production is a logical alternative to the increase of aqueous outflow to lower IOP. Cyclophotocoagulation consists of using a laser to selectively deliver thermal energy to the pigmented tissues of the ciliary body and induce tissue coagulative necrosis.[49] Historically, the technique that emerged in the 1930s as cyclodiathermy has long been exclusively indicated for refractory glaucoma and painful blind eyes. This was mostly due to the relatively high risk of intense and chronic postoperative inflammation, pain, hypotony, vision loss, and phthisis.[50,51] However, recent innovations have allowed for more targeted treatments and less collateral tissue necrosis, leading to reduced complication rates and better safety profiles. This has led to cyclophotocoagulation's gradual acceptance for the treatment of milder forms of glaucoma, and to some surgeons considering it a MIGS. The main theory underlying this change in practice is that the rates and severity of complications after cyclophotocoagulation are directly related to the total amount of energy used during the procedure.[52] However, despite a clear reduction in the rates of complications over the last decades, the risk of permanent visual loss to a sighted eye remains non-negligible,[53,54] and a recent Cochrane review concluded that there was still insufficient evidence to conclude positively on the effectiveness and safety of cyclophotocoagulation in nonrefractory glaucoma.[55]

Furthermore, it has been speculated that the significant perilimbal conjunctival inflammation and scarring produced by transscleral cyclophotocoagulation could affect the outcome of subsequent filtering surgeries, casting further doubt over the indications of this type of treatment as an initial procedure. Table 1 provides a summary of the studied techniques, and Figure 3 illustrates the percentage of IOP reduction reported in all analyzed studies.[56–110]

TABLE 1. Summary of Some MIGS Techniques by Anatomical Category, Detailing the Percentage of Intraocular Pressure and Medication Burden Reduction at the Final Timepoint of Each Analyzed Study, the Mean Reduction Weighted for the Subject Distribution for Each Technique, and the Most Commonly Reported Complications

Technique	Details of the Procedure	Reported Effect on Intraocular Pressure at Timepoints, mo (* Standalone)	Reported Effect on Antiglaucoma Medications (* Wash-Out)	Most Commonly Observed Complications	Ref.
Trabecular stents					
iStent	1.0 × 0.3 mm L-shaped stent inserted through the trabeculum into Schlemm canal	16 mo: 13.4%* 36 mo: 17.0% 12 mo: 9.7% 12 mo: 15.4% 6 mo: 16.4% 36 mo: 30.4%* 12 mo: 22.0% 15 mo: 17.9% 6 mo: 14.9% 12 mo: 13.8% 18 mo: 13.2% **WM: 15.3%**	31.6% 63.0% 65.0% 90.6% 47.4% 0.0%* 12.1% 80.0% 6.4% 64.2% 47.1% **WM: 38.0%**	27.0% Device obstructions 16.7% Device malposition 12.6% Intraocular pressure spikes 2.4%–18.9% Hyphema 0.8% Iridodialysis	56–66

TABLE 1. (Continued)

Technique	Details of the Procedure	Reported Effect on Intraocular Pressure at Timepoints, mo (* Standalone)	Reported Effect on Antiglaucoma Medications (* Wash-Out)	Most Commonly Observed Complications	Ref.
iStent inject	0.3 × 0.2 mm Straight stent inserted through the trabeculum into Schlemm canal Dual implantation	12 mo: 34.2% 12 mo: 21.0% 24 mo: 26.6% 36 mo: 42.0%* 18 mo: 11.6% 24 mo: 28.2% 36 mo: 37.0% 12 mo: 48.4%* 36 mo: 42.7%* 12 mo: 27.0% 12 mo: 27.3% **WM: 29.1%**	0.0% 32.9% 81.0% 82.0% 50.0% 0.0%* 68.0% 0.0%* - 66.7% 100.0% **WM: 34.0%**	45.7% Deep implantation 13.3% Device obstruction 6.0% Hyphema 1.0% Corneal oedema 1.0% Corneal abrasion	66–76
Trabecular dilatation					
Ab interno canaloplasty (iTrack)	Illuminated microcatheter used to cannulate Schlemm's canal and inject a viscoelastic device to dilate it	12 mo: 30.3% 12 mo: 41.0% 36 mo: 34.3% 12 mo: 34.8% **WM: 36.2%**	15.0% 89.0% 52.6% 60.7% **WM: 62.1%**	19.1% Cataract formation 2.8%–13% Hyphema 1.8% Intraocular pressure spikes	77–80
Hydrus Microstent	8.0 × 0.3 mm Crescent-shaped stent inserted as a scaffold into Schlemm canal	12 mo: 18.6%* 24 mo: 31.6% 24 mo: 25.0% 12 mo: 43.2%* 24 mo: 19.1% 24 mo: 37.5%* 24 mo: 80.0% **WM: 34.4%**	61.1% 82.4% 46.2% 60.0% 66.7% - 75.0%	12.2% Device obstruction	81–87
Trabeculotomy					
Gonioscopy-assisted transluminal trabeculotomy (GATT)	Trabeculotomy via an illuminated microcatheter or a suture used to cannulate Schlemm canal and tear through the trabeculum	6 mo: 6.2%* 24 mo: 38.6% 19 mo: 36.4% 24 mo: 55.0%* 6 mo: 67.3% 24 mo: 37.3% 12 mo: 44.0%* 24 mo: 40.1%* **WM: 36.5%**	58.3% 63.6% 64.7% 74.2% 77.1% 43.8% 61.3% 37.5% **WM: 56.1%**	28.0%-38.0% Hyphema 15.4% Intraocular pressure spikes	88–95
Trabectome	Trabeculotomy via electrocautery	18 mo: 23.0%* 12 mo: 24.8%* 24 mo: 9.2% 42 mo: 27.2%* 12 mo: 16.0% 60 mo: 22.0%* 12 mo: 25.9%* **WM: 24.0%**	34.7% 30.8% 46.1% 31.0% 75.5% 44.4% 16.7% **WM: 31.6%**	35.0%–48.4% Hyphema (including 4.9% of persistent hyphema after 2 mo) 27.4% Early intraocular pressure spikes	96–102
Kahook Dual Blade	Trabeculotomy via a beveled dual blade	6 mo: 14.4% 6 mo: 13.0%* 12 mo: 47.2% 12 mo: 27.5% 12 mo: 14.0% 12 mo: 26.2% 12 mo: 13.8% 6 mo: 23.7% **WM: 25.1%**	47.9% 44.5% 91.7% 71.0% 33.3% 50.0% 27.3% 64.7% **WM: 64.1%**	3.5%–30.8% Hyphema 3.8%–18.2% Intraocular pressure spikes 1.6%–3.8% Posterior capsule opacification	57,59,63,64,88,102–105
Suprachoroidal outflow					
CyPass Micro-Stent	6.35 × 510.0 mm Polyimide fenestrated micro-stent inserted into the suprachoroidal space—discontinued in 2018	24 mo: 30.2%	85.7%	Withdrawn due to concerns over endothelial cell density loss	106
iStent Supra	4.0 × 0.2 mm Titanium and polyethersulfone stent inserted into the suprachoroidal space	Not commercially available.			
Subconjunctival Outflow (bleb-forming procedures)					
XEN 45 gel stent	6.0 × 0.5 mm Gelatin stent inserted into the subconjunctival space from the anterior chamber	24 mo: 29.0% 12 mo: 40.0% 12 mo: 42.0% 12 mo: 42.0%* 24 mo: 43.2% **WM: 38.8%**	70.0% 74.7% 65.8% 76.7% 47.1% **WM: 59.9%**	21.3% Hypotony 11% Cataract progression 2.0%–4.3% Conjunctival erosion 2.1% Choroidal haemorrhage	45,89,107–109
PreserFlo (formerly known as InnFocus/ Arrow)	8.5 × 0.4 mm Stent inserted into the anterior chamber from the subconjunctival space—ab externo	24 mo: 50.0%	83.3%	13.0% Hypotony with shallow anterior chamber (including 8.7% of choroidal detachments)	110

MIGS indicates minimally invasive glaucoma surgeries; WM, weighted mean. Asterisks in the pressure reduction column indicate the effect was obtained from a standalone procedure, as opposed to combined surgeries. Asterisks in the medication reduction column indicate the null result is due to a preoperative medication wash-out.

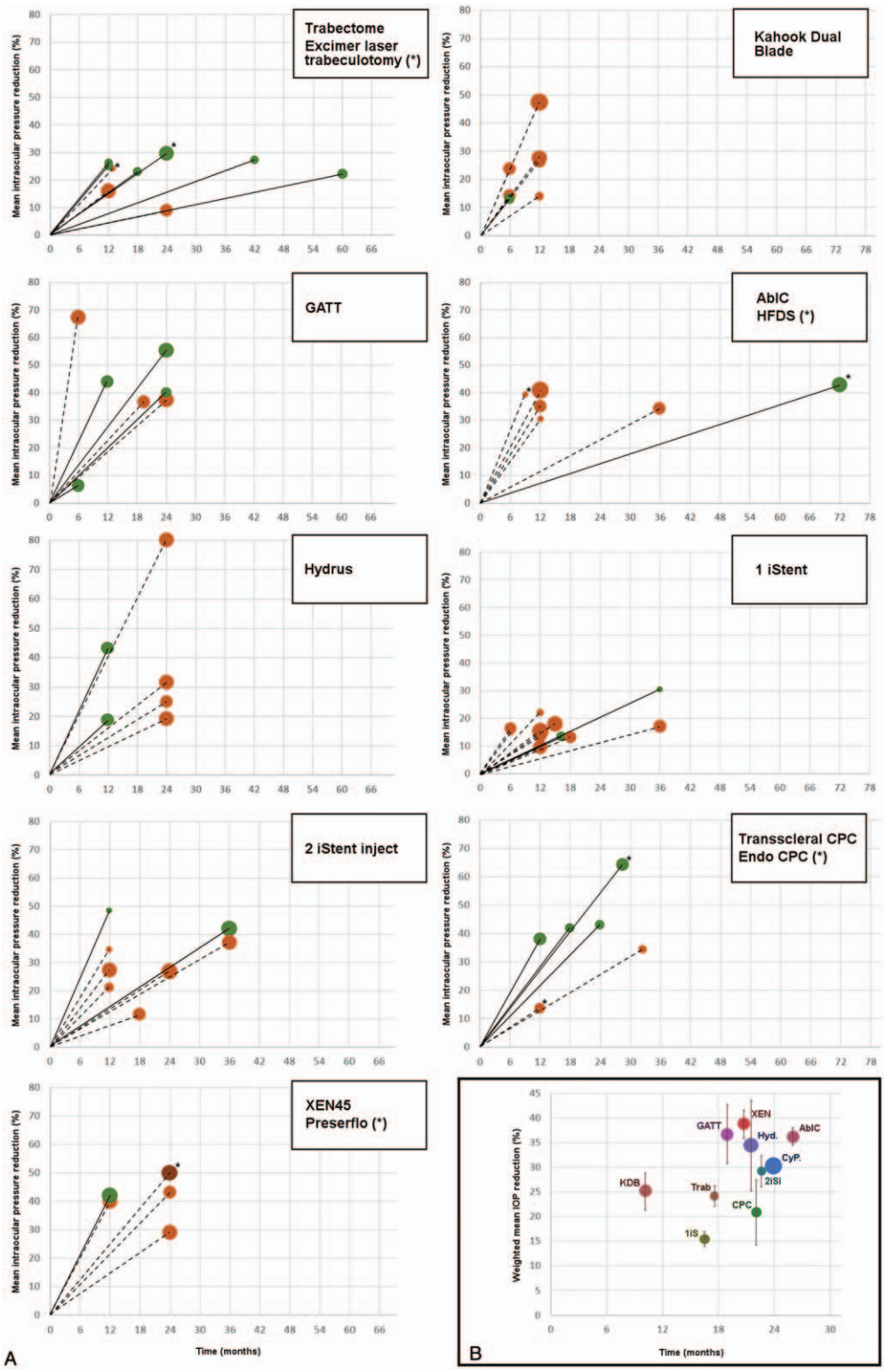

FIGURE 3. A, Percentage of intraocular pressure reduction reported at the final timepoint of each analyzed study. The size of the dots is proportional to the reduction in antiglaucoma medications. Solid lines represent studies of standalone procedures, whereas dotted lines represent studies of combined procedures. The asterisks mark alternative procedures. B, Weighted mean intraocular pressure reduction of all reported studies for each surgical technique. The vertical bars show the 95% confidence interval. 1iS indicates 1 iStent; 2iSi, 2 iStent inject; AbIC, ab interno canaloplasty; CPC, cyclophotocoagulation; CyP., CyPass; GATT, gonioscopy-assisted transluminal trabeculotomy; Hyd., hydrus; IOP, intraocular pressure; KDB, Kahook Dual Blade; Trab, trabeculotomy; XEN, XEN45 gel stent.

Comparative Studies

Of all the studies reviewed, 28 were comparative studies, among which there were 12 RCTs. Figure 4 shows a comparison of the techniques assessed in all considered comparative studies.

DISCUSSION AND OPINION

The traditional landscape of glaucoma management has changed dramatically over the last decade, with the development of a large array of novel surgical techniques. Although a surge in

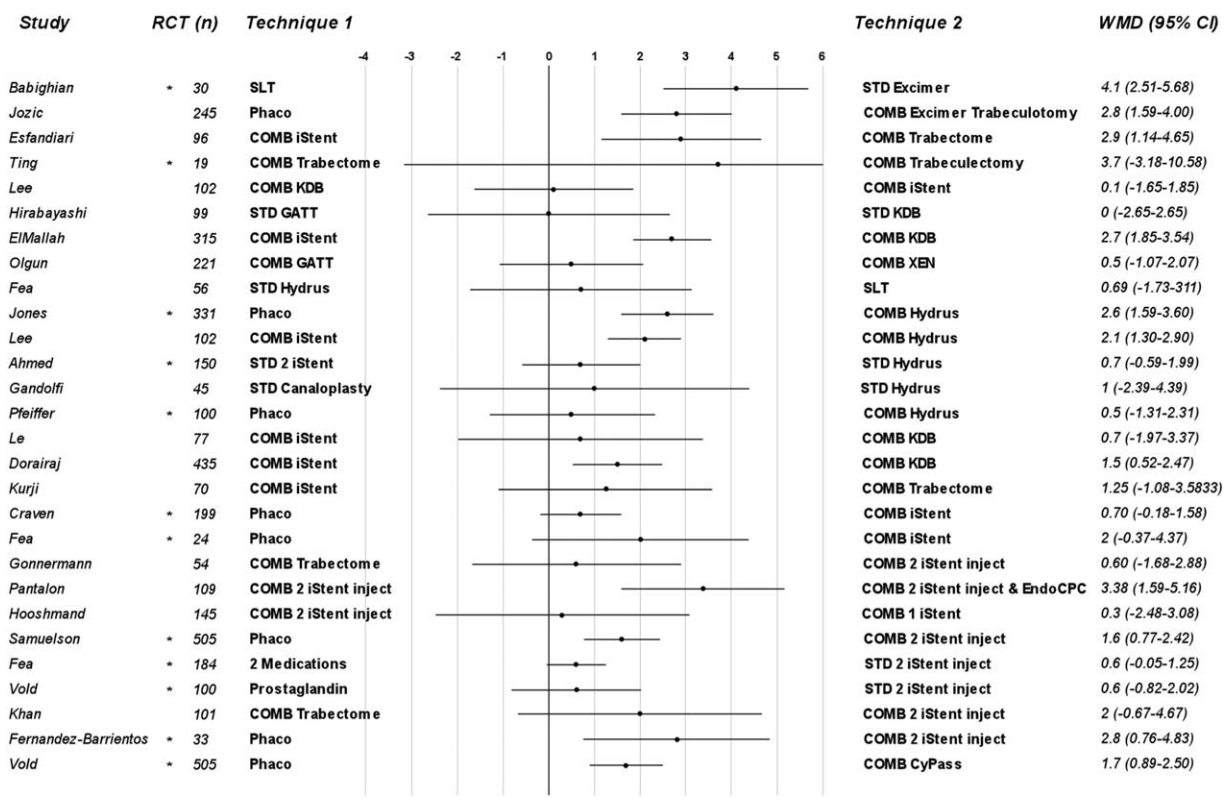

FIGURE 4. Forest plot for WMD in intraocular pressure reduction. The asterisk indicates RCT and (n) is the total number of subjects enrolled in each study. CI indicates confidence interval; COMB, combined; GATT, gonioscopy-assisted transluminal trabeculotomy; KDB, kahook dual blade; RCT, randomized controlled trial; STD, standalone; WMD, weighted mean difference.

attention, investment, and innovation and, eventually, treatment options foretells a bright future for the sub-specialty, at a clinical level, it rises the questions of patient-centered treatment choices and evidence-based decisions. Indeed, one of the advantages of such a heterogenous range of surgical options is the chance to tailor therapy in an individualized manner. High-quality data are required to make this choice more than an educated guess. Figure 5 illustrates the advantages and inconvenience of surgical

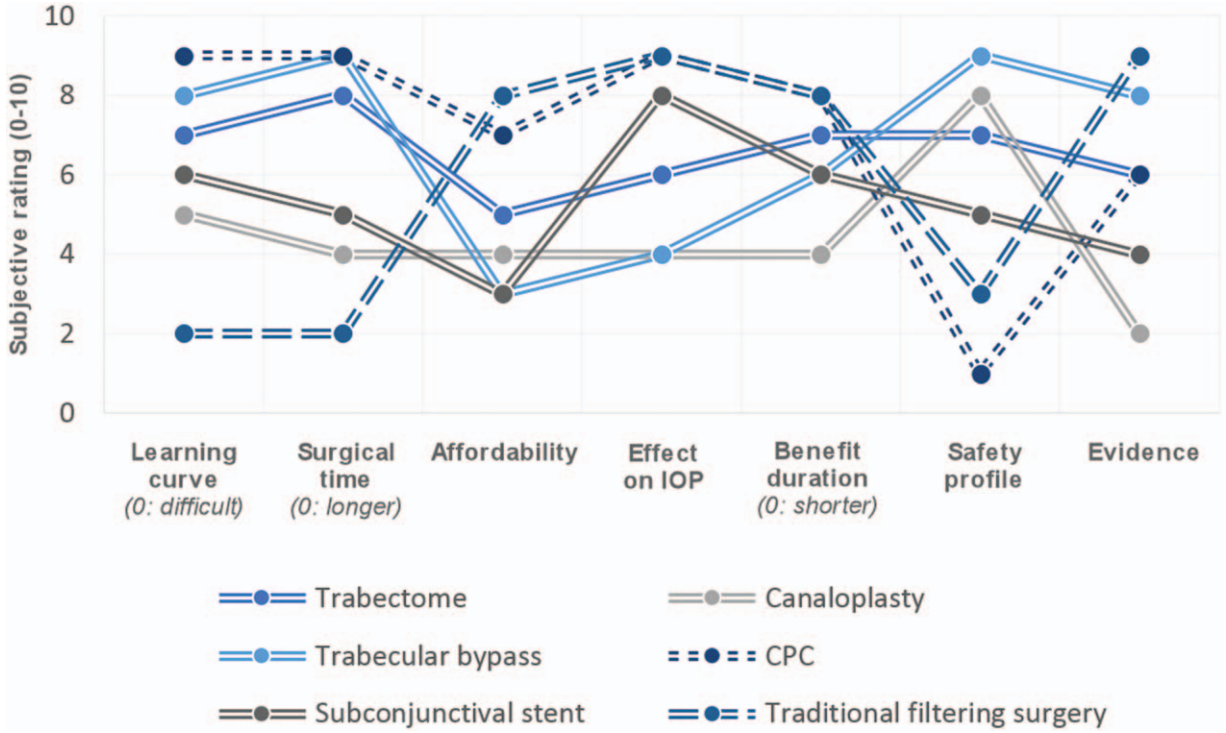

FIGURE 5. This graph shows the value curves of various surgical approaches to glaucoma management based on the authors' subjective assessment. It illustrates how benefit profiles of different surgical techniques vary widely. CPC, cyclophotocoagulation; IOP, intraocular pressure.

techniques, as perceived by the authors. This illustrates the diversity of benefit profiles and the subjectivity of some assessments in absence of research data.

To provide some objective criteria in the assessment of glaucoma surgery, and to guide innovation, the "10-10-10 Goal" was set. According to these criteria, the ideal surgical technique would take <10 minutes to perform, be able to consistently achieve IOPs <10 mm Hg, and be efficient for >10 years, without any significant complications. These objectives were originally set with the aim of achieving them by 2020. So, are we anywhere near achieving these goals?

With procedures typically taking between 15 and 30 minutes to perform, MIGS have managed to significantly reduce surgical times. Although this represents a 50% reduction from most traditional filtering procedure or glaucoma drainage device implantations, MIGS are yet to provide us with a simple-enough procedure to be consistently carried out in <10 minutes by the average glaucoma surgeon. In terms of IOP reduction potential, considering that the average candidate for MIGS surgery has a preoperative IOP in the 20- to 25-mm Hg range, it would require a 50% to 60% reduction to achieve postoperative pressures under the 10 mm Hg threshold. In the examined studies, only rarely did some MIGS provide IOP reduction of ≥50%. Furthermore, the few incidences of IOP reductions >50% could not be replicated, and—aside from the PreserFlo that was only represented in a single study—the same surgical techniques showed more modest effects in alternative studies. It does, however, appear that of all the results assessed, the subconjunctival approach is more likely than other categories of MIGS to achieve IOPs in the low-teens. But in this context of intense innovation, new technologies will likely appear and reshuffle the cards in the years to come, including new devices offering variations on existing techniques, or all-new approaches such as drug-coated devices or ocular surface shunts. Finally, it is at present difficult to assess the sustainability of MIGS efficiencies. Since most MIGS have been commercially available for <5 years, there is a general lack of long-term data in the field, but knowledge is slowly accruing. This aim of longevity, however, should prompt us to design sound clinical trials early on, to obtain not only extensive, but also reliable long-term data.

Overall, the results of this review confirm the efficiency of all assessed MIGS compared with standalone phacoemulsification, with a decrease in IOP and medication burden in the vast majority of cases. The reported rates of complications also compare favorably with traditional filtering surgeries. But to be clinically advisable, a procedure needs not only be safe, but also to prove its noninferiority to commonly accepted alternatives. However, this analysis shows that there are only few studies comparing different MIGS techniques, especially considering the vast and growing number of procedures available nowadays, and even fewer assessing MIGS against topical medications. More comparative data, especially with criterion standard therapies and common practice options, could be extremely relevant for ophthalmologists and health care authorities, allowing to ascertain the best therapeutic option for the patients, and potentially reducing the medication burden and its associated costs. But considerably more evidence will be needed to achieve this level of certainty. Indeed, current evidence, although non-negligible, is still mostly limited to nonrandomized studies and uncontrolled retrospective comparisons, with few quality RCTs. This leads to significant variability in studies' results and a blurring of the outcomes, and further highlights the need for carefully designed RCTs.

The present review considered the IOP reduction potential rather than each individually reported success rates, due to the great heterogeneity of the criteria used in determining the latter, and to the fact that pressure reduction was one of the only results to be consistently reported in most studies. However, we recognize that this does not constitute an ideal comparison criterion either, and oversimplifies the question of surgical outcome. Therefore, we suggest that future research should be standardized to systematically report key outcome features, comparative including alternative treatments that are relevant and include a criterion standard therapy, long term to assess the sustainability of treatment options and the rates of late complications, and ideally randomized. When possible, washed-out IOPs should be reported to permit meaningful comparison, and long-term definitions of success should include functional and structural markers of glaucoma progression. Finally, and perhaps most challengingly, cohorts should be large enough to ensure that statistical tests will have adequate power and to allow identification of individual biomarkers to help achieve truly individualized therapy.

Eventually, all these data will provide clinicians with the necessary knowledge to make evidence-based decisions and decide on the best treatment option for each individual glaucoma patient.

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