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Minimally Invasive Glaucoma Surgery: A Critical Appraisal of the Literature

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Abstract

Micro- or minimally invasive glaucoma surgeries (MIGS) have been the latest addition to the glaucoma surgical treatment paradigm. This term refers not to a single surgery, but rather to a group of distinct procedures and devices that aim to decrease intraocular pressure. Broadly, MIGS can be categorized into surgeries that increase the trabecular outflow [Trabectome, iStent (first and second generations), Hydrus microstent, Kahook Dual Blade and gonioscopy-assisted transluminal trabeculotomy], surgeries that increase suprachoroidal outflow (Cypass microstent and iStent Supra), and conjunctival bleb-forming procedures (Xen gel stent and InnFocus microshunt). Compared to traditional glaucoma surgeries, such as trabeculectomy and glaucoma drainage device implantation (Ahmed, Baerveldt, and Molteno valves), MIGS are touted to have less severe complications and shorter surgical time. MIGS represent an evolving field, and the efficacy and complications of each procedure should be considered independently, giving more importance to high-quality and longer-term studies.

1. INTRODUCTION

1.1. Minimally Invasive Glaucoma Surgery Terminology

The previous two decades in the field of glaucoma surgery have seen the introduction of micro- or minimally invasive glaucoma surgeries (MIGS) (Lavia et al. 2017, SooHoo et al. 2014). Given the limited traditional surgical options for glaucoma management, such as trabeculectomy and implantation of glaucoma drainage devices such as the Ahmed, Baerveldt and Molteno implants, MIGS have expanded the armamentarium of options for glaucoma surgeons (Conlon et al. 2017).

The US Food and Drug Administration (FDA) and American Glaucoma Society jointly defined MIGS as procedures and devices that lower intraocular pressure (IOP) by increasing the aqueous humor outflow via an ab interno or ab externo approach, with limited or no dissection of the sclera and minimal or no manipulation of the conjunctiva (Ahmed 2015, Caprioli et al. 2015, Malvankar-Mehta et al. 2015). Other definitions of MIGS include only conjunctiva-sparing ab interno procedures and devices (Bloom & Au 2018, SooHoo et al. 2014).

As of September 2019, six MIGS have been approved for use by the US FDA. The CyPass suprachoroidal microstent was voluntarily withdrawn from the market in August 2018 over concerns of corneal endothelial damage at five years (U.S. Food Drug Admin. 2018).

1.2. Advantages and Limitations

The advantages and limitations of MIGS are usually stated in comparison to traditional glaucoma surgeries, namely trabeculectomy and glaucoma drainage devices. The advantages and limitations also determine the relative position of MIGS in the glaucoma treatment paradigm.

Glaucoma is usually initially managed with pharmacotherapy and laser therapy (Conlon et al. 2017). These modalities are associated with less risk than traditional glaucoma surgeries. Traditional glaucoma surgeries are associated with potentially vision-threatening intra- and postoperative risks, such as hypotony, infection, suprachoroidal hemorrhage, cataract formation, and need for more surgeries (Vijaya et al. 2011). The Primary Tube Versus Trabeculectomy study reported postoperative complications in 29% and 41% of patients in the tube and trabeculectomy groups, respectively, after one year of follow-up. Serious complications at one year of follow-up that resulted in loss of two or more Snellen lines or repeat surgery were reported in 1% and 7% of patients, respectively (Gedde et al. 2018). In terms of the risk of complications, MIGS may be placed between pharmacotherapy and laser therapy, which are associated with lower risks, and traditional glaucoma surgeries, which are associated with higher risks (Conlon et al. 2017).

Compared to traditional glaucoma surgeries, MIGS may have a better safety profile and more rapid recovery. They are usually indicated for treating mild to moderate glaucoma, as the IOP-lowering effect of MIGS is inferior to that of traditional glaucoma surgeries (Bloom & Au 2018, Lavia et al. 2017, SooHoo et al. 2014).

1.3. Literature Search Details

A literature search was performed using the following keywords on PubMed to identify MIGS studies in English: *Trabectome*, *iStent*, *i-stent*, *I stent*, *hydrus*, *trabecular stent*, *gonioscopy assisted transluminal trabeculotomy*, *kahook dual blade*, *dual blade*, *cypass*, *suprachoroidal shunt*, *suprachoroidal stent*, *xen*, *gel stent*, *Innfocus*, *poly(styrene-block-isobutylene-block-styrene)*. The references of identified MIGS

studies were also searched to identify other eligible studies published from January 1, 2000, to September 1, 2019. Conference abstracts were not considered.

1.4. Clinically Meaningful Intraocular Pressure Reduction and Evidence-Based Practice in Glaucoma

Reduction in IOP as a glaucoma endpoint should be assessed as a combination of a percentage reduction and an absolute upper limit (Shaarawy et al. 2009). For example, IOP reductions from 50 to 40 mm Hg and from 40 to 32 mm Hg both constitute 20% reductions; however, such reductions are not clinically meaningful. An upper IOP limit of 21 or 18 mm Hg used in combination with the percentage reduction resolves this problem (Kass et al. 2002, Mathew et al. 2019). The percentage reduction and upper IOP limit to be used depend on the severity of glaucoma and baseline IOP. However, an upper limit of 21 mm Hg cannot be used for all glaucoma patients (Eur. Glaucoma Soc. 2017). The upper IOP limit varies with the severity of glaucoma and the guidelines being followed. For example, the Canadian Ophthalmological Society recommends 20, 17, and 14 mm Hg as the upper limits for early, moderate, and advanced glaucoma cases, respectively. A patient with early glaucoma, who progresses at 20 mm Hg, should have a further 20% IOP reduction to 16 mm Hg (Damji et al. 2003).

Similarly, surgical success should be defined using a combination of percentage IOP reduction and an upper IOP limit. In addition, surgical success should also be described in terms of complete and qualified success. Complete success is defined as achieving the desired IOP reduction without the use of additional ocular hypotensive medications, and qualified success is defined as achieving the desired IOP reduction with additional ocular hypotensive medication. In this context, the number of ocular hypotensive classes used before and after the surgical procedure should also be mentioned (Shaarawy et al. 2009).

Incorporating evidence-based practice in the management of glaucoma patients involves not only the evaluation of evidence and its quality, but also the combination of critical appraisal of evidence with patient's preferences and values via shared decision making (Djulbegovic & Guyatt 2017). The traditional hierarchy of evidence recognizes randomized controlled trials (RCTs) as the highest level of evidence, followed by cohort studies, case-control studies, case series, case reports, animal research, in vitro research, and expert experience, in that order (Guyatt et al. 1995). However, over the years, the potential for biases in RCTs has been recognized (Kaptchuk 2001). To further assess the quality of evidence, many systems have been proposed. According to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, a large effect size, evidence of a dose–response gradient, and lack of confounders add to the quality of the study. The study quality is lowered by study limitations, inconsistency, indirectness (lack of applicability), and publication bias (Atkins et al. 2004). In the context of glaucoma surgical trials, the World Glaucoma Association (WGA) has published guidelines for conducting clinical trials with recommendations regarding methodology, definition of success, ethical considerations, reporting of postoperative complications, economic evaluation, and statistical analysis (Shaarawy et al. 2009).

Glaucoma is a chronic neurodegenerative disease, and treatment modalities for glaucoma should be subjected to long-term studies to ascertain safety and efficacy before being adopted widely. Exercising caution in the interest of patient well-being when there is a lack of long-term evidence of safety is in keeping with the principles of evidence-based medicine (Sackett et al. 1996). However, the practice of medicine should be based on the best available evidence. The totality of evidence should be evaluated, not just evidence that supports a particular claim (Djulbegovic et al. 2009). Finally, clinical decision making should take into consideration the patient's values and preferences (Djulbegovic & Guyatt 2017).

2. MINIMALLY INVASIVE GLAUCOMA SURGERY DEVICES AND PROCEDURES

The United States FDA approved ab interno trabeculectomy for the treatment of open-angle glaucoma using Trabectome (Neomedix Corporation, Tustin, CA) in April 2004, and it was first used in the United States in January 2006 (Minckler et al. 2008). The first-generation iStent (Glaukos, Laguna Hills, CA) was approved for use in Europe in June 2004 and as an investigational device by the FDA in June 2012 (Wellik & Dale 2015). The Kahook Dual Blade (KDB) (New World Medical, Rancho Cucamonga, CA) was registered with the FDA in 2015. The Xen gel stent (Allergan, Dublin, Ireland), iStent inject (Glaukos, Laguna Hills, CA) and Cypass (Alcon, Fort Worth, TX) were approved by the FDA in 2016. The latest FDA approval in 2018 was for Hydrus (Ivantis, Inc., Irvine, CA). The Cypass suprachoroidal stent was withdrawn from the market in September 2018 due to significant corneal endothelial loss after evaluating the five-year data (Reiss et al. 2019, U.S. Food Drug Admin. 2018). Other MIGS devices, such as the iStent Supra (Glaukos, Laguna Hills, CA) and the PreserFlo, formerly known as InnFocus, microshunt (Santen Pharmaceutical Company, Ltd., Osaka, Japan), have not yet received FDA approval. The MIGS devices and procedures considered in this review are listed in **Table 1**.

3. REVIEW OF CLINICAL STUDIES

The efficacy of various MIGS in terms of IOP and medication reduction, changes in visual acuity and visual field, and specific limitations of prospective MIGS studies considered are listed in **Table 2**.

3.1. Trabectome

Trabectome was invented by George Baerveldt and Roy Chuck, and a joint patent was filed in 2002 (Baerveldt & Chuck 2005). The device was approved by the FDA in 2004. This device consists of a bipolar 550 kHz electrode, which is used to ablate the trabecular meshwork. The footplate minimizes thermal impact on the surrounding tissues and acts as a guide for the electrosurgical tip during ablation. Continuous infusion and aspiration allow for removal of debris and further decreases the risk of thermal injury to adjacent structures (Kaplowitz et al. 2014; Minckler et al. 2006, 2008). Under a gonioscopic view, the trabecular meshwork is ablated over approximately 180° (Kaplowitz et al. 2014). Although it was initially used in primary open-angle glaucoma, it has also been used in pseudoexfoliation (Tojo et al. 2017), pigmentary (Akil et al. 2016), steroid-induced (Dang et al. 2016), inflammatory (Kaplowitz & Loewen 2015), and angle-closure glaucoma (Bussel et al. 2015a); in cases of failed trabeculectomy (Bussel et al. 2015b); in cases of failed glaucoma drainage device implantation (Mosaed et al. 2015); and in combination with a Baerveldt glaucoma implant (H. Esfandiari, K. Hassanpour, P. Knowlton, T. Shazly, M. Yaseri & N. Loewen, unpublished manuscript). Low preoperative IOP and younger age are associated with worse outcomes (Jea et al. 2012). Trabectome surgery has been found to reduce nocturnal IOP peaks, thus decreasing diurnal IOP fluctuation (Tojo et al. 2017).

The most common complication occurring in almost all cases is reflux of blood from the collector channels. However, the resulting hyphema usually resolves without surgical intervention (Francis et al. 2008; Kaplowitz & Loewen 2015; Minckler et al. 2005, 2006). Postoperative IOP spikes that exceed 10 mm Hg have been reported in up to 10% of cases (Francis & Winarko 2012, Ting et al. 2012). Peripheral anterior synechiae may form in up to 14% of patients, more commonly in younger individuals (Minckler et al. 2006). Compared to traditional trabeculectomy, Trabectome results in significantly fewer instances of loss of more than two Snellen lines of visual acuity (10% versus 1%, respectively) (Kinoshita-Nakano et al. 2018).

Table 1 MIGS procedures and classifications

MIGS device or procedure (based on route of outflow)	Manufacturer	Approach	Mechanism of action	Material	Equipment	Size	Year of FDA approval
Trabecular							
Trabectome	NeoMedix Corporation, Tustin, CA	Ab interno	Trabecular meshwork electroablated, continuous irrigation, and aspiration to remove debris	Not an implant	Sterile single-use handpiece that administers bipolar electrosurgical pulse with simultaneous irrigation and aspiration	19.5-gauge handpiece	2004; tip design updated in 2012
iStent	Glaukos, Inc., Laguna Hills, CA	Ab interno	Inserted into the Schlemm's canal after penetrating the trabecular meshwork	Heparin-coated nonferromagnetic titanium	Preloaded injector with one device	1 mm long, 0.3 mm high	2012
iStent inject	Glaukos, Inc., Laguna Hills, CA	Ab interno	Inserted into the Schlemm's canal after penetrating the trabecular meshwork	Heparin-coated nonferromagnetic titanium	Preloaded injector with two devices	360 μm long, diameter 230 μm	2016
Hydrus	Ivantis, Inc., Irvine, CA	Ab interno	Inserted into the Schlemm's canal, acts like a scaffold, maintaining the canal patency	Nickel-titanium alloy (nitinol)	Preloaded injector	8 mm long	2018
GATT	Ellex, Fremont, CA (iTrack microcatheter)	Ab interno	360° or 180° trabeculotomy performed after passing a suture or microcatheter ab interno through a 1–2-mm goniotomy	Not an implant	5–0 or 6–0 blunted Prolene or Nylon suture, illuminated microcatheter (iTrack, Ellex)	Microcatheter has a 200-μm diameter shaft	NA

(*Continued*)

Table 1 (*Continued*)

MIGS device or procedure (based on route of outflow)	Manufacturer	Approach	Mechanism of action	Material	Equipment	Size	Year of FDA approval
Kahook Dual Blade	New World Medical, Rancho Cucamonga, CA	Ab interno	Trabecular meshwork strip excised along 3–5 clock hours	Not an implant	Single-use stainless steel blade with a sharp tip for trabecular meshwork penetration, ramp and dual blades for excising a strip of meshwork tissue	NA	FDA registered in 2015
Suprachoroidal							
Cypass	Alcon, Inc., Fort Worth, TX	Ab interno	Stent placed in the suprachoroidal space via controlled cyclodialysis	Polyimide	Guidewire used to place the stent in the supra-choroidal space	6.35 mm long, outer diameter 510 μm	2016; withdrawn 2018
iStent Supra	Glaukos, Inc., Laguna Hills, CA	Ab interno	Suprachoroidal stent	Polyethersulfone and titanium	Ab interno insertion between anterior chamber and supra-choroidal space	4 mm long, diameter 0.16 mm	Approval pending

(*Continued*)

Table 1 (*Continued*)

MIGS device or procedure (based on route of outflow)	Manufacturer	Approach	Mechanism of action	Material	Equipment	Size	Year of FDA approval
Subconjunctival							
Xen	Allergan, Inc., Dublin, Ireland	Ab interno or externo	Stent drains aqueous humor from the anterior chamber to the subconjunctival space	Collagen-derived porcine gelatin cross-linked with glutaraldehyde	Preloaded injector	6 mm long, lumen 45 μm	2016
PreserFlo, formerly known as InnFocus	Santen Pharmaceutical Company, Ltd., Osaka, Japan	Ab externo	Larger stent inserted ab externo, drains aqueous humor from the anterior chamber to the subconjunctival space	Poly(styrene-block-isobutylene-block-styrene)	Manual ab externo placement through a scleral needle track into the anterior chamber, connecting it to the sub-Tenon's space	Flexible microshunt, 8.5 mm × 0.350 mm, lumen 70 μm	Approval pending

Abbreviations: FDA, US Food and Drug Administration; GATT, gonioscopy-assisted transluminal trabeculotomy; MIGS, minimally invasive glaucoma surgery; NA, not applicable.

Table 2 Efficacy of MIGS procedures and devices

Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Trabectome											
Minckler et al. (2005)	Prospective case series	Trabectome	37	Up to 13	28.2 ± 4.4 mm Hg (washout, $n = 37$), 17.4 ± 3.5 mm Hg (6 months, $n = 25$), 16.3 ± 2.0 mm Hg (12 months, $n = 15$)	1.2 ± 0.6, 0.4 ± 0.6 (6 months)	Returned to within two lines of preoperative visual acuity within 3 weeks, except for one patient who suffered a blunt trauma	NR	NR	NR	59% had hyphema on day 1, cleared by day 6.4 ± 4.1
Minckler et al. (2006)	Prospective case series	Trabectome	101	30	27.6 ± 7.2 mm Hg ($n = 101$), 16.4 ± 2.2 (12 months, $n = 37$), 16.3 ± 3.3 (30 months, $n = 11$)	NR	NR	NR	NR	NR	Significant dropout Success, defined as IOP ≤ 21 mm Hg with medications and no subsequent surgery, was 84%
Francis et al. (2008)	Prospective case series	Phaco+ Trabectome	304	21	20.0 ± 6.3, 15.5 ± 2.9 (1 year, $n = 34$), 16.7 ± 3.5 (21 months, $n = 7$)	2.65 ± 1.13, 1.44 ± 1.29 (1 year), 1.43 ± 1.28 (21 months)	No patient lost two or more Snellen lines	NR	NR	NR	Significant dropout
Ting et al. (2018)	Prospective cohort	Trabectome in POAG versus Phaco+ Trabectome in POAG versus Trabectome in PXFG versus Phaco+ Trabectome in PXFG	POAG and Trabectome, 450 POAG and Phaco+ Trabectome, 263 PXFG and Trabectome, 67 PXFG and Phaco+ Trabectome, 45	12	25.5 ± 7.9, 16.8 ± 3.9 versus 19.9 ± 5.4, 15.6 ± 3.2 versus 29.0 ± 7.5, 16.1 ± 4.0 versus 21.7 ± 8.4, 14.2 ± 3.1	2.73 ± 1.33, 2.16 ± 1.29 versus 2.40 ± 1.08, 1.65 ± 1.26 versus 3.09 ± 1.15, 2.21 ± 1.38 versus 2.53 ± 0.99, 1.57 ± 1.33	No cases of loss of more than two Snellen lines	NR	NR	NR	Selection bias, large difference in sample sizes of different groups

(*Continued*)

Table 2 (*Continued*)

Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Maeda et al. (2013)	Prospective case series	Trabectome	80	Up to 23	26.6 ± 8.1, 17.9 ± 6.1 (12 months, $n = 27$)	4.0 ± 1.4, 2.3 ± 1.2 (12 months, $n = 27$)	No statistically significant decrease in visual acuity	NR	NR	NR	Significant dropout, three surgeons
Jordan et al. (2013)	Prospective observational study	POAG versus PXFG	POAG, 261 PXFG, 173	204 ± 238 days versus 200 ± 278 days	24 ± 5.5, 18 ± 6.1 versus 25 ± 5.9, 18 ± 8.2	2.1 ± 1.3, 1.2 ± 1.1 versus 2.0 ± 1.2, 1.1 ± 1.1	NR	NR	NR	NR	Trabectome and Phaco+ Trabectome mostly analyzed together
Bussel et al. (2015a,b)	Prospective cohort of failed trabeculectomy patients	Trabectome versus Phaco+ Trabectome	Trabectome, 58 Phaco+ Trabectome, 15	12	23.7 ± 5.5, 16.2 ± 3.9 versus 20.0 ± 5.9, 15.6 ± 5.1	2.8 ± 1.2, 2.0 ± 1.3 versus 2.5 ± 1.5, 1.6 ± 1.4	0.39 ± 0.49, 0.48 ± 0.71 versus 0.51 ± 0.28, 0.14 ± 0.13	NR	NR	NR	Failed trabeculectomy patients, selection bias toward worse outcomes
Mosaed et al. (2015)	Cohort of patients with failed tube shunt	Trabectome	20	12	23.7 ± 6.4, 15.5 ± 3.2 (1 year, $n = 12$)	3.2 ± 1.5, 2.4 ± 1.5 (1 year, $n = 12$)	NR	NR	NR	NR	Cohort of failed tube shunt patients
Mizoguchi et al. (2015)	Prospective case-control	POAG versus PXFG	POAG, 43 PXFG, 39	24	23.5 ± 7.2, 14.1 ± 2.2 (2 years, $n = 8$) versus 21.7 ± 6.2, 13.9 ± 4.7 (2 years, $n = 14$)	2.8 ± 0.8, 1.8 ± 1.0 (2 years, $n = 8$) versus 2.7 ± 0.8, 2.9 ± 0.7 (2 years, $n = 14$)	One patient in the POAG group had more than two lines of Snellen visual acuity loss	NR	NR	NR	Selection bias Difference in surgical technique of two surgeons
Yildirim et al. (2016)	Prospective single-arm	Trabectome	70	18	28.77 ± 5.34, 17.62 ± 2.81	3.3 ± 1.01, 1.7 ± 1.16	No significant change in visual acuity	NR	NR	NR	8.5% had prior trabeculectomy, 40% were pseudophakic
Lee et al. (2016)	Prospective case series	Trabectome	19	6	24.4 ± 4.4, 15.9 ± 5.1	3.9 ± 0.8, 2.8 ± 1.6	0.8 ± 0.6 logMAR, 0.8 ± 0.6 logMAR	NR	NR	NR	Small sample size

(*Continued*)

Table 2 (*Continued*)

Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Hashemian et al. (2017)	Prospective case series	Phaco+ Trabectome	27	12	18.25 ± 3.28, 13.50 ± 2.53 (12 months, $n = 19$)	2.52 ± 0.60, 1.40 ± 0.53 (12 months, $n = 19$)	0.68 ± 0.26, 0.11 ± 0.12 (12 months, $n = 19$)	NR	NR	NR	Small sample size, dropout
Akil et al. (2017)	Prospective nonrandomized	Phaco+ Trabectome versus Trabectome	Phaco+ Trabectome, 21 Trabectome, 28	12	33.0 ± 4.9, 16.6 ± 4.8 versus 37.6 ± 6.6, 14.3 ± 5.6	2.7 ± 1.1, 1.8 ± 1.5 versus 3.4 ± 1.3, 1.8 ± 1.3	NR	NR	NR	NR	Nonrandomized
Tojo et al. (2017)	Prospective open label	Trabectome versus Phaco+ Trabectome	Trabectome, 12 Phaco+ Trabectome, 12	3	23.5 ± 6.5, 14.6 ± 2.8 versus 22.5 ± 3.0, 11.5 ± 2.9	Postoperative values not reported	NR	NR	NR	NR	Short-term study aimed to evaluate IOP fluctuation
Kinoshita-Nakano et al. (2018)	Prospective and retrospective cohort	Trabectome versus Trabeculectomy	Trabectome, 68 Trabeculectomy, 59	36	22.6 ± 7.4, 15.7 ± 5.5 (3 years, $n = 27$) versus 24.3 ± 6.6, 15.2 ± 3.8 (3 years, $n = 34$)	3.5 ± 1.0, 3.1 ± 1.5 (3 years, $n = 27$) versus 3.3 ± 0.8, 2.5 ± 1.3 (3 years, $n = 34$)	NR	NR	NR	NR	Partially prospective, nonrandomized
Ting et al. (2018)	Randomized controlled trial	Phaco+ Trabectome versus Phaco+ Trabeculectomy	Phaco+ Trabectome, 10 Phaco+ Trabeculectomy, 9	12	20.0 ± 5.3, 16.8 ± 2.7 versus 23.1 ± 6.4, 17.1 ± 5.0	1.8 ± 1.3, 0.78 ± 1.39 versus 1.4 ± 1.1, 0.38 ± 0.74	NR	NR	NR	NR	Desired sample size not achieved
Arora et al. (2018)	Prospective cohort	No prior incisional surgery versus Prior incisional surgery	No prior incisional surgery, 40 Prior incisional surgery, 20	12	27.4 ± 8.1, 16.8 ± 4.3 versus 27.1 ± 6.4, 18.3 ± 2.3	3.1 ± 1.3, 2.7 ± 1.3 versus 4.10 ± 1.2, 2.7 ± 1.7	NR	NR	NR	NR	Juvenile open-angle glaucoma eyes
Nazarali & Damji (2018)	Prospective, case-control study	African American versus Caucasian	African American, 82 Caucasian, 82	12	21.2 ± 6.8, 16.1 ± 4.1 versus 21.2 ± 6.8, 15.7 ± 4.2	2.4 ± 1.3, 2.0 ± 1.4 versus 2.4 ± 1.2, 1.7 ± 1.3	NR	NR	NR	NR	No significant difference between the groups

(*Continued*)

Table 2 (*Continued*)

Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Ahmed et al. (2018)	Prospective outcome analysis	Mild versus Moderate to severe	Mild, 1,127 Moderate to severe, 1,071	12	24.0 ± 7.9, 16.1 ± 4.0 versus 22.6 ± 7.4, 15.7 ± 4.0	2.6 ± 1.4, 1.9 ± 1.4 versus 2.8 ± 1.2, 2.1 ± 1.4	NR	NR	NR	NR	Trabectome effective in moderate to severe and mild glaucoma
iStent											
Spiegel et al. (2008)	Prospective nonrandomized, uncontrolled, multicenter	iStent	47	6	21.5 ± 3.7, 15.8 ± 3.0	1.5 ± 0.7, 0.5 ± 0.8	No patient lost more than one Snellen line	NR	NR	NR	Short duration, low dropout rate
Spiegel et al. (2009)	Prospective nonrandomized, uncontrolled, multicenter	iStent	42	12	21.7 ± 3.98, 17.4 ± 2.99	1.6 ± 0.8, 0.4 ± 0.62	No patient lost more than one Snellen line	NR	NR	NR	Stent lumen obstruction in 7/42 eyes, stent malposition in 6/42 eyes
Vandewalle et al. (2009)	Prospective case series	iStent	10	12	19.6, 15.8	2.7, 1.7	No significant decrease in vision	NR	NR	NR	Small sample size
Fea (2010)	Prospective double-masked randomized clinical trial	Phaco+iStent versus Phaco	Phaco+iStent, 12 Phaco, 24	15	17.9 ± 2.6, 14.8 ± 1.2 versus 17.3 ± 3.0, 15.7 ± 1.1	2.0 ± 0.9, 0.4 ± 0.7 versus 1.9 ± 0.7, 1.3 ± 1.0	NR	NR	NR	NR	Small sample size
Fernández-Barrientos et al. (2010)	Prospective, randomized, clinical study	Phaco+two iStents versus Phaco	Phaco+two iStents, 17 Phaco, 16	12	24.2 ± 1.8, 17.6 ± 2.8 versus 23.6 ± 1.5, 19.8 ± 2.3	1.1 ± 0.5, 0 versus 1.2 ± 0.7, 0.7 ± 1.0	NR	NR	NR	NR	18% of the implanted stents were malpositioned

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Table 2 (*Continued*)

Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Samuelson et al. (2011)	Prospective, randomized, open-label, controlled, multicenter clinical trial	Phaco+iStent versus Phaco	Phaco+iStent, 117 Phaco, 123	12	18.7 ± 3.3 versus 18.0 ± 3.0 Postoperative IOP values not reported IOP reduction from unmedicated baseline: 8.4 ± 3.6 versus 8.5 ± 4.3	1.5 ± 0.7, 0.2 ± 0.6 versus 1.5 ± 0.6, 0.4 ± 0.7	Improvement in BCVA in 97% of treatment group and 95% of control group	Only preoperative MD reported: −3.75 ± 3.03 versus −3.74 ± 3.86,	NR	NR	Open label Only preoperative washout IOPs
Ahmed et al. (2014)	Prospective nonrandomized	Phaco+two iStents	39	18	25.3 ± 1.8, 17.1 ± 2.2 (washout IOPs, baseline and 13 month) 22.2 ± 2.0, 11.8 ± 2.1 (screening and 18 month, with medication use)	Only Travoprost used during the study period, except during washout	Four patients had progression of cataract	−6.47 ± 7.20, −5.32 ± 8.29	NR	NR	Open-label nonrandomized study involving only Caucasians
Buchacra et al. (2011)	Prospective nonrandomized case series	iStent	10	12	26.5 ± 7.9, 17.0 ± 2.5	2.9 ± 0.7, decreased by 1.1 ± 0.6	No significant change	NR	NR	NR	All patients had secondary glaucoma, small sample size
Arriola-Villalobos et al. (2012)	Prospective nonrandomized	Phaco+iStent	19	60	19.42 ± 1.89, 16.08 ± 4.25 (60 months, $n = 13$)	1.32 ± 0.48, 0.84 ± 0.89 Eight patients were medication free at 5 years	One patient had significant decrease in vision due to macular degeneration	NR	NR	NR	Small sample size, uncontrolled study

(*Continued*)

Table 2 (*Continued*)

Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Craven et al. (2012)	Randomized controlled trial, multicenter	Phaco+iStent versus Phaco	Phaco+iStent, 98 Phaco, 101	24	18.6 ± 3.4, 17.1 ± 2.9 versus 17.9 ± 3.0, 17.8 ± 3.3	1.6 ± 0.8, 0.3 ± 0.6 versus 1.5 ± 0.6, 0.5 ± 0.7	Corrected distance visual acuity worse than 20/40 postoperatively in:Phaco+iStent, 7 Phaco, 9	−3.77 ± 3.03, −3.22 ± 3.01 versus −3.94 ± 3.60, −3.16 ± 3.66	NR	NR	Good patient retention, industry employee authors
Patel et al. (2013)	Prospective case series	Phaco+iStent or iStent alone	Phaco+iStent or iStent alone, 40 + 4	6	21.5, 16.5	2.3, 0.59	0.53 logMAR, 0.23 logMAR	NR	NR	NR	Short follow-up duration, heterogenous glaucoma diagnoses
Arriola-Villalobos et al. (2013)	Prospective nonrandomized	Phaco+two iStents	20	12	19.95 ± 3.71, 16.75 ± 2.24	1.3 ± 0.66, 0.3 ± 0.57	0.4 ± 0.12, 0.8 ± 0.17	NR	NR	NR	Small sample size, uncontrolled study
Voskanyan et al. (2014)	Prospective open-label multicenter study	Two iStent inject	99	12	22.1 ± 3.3, 15.7 ± 3.7	2.21 ± 0.44, 66% off meds	84% and 86% were 20/40 or better at baseline and 12 months, respectively	NR	NR	NR	No control group
Fea et al. (2014)	Prospective, randomized	Two iStent inject implants versus Xalacom	Two iStent inject, 94 Xalacom, 98	12	21.1 ± 1.7, 13.0 ± 2.3 versus 20.7 ± 1.7, 13.2 ± 2.0	-	Slight decrease in BCVA: iStent, 5 Xalacom, 9	NR	NR	NR	Industry-sponsored study and investigators
Fea et al. (2015)	Prospective randomized trial	Phaco+iStent versus Phaco	Phaco+ iStent, 10 Phaco, 14	48	17.8 ± 2.7, 15.9 ± 2.3 versus 16.7 ± 3.0, 17.0 ± 2.5	1.9 ± 0.9, 0.5 ± 0.8 versus 1.8 ± 0.7, 0.9 ± 1.0	No significant decrease in vision	NR	NR	NR	Small sample size, no predefined strategy for adding medications
Donnenfeld et al. (2015)	Prospective open label	Two iStents	39	24–36	24.1 ± 1.4 (washout), 13.5 ± 2.1 (24 months, $n = 36$, no meds), 15.2 ± 2.1 (36 months, $n = 25$, no meds)	NR	Two eyes had loss of one or more Snellen lines due to progressing cataract	−4.95 ± 2.52, −4.0 ± 3.14 (24 months), −3.97 ± 2.31 (36 months)	NR	NR	No control group, small number of pseudophakic eyes, all subjects were Caucasian

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Table 2 (*Continued*)

Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Katz et al. (2015)	Prospective randomized controlled trial	One iStent versus Two iStents versus Three iStents	One iStent, 38 Two iStents, 41 Three iStents, 40	18	19.8 ± 1.3, 15.6 ± 1.5 versus 20.1 ± 1.6, 13.8 ± 1.3 versus 20.4 ± 1.8, 12.1 ± 1.2	All patients were on meds preoperatively: 1.71 ± 0.61 versus 1.76 ± 0.54 versus 1.51 ± 0.69 At 18 months, 11.1%, 9.8%, and 7.9%, respectively, were on meds	No significant decrease in vision	−4.72 ± 4.42, −4.9 ± 4.71 versus −5.20 ± 5.65, −5.96 ± 5.84 versus −4.81 ± 4.22, −5.24 ± 4.13	NR	NR	All participants were Caucasian, open-label study
Neuhann (2015)	Prospective open-label, nonrandomized	Phaco+iStent	41	36	24.1 ± 6.9, 14.9 ± 2.3	1.8 ± 0.9, 0.3 ± 0.5	93% had 20/40 or better vision	NR	NR	NR	No control group, visual field data not available
Tan & Au (2016)	Prospective uncontrolled, interventional case series	Phaco+iStent	41	36	21.2 ± 4.7, 17.1 ± 2.4	2.1 ± 1.0, 1.3 ± 1.2	0.52 ± 0.28 logMAR, 0.23 ± 0.31 logMAR at 6 months	NR	NR	NR	No control group, heterogenous glaucoma diagnoses
Arriola-Villalobos et al. (2016)	Prospective single-arm study	Phaco+two iStent inject implants	20	47.4 ± 18.46	19.95 ± 3.71, 16.25 ± 1.99	1.3 ± 0.66, 0.75 ± 0.79	0.42 ± 0.16, 0.18 ± 0.16	NR	NR	NR	Small sample size, significant dropout
Shiba et al. (2017)	Prospective, nonrandomized interventional pilot study	Two iStents	10	6	22.0 ± 3.0, 16.9 ± 3.6	NR	−0.014 logMAR, −0.0059 ± 0.11 logMAR	−15.4 ± 8.1, postoperative value not reported	NR	NR	Small sample size, short duration

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Table 2 (*Continued*)

Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Katz et al. (2018)	Prospective randomized controlled trial	One iStent versus Two iStents versus Three iStents	One iStent, 38 Two iStents, 41 Three iStents, 40	42	Washout IOPs 25.0 ± 1.2, 17.4 ± 0.9 versus 25.0 ± 1.7, 15.8 ± 1.1 versus 25.1 ± 1.9, 14.2 ± 1.5	NR	No significant drop in vision	−4.72 ± 4.42, −6.43 ± 4.95 versus −5.20 ± 5.65, −7.11 ± 5.78 versus −4.81 ± 4.22, −6.91 ± 5.40	NR	NR	Open-label study, IOP readings were not averaged over multiple readings
Myers et al. (2018)	Prospective single-arm open-label study	Each eye received two iStents and one iStent Supra	80	48	Washout IOPs 26.4 ± 2.4, 18.4 ± 1.4	NR	12 had vision decrease of three or more Snellen lines: 11 had cataract progression and one had worsening of visual field	−13.0 ± 8.6, −13.2 ± 8.5	NR	NR	Open-label study No control group All subjects were Caucasian
Hengerer et al. (2018)	Prospective nonrandomized consecutive cohort study	Phaco+iStent inject	81	36	22.6 ± 6.2, 14.3 ± 1.7 (36 months, $n = 41$)	2.5 ± 1.1, 0.8 ± 0.9 (36 months, $n = 41$)	Only one eye had postoperative vision less than 20/40 (20/50)	NR	NR	NR	No control group, significant dropout, consecutive series
Hernstadt et al. (2019)	Prospective interventional case series	Phaco+one or two iStent injects	37	12	17.5 ± 3.82, 14.8 ± 3.94	1.49 ± 0.77, 0.14 ± 0.48	0.32 ± 0.22 logMAR, 0.10 ± 0.10 logMAR	NR	NR	NR	No control group, PAC and PACG patients, five of eight single iStents were fully occluded by the iris

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Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Samuelson et al. (2019b)	Prospective randomized single-masked, concurrently controlled multicenter trial	Phaco+two iStent injects versus Phaco	Phaco+two iStent injects, 387 Phaco, 118	24	Washout IOPs 24.8 ± 3.3, 17.1 ± 3.6 versus 24.5 ± 3.1, 17.8 ± 3.5	NR	Loss of two or more Snellen lines 2.6% versus 4.2%	NR	NR	NR	Includes surgeons' learning curves, iStent occlusion in 6.2%
Hengerer et al. (2019)	Prospective nonrandomized consecutive case series	Two iStent inject implants	44	36	25.3 ± 6.0, 14.6 ± 2.0	2.98 ± 0.88, 0.55 ± 0.79	No significant decrease in vision	NR	NR	NR	No control group, consecutive series
Fechtner et al. (2019)	Prospective randomized controlled trial	Two iStents versus Travoprost	Two iStents, 54 Travoprost, 47	60	Unmedicated IOP 25.5 ± 2.5, 16.5 ± 1.2 versus 25.1 ± 4.6, 16.3 ± 1.9	NR	No significant decrease in vision	−7.5 ± 8.8, −7.8 ± 7.9 versus −5.8 ± 7.7, −7.5 ± 7.5	NR	NR	Endothelial cell counts not evaluated; subjects were all Caucasians
Ahmed et al. (2020)	Prospective randomized multicenter trial	Hydrus versus Two iStents	Hydrus, 75 Two iStents, 77	12	19.0 ± 3.9, 17.3 ± 3.7 versus 19.1 ± 3.6, 18.1 ± 3.7	2.5 ± 0.7, 46.6% medication free versus 2.7 ± 0.8, 24.0% medication free	More than two lines of Snellen acuity decrease Hydrus, 2 iStent, 1	NR	NR	NR	Sample size too small to evaluate safety differences, 12 month washout not performed (protocol deviation)
Hydrus											
Pfeiffer et al. (2015)	Prospective randomized controlled multicenter trial	Hydrus+ Phaco versus Phaco	Hydrus+ Phaco, 50 Phaco, 50	24	26.3 ± 4.4, 16.9 ± 3.3 versus 26.6 ± 4.2, 19.2 ± 4.7	Washout IOPs	No patient in the Hydrus group lost more than two Snellen lines	NR	NR	NR	Study subjects were all Caucasian, poor final follow-up washout compliance, IOP measurement not masked

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Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Fea et al. (2017a,b)	Prospective case series	Hydrus versus SLT	Hydrus, 31 SLT, 25	12	23.09 ± 5.08, 16.5 ± 2.6 versus 23.18 ± 2.15, 15.9 ± 2.49	2.29 ± 0.83, 0.9 ± 1.04 versus 2.48 ± 0.92, 2.0 ± 0.91	0.25 ± 0.15, 0.22 ± 0.1 versus 0.30 ± 0.1, 0.33 ± 0.12	NR	NR	NR	Non-randomized, Hydrus implanted in more severe glaucoma cases
Samuelson et al. (2019b)	Prospective randomized controlled multicenter trial	Hydrus+ Phaco versus Phaco 2:1 ratio	Hydrus+ Phaco, 369 Phaco, 187	24	25.5 ± 3.0, 17.4 ± 3.7 versus 25.4 ± 2.9, 19.2 ± 3.8	Washout IOPs	Only one eye in the study group lost two or more Snellen lines	NR	NR	NR	IOP endpoint not a combination of percentage reduction and upper limit
Ahmed et al. (2020)	Prospective randomized controlled multicenter trial	Hydrus versus Two iStents	Hydrus, 75 Two iStents, 77	12	19.0 ± 2.5, 17.3 ± 3.7 versus 19.1 ± 3.6, 18.1 ± 3.7	2.5 ± 0.7, 46.6% medication free 2.7 ± 0.8, 24.0% medication free	More than two lines of Snellen acuity decrease Hydrus, 2 iStent, 1	NR	NR	NR	Sample size too small to evaluate safety differences, 12-month washout not performed (protocol deviation)
Jones et al. (2019)	Prospective randomized controlled multicenter trial	Hydrus+ Phaco versus Phaco	Hydrus+ Phaco, 219 Phaco, 112	24	25.6 ± 3.2, 17.5 ± 3.9 versus 25.3 ± 2.9, 19.3 ± 4.2	Washout IOPs	Loss of two or more Snellen lines: Hydrus+Phaco, 1.8% Phaco, 1%	Decrease in MD of more than 2.5 dB: Hydrus+ Phaco, 0% Phaco, 1%	NR	NR	No significant endothelial cell loss, US cohort of the HORIZON trial
KDB											
Greenwood et al. (2017)	Prospective case series	Phaco+KDB	71	6	17.4 ± 5.2, 12.8 ± 2.6	1.6 ± 1.3, 0.9 ± 1.0	NR	NR	NR	NR	No control group, postoperative management not uniform, short follow-up

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Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Dorairaj et al. (2018b)	Prospective case series	Phaco+KDB	52	12	16.8 ± 0.6, 12.4 ± 0.3	1.6 ± 0.2, 0.8 ± 0.1	0.439 ± 0.041 logMAR, 0.137 ± 0.016 logMAR	NR	NR	NR	No control group
GATT											
Grover et al. (2014)	Retrospective case series	NR	85	12	Absolute IOP values not reported For open-angle glaucoma cases, IOP decreased by 11.1 ± 6.1 at 12 months	Absolute values not reported For open-angle glaucoma cases, medications decreased by 1.1 ± 1.8	NR	NR	NR	NR	Retrospective and noncomparative study, significant dropout at 12 months ($n = 36$), heterogenous group
Grover et al. (2015)	Retrospective chart review of juvenile open-angle glaucoma and primary congenital glaucoma cases	NR	14	Mean 20.4 (range, 12–33)	Mean IOP not reported Mean IOP reduction, 12.5	2.6, 0.86	NR	NR	NR	NR	Retrospective, small sample size
Rahmatnejad et al. (2017)	Retrospective chart review	NR	66	12	26.1 ± 9.9, 14.6 ± 4.7	3.1 ± 1.1, 1.2 ± 0.9	No significant decrease	Postoperative values not reported	NR	NR	Retrospective, includes surgeon's learning curve, no control group
Grover et al. (2017a)	Retrospective chart review	NR	35	24	25.7 ± 6.5, 15.4 ± 4.9	3.2 ± 1.0, 2.0 ± 1.4	NR	NR	NR	NR	Retrospective study, no control group

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Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Grover et al. (2018)	Retrospective chart review	NR	198	24	Overall values not reported	Overall values not reported	0.29 ± 0.4 logMAR, 0.34 ± 0.54 logMAR	NR	NR	NR	Retrospective study, six subgroups
Baykara et al. (2019)	Retrospective study	NR	32	6	34.2 ± 10.6, 11.2 ± 2.4 (6 months, $n = 18$)	3.8 ± 0.4, 0.3 ± 0.7	logMAR 1.57 ± 1.2, logMAR 0.39 ± 0.38	NR	NR	NR	Retrospective, no control group
Boese & Shah (2019)	Retrospective chart review	Steroid-induced glaucoma	13	24	IOP decreased by 19.5 mm Hg	3.1, 0.8	NR	NR	NR	NR	Retrospective, low sample size
Aktas et al. (2019a,b)	Retrospective study	Moderate to advanced open-angle glaucoma	104	18	25.0 ± 7.3, 15.9 ± 4.3	3.4 ± 0.6, 1.2 ± 0.5	0.51 ± 0.24, 0.47 ± 0.21	NR	NR	NR	Retrospective study
Cypass											
García-Feijoo et al. (2015)	Prospective multicenter single-arm trial	Open-angle glaucoma	65	12	24.5 ± 2.8, 16.4 ± 5.5 (12 months, $n = 55$)	2.2 ± 1.1, 1.4 ± 1.3 (12 months, $n = 55$)	No patient lost two or more Snellen lines over 12 months	NR	NR	NR	No control group, short follow-up, no predefined medication strategy
Hoeh et al. (2016)	Prospective open-label multicenter study	Open-angle glaucoma, Phaco+Cypass	167	12	20.2 ± 6.0, 15.9 ± 3.1 (12 months, $n = 111$)	2.0 ± 1.1, 1.1 (12 months, $n = 111$, SD not reported)	No implant-related significant loss of vision, endothelial touch in two eyes	NR	NR	NR	No control group, significant attrition rate
Höh et al. (2014)	Prospective single-arm study	Open-angle glaucoma Phaco+Cypass	Cohort 1 (baseline IOP>20), 51 Cohort 2 (baseline IOP<21), 85	24	25.5 ± 4.9, 15.8 ± 3.8 versus 16.4 (SD not reported), 16.1 ± 3.2	Baseline values for each cohort not reported	NR	NR	NR	NR	No control group

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Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Hoeh et al. (2013)	Prospective multicenter case series	Open-angle glaucoma Phaco+Cypass	184	6	21.1 ± 5.91, postoperative value not reported Cohort baselines not reported	2.1 ± 1.1, postoperative value not reported Cohort baselines not reported	NR	NR	NR	NR	No control group, medication strategy not predefined, short follow-up
Vold et al. (2016)	Randomized controlled trial	Phaco+ Cypass Phaco	Phaco+ Cypass, 374 Phaco, 131	24	24.4 ± 2.8, 7.4 ± 4.4 decrease versus 24.5 ± 3.0, 5.4 ± 3.9 decrease Absolute postoperative values not reported	1.4 ± 0.9, 0.2 ± 0.6 versus 1.3 ± 1.0, 0.6 ± 0.8	Unresolved BCVA loss: Phaco+ Cypass, 6 Phaco, 3	Field loss progression: Phaco+ Cypass, 6.7% Phaco, 9.9%	NR	NR	Latino/Hispanic population underrepresented
Garcìa-Feijoo et al. (2018)	Prospective multicenter single-arm trial	POAG, standalone Cypass	65	24	24.5 ± 2.8, 16.8 ± 3.9	2.2 ± 1.1, 1.5 ± 1.2	NR	NR	NR	NR	No control group, no predefined medication strategy
Grisanti et al. (2018)	Prospective and retrospective multicenter registry trial	Standalone Cypass	225	36	22.6 ± 6.7, 16.0 ± 3.3 (36 months, $n = 58$)	2.2 ± 1.2, 2.1 ± 1.2 (36 months, $n = 58$)	2.7% had a BCVA loss of two or more Snellen lines	NR	NR	NR	No control group, significant dropout
Reiss et al. (2019)	Randomized controlled multicenter trial	Phaco+ Cypass Phaco	Phaco+ Cypass, 215 Phaco, 67	60	Mean IOP reduction: 8.4 versus 8.0 Absolute postoperative values not reported	NR	BCVA loss of two or more lines: Phaco+Cypass, 11.2% Phaco, 6%	Mean deviation worsening by ≥2.5 dB compared to 2-year data: Phaco+ Cypass, 10.2% Phaco, 9%	NR	NR	Significantly more endothelial cell loss in the microstent group

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Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Xen											
Grover et al. (2017a)	Prospective, multicenter, single-arm, open-label study	Xen	65	12	25.1 ± 3.7, 15.9 ± 5.2	3.5 ± 1.0, 1.7 ± 1.5	Seven eyes experienced loss of two or more Snellen lines (lasted more than 30 days)	−15.0 ± 7.7, −15.8 ± 8.9	NR	NR	No control group, industry involvement in all aspects of the study
Fea et al. (2017a,b)	Prospective single-arm study	Xen with or without Phaco	12	12	21.8 ± 2.8, 14.9 ± 2.1	2.92 ± 1.16, 0.50 ± 0.53	6.38 ± 3.23, 7 ± 2.11	−12.5 ± 8.69, −12.47 ± 8.63	NR	NR	No control group, small sample size, bleb morphology study
Olate-Pérez et al. (2017)	Prospective noncontrolled study	Xen+Phaco	30	12	21.2 ± 3.4, 14.48 ± 1.89	3.07 ± 0.69, postoperative value not reported	NR	NR	NR	NR	No control group, bleb morphology study
Galal et al. (2017)	Prospective single-arm study	Xen with or without Phaco	13	12	16 ± 4, 12 ± 3	1.9 ± 1, 0.3 ± 0.49	0.33 ± 0.34, 0.13 ± 0.11	NR	NR	NR	No control group, small sample size
Sng et al. (2018)	Prospective case series	Xen in uveitic eyes	24	12	30.7 ± 9.7, 12.2 ± 3.1	3.1 ± 0.9, 0.4 ± 0.9	Three eyes lost two or more Snellen lines due to cataract progression	NR	NR	NR	Small sample size, no control group
Lenzhofer et al. (2019c)	Prospective study	Xen versus Xen+Phaco	Xen, 69 Xen+Phaco, 68	24	22.5 ± 6.5, 13.0 ± 5.15 versus 23.4 ± 6.3, 12.7 ± 6.88	3.0 ± 0.9, 0.76 ± 0.91 versus 2.9 ± 1.0, 1.4 ± 1.28	Loss of two or more Snellen lines: Xen, 4% Xen+Phaco, 7%	NR	NR	NR	Non-randomized, significant differences between groups

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Table 2 (*Continued*)

Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Kalina et al. (2019)	Prospective noncomparative study	Xen versus Xen+Phaco	Xen, 20 Xen+Phaco, 27	12	24.18 ± 8.18, 13.04 ± 4.50 versus 20.98 ± 6.47, 13.61 ± 2.90	Overall: 2.96 ± 1.20, 0.75 ± 1.27 Group-wise values not reported	No significant decrease in vision	NR	NR	NR	No control group, washout IOP not obtained, all except one patient were Caucasians
Gillmann et al. (2019a,b)	Prospective study	Xen+Phaco in: POAG versus PXFG	POAG, 57 PXFG, 53	24	19.8 ± 5.83, 14.5 ± 3.6 versus 19.77 ± 8.23, 14.2 ± 3.8	1.98 ± 1.16, 0.6 ± 0.9 versus 2.02 ± 1.34, 0.4 ± 0.7	NR	NR	NR	NR	Not matched or randomized, no predefined medication strategy
Reitsamer et al. (2019)	Prospective, nonrandomized, open-label, multicenter	Xen versus Xen+Phaco	Xen, 106 Xen+Phaco, 79	24	21.7 ± 3.8, 15.4 versus 21.0 ± 3.4, 14.9 Final follow-up SD not reported	2.7 ± 0.9, decreased by 1.5 ± 1.5 versus 2.5 ± 0.9, decreased by 1.5 ± 1.2	Vision improved: Xen, 0.01 ± 0.21 Xen+Phaco, −0.23 ± 0.24	NR	NR	NR	No control group, postoperative management variable
Lenzhofer et al. (2019a)	Prospective nonrandomized multicenter study	Xen-GGM (63 μm inner diameter) with or without Phaco	34	48	22.5 ± 4.2, 13.4 ± 3.1	2.4 ± 1.3, 1.2 ± 1.3	Three eyes lost two or more Snellen lines	−10.2 ± 7.0, −11.9 ± 10.0	NR	NR	No control group, Xen with and without cataract surgery grouped together
Lenzhofer et al. (2019b)	Prospective cohort study	Xen with or without cataract surgery	78	12	23.7, 15.2	3.4, 0.9	NR	NR	NR	NR	No control group, timing and frequency of needling variable, bleb morphology study

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Table 2 (*Continued*)

Study[a]	Study type	Groups studied	Number of eyes	Duration of follow-up (months)	IOP (preoperative, postoperative)	Medication (preoperative, postoperative)	Visual acuity (preoperative, postoperative)	Visual field MD (preoperative, postoperative)	OCT RNFL	Quality of life	Comments
Mansouri et al. (2018)	Prospective interventional study	POAG versus PXFG	POAG, 57 PXFG, 53	12	19.8 ± 5.8, 13.9 ± 4.6 versus 19.7 ± 8.2, 13.6 ± 4.3	1.9 ± 1.6, 0.4 ± 0.8 versus 2.0 ± 1.3, 0.5 ± 0.8	NR	NR	NR	NR	No control group
Hohberger et al. (2018)	Prospective cohort	Xen+Phaco versus Xen	Xen+Phaco, 30 Xen, 81	6	Values not reported Complete success rates: Xen+Phaco, 53.3% Xen, 46.9%	NR	NR	NR	NR	NR	Complete success defined as IOP < 18 without medication at any time point within 6 months
PreserFlo, formerly known as InnFocus											
Batlle et al. (2016)	Prospective nonrandomized	InnFocus with or without cataract surgery	23	36	23.8 ± 5.3, 10.7 ± 3.5 (36 months, $n = 22$)	2.4 ± 0.9, 0.7 ± 1.1	No eye lost more than one Snellen line	NR	NR	NR	No control group, small sample size

[a]Only prospective studies were considered, except for in the case of GATT, which did not have any prospective studies at the time of the literature search.

Abbreviations: BCVA, best corrected visual acuity; GATT, gonioscopy-assisted transluminal trabeculotomy; IOP, intraocular pressure; KDB, Kahook Dual Blade; MD, mean deviation; NR, not reported; OCT RNFL, optical coherence tomography retinal nerve fiber layer thickness; PAC, primary angle closure; PACG, primary angle closure glaucoma; POAG, primary open-angle glaucoma; PXFG, pseudoexfoliation glaucoma; SD, standard deviation; SLT, selective laser trabeculoplasty.

3.2. iStent (First Generation)

The first-generation iStent (Glaukos, Laguna Hills, CA) was an L-shaped heparin-coated titanium implant. It was approved by the FDA in 2012 for use in combination with cataract surgery. This single-piece stent measures approximately 1.0 mm in length and 0.33 mm in height. The bore diameter of the snorkel is 120 μm (Ahmed et al. 2020, Francis & Winarko 2012, Wellik & Dale 2015). This implant is inserted via an ab interno approach, usually into the nasal trabecular meshwork, when the surgeon is seated temporally. The stent enters the Schlemm's canal, forming a bypass that gives aqueous humor access to the conventional outflow (Craven et al. 2012, Myers et al. 2018). More than one iStent may be inserted 1–3 clock hours apart (Ahmed et al. 2014, Arriola-Villalobos et al. 2012, Katz et al. 2015, Myers et al. 2018).

The advantage of this implant is that it can be combined with cataract surgery in mild to moderate glaucoma eyes to achieve a modest reduction in IOP and a reduction in medication (Arriola-Villalobos et al. 2012, 2016; Craven et al. 2012; Malvankar-Mehta et al. 2015). IOP reduction is greater with increasing numbers of iStent implants. In a randomized trial investigating the efficacy of multiple iStents, 92.1% of patients who were on an average of 1.51 medications preoperatively became medication-free at 12 months postoperatively after receiving three iStent implants (Katz et al. 2015, 2018).

The most common complications include malposition, and obstruction by iris, blood, or vitreous humor occurs in 3–20% of cases (Resende et al. 2016; Spiegel et al. 2008, 2009). The risks of allergy, hypersensitivity, and toxicity are minimal, as the implant is made of surgical grade titanium. However, titanium implants in dentistry have caused hypersensitivity on rare occasions (Kim et al. 2019). A recent report showed evidence of metallic intraocular particles resting on the nasal iris, the source of which might have been the injector or the implant itself (Tassel et al. 2019).

3.3. iStent Inject

The second-generation iStent, the GTS-400 iStent inject (Glaukos, Laguna Hills, CA), is smaller than the first-generation iStent. This device was proposed to have a shorter learning curve than its predecessor. Absence of a snorkel makes the device structurally different from the first-generation iStent. The G2-M-IS injector system has the capacity to house two implants, thus enabling the surgeon to implant two devices with a single intraocular entry (Ahmed et al. 2020, Fea et al. 2014, Katz et al. 2015). Bahler et al. (2012) reported that the first iStent inject implant increased the outflow facility from 0.16 ± 0.05 to 0.38 ± 0.23 μL/min/mm Hg, and the second iStent inject further increased the outflow facility to 0.78 ± 0.66 μL/min/mm Hg. FDA approval for this device was obtained in 2016.

Complications associated with the iStent inject are similar to those associated with the first-generation iStent (Arriola-Villalobos et al. 2016, Fea et al. 2014, Gonnermann et al. 2017, Voskanyan et al. 2014).

3.4. Hydrus

The Hydrus (Ivantis, Inc, Irvine, CA) is an 8-mm-long curved aqueous drainage device. Structural support is provided by alternating spines. It is made of nitinol, a nickel and titanium alloy, and is superelastic, returning to its original shape after deformation. The Hydrus microstent acts as a scaffold within the Schlemm's canal, dilating the canal to approximately four to five times its natural width. Once within the Schlemm's canal, it spans 90° (one quadrant) and provides access to multiple collector channels. It was approved by the FDA in 2018 for use in conjunction with cataract surgery in adult patients with primary open-angle glaucoma (Ahmed et al. 2020, Cent. Devices Radiol. Health 2019, Samuelson et al. 2019a).

A preloaded injector is introduced into the anterior chamber through a 1.5-mm clear corneal incision. The stent is introduced into the trabecular meshwork under gonioscopic guidance. After the position of the distal tip within the Schlemm's canal has been confirmed, the stent can be advanced using the tracking wheel on the injector. A 1-mm inlet segment is situated external to the trabecular meshwork, in the anterior chamber (Ahmed et al. 2020, Samuelson et al. 2019a).

Intraoperative complications are infrequent and include malposition and transient hyphema. Layered hyphema of more than 2 mm on the first postoperative day has been reported in 0.5–1.4% of cases (Jones et al. 2019, Samuelson et al. 2019a). Peripheral anterior synechiae or iris adhesions form at the inlet segment in up to 18.7% of cases, and 3.4% of such adhesions are completely obstructive. Persistent iritis requiring steroids for more than 3 months was reported in 0.5% of cases (Jones et al. 2019).

3.5. Gonioscopy-Assisted Transluminal Trabeculotomy

Gonioscopy-assisted transluminal trabeculotomy (GATT) involves a 360° trabeculotomy using an ab interno approach. An iTrack microcatheter (Ellex, Fremont, CA) is used to perform the trabeculotomy (Grover et al. 2014). Alternatively, a suture, such as 5–0 or 6–0 Prolene or Nylon with one tip blunted using heat cautery, may be used (Aktas et al. 2019b, Grover & Fellman 2016). A 1–2-clock-hour goniotomy is created and the microcatheter or suture introduced using microsurgical forceps. The iTrack microcatheter may be visualized in lieu of its lighted tip as it courses through the Schlemm's canal. The microcatheter or suture emerges from the other end of the goniotomy incision after it has coursed through the entire circumference of the Schlemm's canal. The leading tip is then brought to the center of the anterior chamber and held securely while gentle traction is applied to the trailing end outside the incision, creating a constricting loop that cuts through the trabecular meshwork (Grover et al. 2014, 2017b). Trabeculotomy may be limited to 90°, 180°, or 270° (Nazarali et al. 2019).

GATT has been used in the treatment of primary and secondary open-angle glaucoma, including steroid-induced glaucoma (Boese & Shah 2019). It has also been used in pediatric and juvenile glaucoma (Grover et al. 2015).

The most common complication is hyphema in the first postoperative week, seen in 23–38% of cases (Grover et al. 2014, Rahmatnejad et al. 2017). Intracapsular hematoma has also been reported (Yalinbas et al. 2018). Other rare complications include Descemet's membrane detachment, corneal edema, iridodialysis, hypotony, and panscleritis (Aktas et al. 2019a, Baykara et al. 2019, Grover et al. 2014, Rahmatnejad et al. 2017).

3.6. Kahook Dual Blade

The KDB (New World Medical, Rancho Cucamonga, CA) is a modified goniotomy blade used to excise a strip of trabecular meshwork. Other trabeculotomy procedures, such as GATT and Trabectome, can leave residual trabecular meshwork leaflets, which can lead to fibrosis over time (Seibold et al. 2013). Thus, KDB has a theoretical advantage over other trabeculotomy procedures of better long-term outcomes. The sharp tip allows the blade to enter the trabecular meshwork. The heel of the instrument fits into the Schlemm's canal, and when the knife is advanced, it creates parallel incisions in the trabecular meshwork, resulting in the removal of a strip of trabecular meshwork tissue. The knife may be advanced in clockwise or counter-clockwise directions over 3–5 clock hours, depending on the surgeon's preference (Seibold et al. 2013). KDB was registered by the FDA in 2015.

KDB has been used in adult and childhood glaucoma (Khouri & Wong 2017), uveitic glaucoma (Miller et al. 2019), angle-closure glaucoma following goniosynechialysis (Dorairaj & Tam 2019),

and severe and refractory glaucoma (Salinas et al. 2018a). It may be combined with other MIGS procedures, such as iStent and GATT (ElMallah et al. 2019, Widder & Schmitz 2019). Complications include hyphema, IOP spikes in 6% of cases, corneal edema, rebound iritis, cyclodialysis cleft, and Descemet's membrane tears in 4% of cases (Dorairaj & Tam 2019, Dorairaj et al. 2018a, ElMallah et al. 2019, Greenwood et al. 2017).

3.7. Cypass

The Cypass microstent (Alcon, Fort Worth, TX) is 6.35 mm long, with an outer diameter of 510 μm and an inner diameter of 300 μm. This polyimide tube has fenestrations along its entire length and three protruding retention rings at the proximal end. The guidewire used to implant this stent is introduced into the anterior chamber and is used to create a controlled small cyclodialysis by gently dissecting the ciliary body from the scleral spur. The stent is then inserted into the suprachoroidal space along the guidewire. At its final position, only one retention ring should be visible externally. This is followed by withdrawal of the guidewire (Hoeh et al. 2013, 2016; Reiss et al. 2019; Vold et al. 2016). Cypass was approved by the FDA in 2016.

Cypass has been used in primary open-angle glaucoma (Reiss et al. 2019, Vold et al. 2016) and even chronic angle-closure glaucoma postvitrectomy (Hopen et al. 2018). It has been used in conjunction with iStent implantation (Chen & Kim 2018). Complications include IOP elevations above 30 mm Hg, hypotony, transient hyphema, and progression of cataracts (Hoeh et al. 2016, Reiss et al. 2019, Sii et al. 2019). The five-year results of the COMPASS trial showed that the annualized endothelial cell loss was 2.84% in the Cypass group and 0.36% in the control group. Compared to the control group, the endothelial cell loss was 5.8 times higher in the group with two or more retention rings visible. The annualized endothelial cell loss rates for stents with zero, one, two, and three rings visible were 1.39%, 2.74%, 6.02%, and 9.96%, respectively (Lass et al. 2019, Reiss et al. 2019). Based on these results, the Cypass microstent was voluntarily withdrawn from the market in August 2018 (U.S. Food Drug Admin. 2018).

3.8. iStent Supra

The iStent suprachoroidal bypass system (iStent Supra, Model G3) (Glaukos, Laguna Hills, CA) is made up of polyethersulfone and a titanium sleeve. It is 4 mm in length and has an internal diameter of 165 μm. It is currently undergoing clinical trials in the United States.

Insertion steps are similar to those of the Cypass microstent, using a preloaded disposable injector. This implant has been studied in moderate and advanced open-angle glaucoma (Junemann 2013, Myers & Katz 2013). It has also been used in conjunction with iStent implants (Myers et al. 2018). Hypotony that resolved in 1 month was reported in 2 out of 25 eyes. One eye had a choroidal effusion that resolved by the third postoperative month. Best corrected visual acuity did not show any significant change (Junemann 2013, Myers & Katz 2013).

3.9. Xen

The Xen gel stent (Allergan, Irvine, CA) is a 6-mm-long tube made of collagen-derived gelatin cross-linked with glutaraldehyde. It is hydrophilic and is hydrated on contact with water, becoming flexible and conforming to the surrounding tissue (Chatzara et al. 2019, Green et al. 2018). Three Xen models have been manufactured with varying lumen diameters: 45, 63, and 140 μm. Of these, only the Xen45 is currently available. The Xen gel stent was approved by the FDA in 2016.

The most common site of implantation is the superonasal quadrant. Mitomycin C is usually injected subconjunctivally in the superonasal quadrant and massaged over the planned site of stent

exit. The injector with the stent is introduced into the anterior chamber from a diametrically opposite inferotemporal clear corneal incision. A second instrument is used to provide counter-traction at a side port. Under gonioscopic guidance, the injector needle is directed anterior to the Schlemm's canal, tunneled through the sclera, and brought out subconjunctivally at a marked point 3 mm from the limbus. The stent is deployed and the needle withdrawn. Ideally, the stent is placed such that 2 mm of the distal end are in the subconjunctival space, 3 mm are in the scleral tunnel, and 1 mm is in the anterior chamber (Chatzara et al. 2019, Green et al. 2018). Variations include an ab externo approach (Lee et al. 2019) and supra-Tenon air and viscoelastic injection for a supra-Tenon Xen placement (Ahmed et al. 2019). The Xen gel stent is a bleb-forming device, and its advantages over conventional trabeculectomy are its minimally invasive nature, shorter surgical and recovery times, and decreased risk of hypotony. This stent has been used in open-angle glaucoma (Schlenker et al. 2017), uveitic glaucoma (Sng et al. 2018), iridocorneal endothelial syndrome (Lin et al. 2019), and pediatric glaucoma (Arad et al. 2019). Postoperative needling is required in 43% of cases, and the subconjunctival segment may be accidentally amputated during needling (Bustros et al. 2020, Schlenker et al. 2017). High IOP on postoperative day one is the most important predictor for needling (Midha et al. 2019).

Immediate complications include misplacement, bleeding, wound leak, hypotony, and failure due to obstruction (Chatzara et al. 2019, Gillmann et al. 2019b, Green et al. 2018). Late complications include implant migration (Ali et al. 2019) resulting in dislocation into the anterior chamber and stent–iris touch (Atalay et al. 2018, Chatzara et al. 2019, Dervenis et al. 2017, Gillmann et al. 2018), endothelial cell loss (Gillmann et al. 2019a), erosion or exposure (Arnould et al. 2019), bleb-related complications (Salinas et al. 2018b), persistent hypotony (Sng et al. 2018), suprachoroidal bleeding (Prokosch-Willing et al. 2017), endophthalmitis (Karri et al. 2018, Lapira et al. 2018), and late wound leak (Olate-Pérez et al. 2018, Salinas et al. 2018b).

3.10. PreserFlo, Formerly Known as InnFocus

The PreserFlo microshunt (Santen Pharmaceutical Company, Ltd., Osaka, Japan) is a microtube made of poly(styrene-block-isobutylene-block-styrene). The microshunt has undergone design modifications, including MIDI-Tube and MIDI-Ray and the latest MIDI-Arrow or PreserFlo microshunt. It is 8.5 mm long with a 70-μm lumen. A 1.1-mm-wide fin located 4.5 mm from the anterior tip secures the implant at the desired location (Arrieta et al. 2011, Green et al. 2018, Pinchuk et al. 2016).

The PreserFlo microshunt is implanted ab externo. Mitomycin C is applied using sponges or via a subconjunctival injection prior to creation of a shallow 1-mm-wide scleral pocket with an angled knife. The shunt is introduced into the anterior chamber through a 25G needle track. Aqueous outflow is confirmed before the peritomy is closed. The microshunt has been used in phakic and pseudophakic eyes (Green et al. 2018).

Complications include hypotony in 8–13% of cases and choroidal effusions in 3.4–8.7% of cases, which usually resolve without any surgical intervention. Other rare complications include hyphema, vitreous hemorrhage, encapsulated bleb, and early bleb leak (Batlle et al. 2016, Beckers et al. 2017, Green et al. 2018, Pinchuk et al. 2016, Riss et al. 2015).

4. CRITICAL APPRAISAL OF MINIMALLY INVASIVE GLAUCOMA SURGERY LITERATURE

4.1. Quality of Studies

More than one million scientific publications are produced worldwide every year (Fontelo & Liu 2018). In the field of ophthalmology alone, there was a 51% increase in the number of

publications between 2000 and 2011 (Huang et al. 2013). While the impact factor of a journal is a good instrument to evaluate the quality of scientific journals (Huang et al. 2013), many publications in high-impact journals do not follow established reporting guidelines aimed at enhancing reliable interpretation and comparisons between studies (Glujovsky et al. 2016, Sims et al. 2018).

4.1.1. World Glaucoma Association guidelines for glaucoma surgical trials. The WGA guidelines on designing and reporting glaucoma surgical trials were produced as an initiative to standardize reporting of glaucoma surgical trials. This work was published in March 2009, a time when multiple glaucoma surgical interventions were being reported using variable, diverse, and inconsistent methodologies. To create uniform design and reporting guidelines, the WGA took the lead in inviting more than 70 leaders in the field of glaucoma to formulate a guideline. The WGA guideline consists of six sections: recommended methodology, definitions of success, ethical issues, postoperative complication reporting, economic evaluation, and statistical reporting (Shaarawy et al. 2009).

An RCT is considered the most valid methodology to determine the efficacy and safety of surgical procedures and devices compared to established surgical procedures. Other methodological requirements include CONSORT checklists, masking, and multicenter or international collaboration. Complete demographic reporting, such as the age range, mean age with standard deviation, ethnicity breakdown, preoperative visual field mean deviation, central corneal thickness, disease severity, and nature of glaucoma (open- versus closed-angle and structural and functional status), allows for appropriate generalization of the results. The best corrected visual acuity and perimetry should be reported both pre- and postoperatively. Use of glaucoma medication should be reported; ideally, the number of classes, duration of use, and features of chronic medication-related inflammation should also be reported. To minimize bias, endpoints should be measured by individuals not involved in patient care. IOP should be measured by Goldmann applanation tonometry by two individuals not involved in patient care, one adjusting the tonometer dial, blinded to the dial reading, and the other reading the measurement off the dial. Baseline IOP should be measured after an adequate washout period and should be a mean of three diurnal readings. Each subsequent follow-up IOP should be a mean of two readings within 2 mm Hg or a median of three readings if the difference is more than 2 mm Hg. Only one eye should be enrolled per patient. Randomization should be computer generated or performed using random number tables. The new surgical intervention should be described adequately so that the reader may be able to perform the procedure with additional training. Postoperative visits should be on day 1; week 1; and months 1, 3, 6, 12, 18, 24, and 36 (Shaarawy et al. 2009).

The primary IOP endpoint should be defined as a combination of percentage reduction and an upper limit. For example, if success was defined as only a 20% IOP reduction, then IOP reduction from 50 to 40, 40 to 32, or 30 to 26 would be considered successful. Similarly, if success was defined as an IOP of less than 21 mm Hg, then pre- versus postoperative IOPs of 21 to 20 or 16 to 20 would be considered successful. To avoid such errors, a combination outcome criterion should be used, including consideration of various levels of either percentage reduction or upper IOP limit. Eyes that lose light perception or need additional surgery should be considered failures, rather than just being excluded from the analysis. Success should be classified as complete (without the use of medications) or qualified (with medication), and the number of patients on hypotensive medications, including the number of medication classes used, should be reported (Shaarawy et al. 2009).

In terms of ethics, apart from the use of an appropriate informed consent, approval from a research ethics board, and reporting of the training status of the surgeons in terms of wet lab and clinical experience, the following issues should be considered: clear declaration of conflicts

of interest, industry funding of the study or authors, authors who are shareholders or industry employees, and publications authored by or correspondence directed to the company (Shaarawy et al. 2009).

Prevalence and severity of intra- and postoperative complications should be reported. An economic evaluation serves to furnish patients, physicians, and policy makers with adequate information to evaluate the cost and associated benefit of a particular intervention (Shaarawy et al. 2009).

Sample size calculation, intention-to-treat analysis, and 95% confidence interval reporting are essential requirements for any surgical trial. Both an IOP-based survival curve with the number of patients at each time point mentioned and an IOP scatter plot are mandatory according to the guidelines (Shaarawy et al. 2009).

4.1.2. Main areas of focus while evaluating studies of minimally invasive glaucoma surgeries. To evaluate MIGS studies, it is important to consider the main tenets of the WGA guidelines. An RCT is the preferred means of evaluating a surgical procedure. With IOP often being the primary outcome, masked readers should not be involved in clinical care. Diurnal IOP readings that are averaged over multiple readings decrease the margin of error (Thomas & Mengersen 2013). There should also be a predefined protocol for adding glaucoma medications during the study (Shaarawy et al. 2009).

It is critical to ensure that the primary outcome being evaluated is a combination of percentage IOP reduction and upper IOP limit. Most well-designed studies make this foundational error, thus compromising the generalizability of the results (Craven et al. 2012, Fea et al. 2014, Samuelson et al. 2019a, Voskanyan et al. 2014).

Eyes that need a second procedure for IOP control should be considered failures and not excluded from the study (Shaarawy et al. 2009). Most prospective studies have multiple postoperative study visits, during which the IOP will be measured. This data should be reported in the form of a survival curve, including the number of eyes at each time point. An IOP scatterplot also gives the reader a sense of the correlation between pre- and postoperative IOPs and any outliers that may be influencing the trend.

The WGA guidelines recommend a follow-up of three years for surgical procedures and implants. The importance of long-term follow-up is illustrated by the case of the Cypass microstent, where significant endothelial cell loss was evident at five years postoperatively (Lass et al. 2019, Reiss et al. 2019, Vold et al. 2016).

If cataract surgery is combined with MIGS, then there should be a matched or randomized control group of cataract surgery alone and a predefined strategy for adding medications. Otherwise, it will be difficult to ascertain whether the IOP-lowering effect is predominantly from cataract surgery or MIGS (Mansberger et al. 2012).

4.1.3. Adherence of publications on minimally invasive glaucoma surgeries to World Glaucoma Association guidelines. Mathew et al. (2019) determined the extent of adherence of MIGS trials to the WGA guidelines for glaucoma surgical trials. They identified 25 comparative MIGS studies, including 10 RCTs and 15 non-RCTs. Nearly half of the studies were on iStent [11 studies (44%)], followed by Trabectome [7 studies (28%)]; Hydrus [4 studies (16%)]; and KDB, Cypass, and Xen [1 study (4%) each]. The most common comparator was cataract surgery [7 studies (28%)], followed by one or more iStents [5 studies (20%)]; glaucoma drainage devices [3 studies (12%)]; trabeculectomy, Trabectome, and medication [2 studies (8%) each]; and canaloplasty, goniotomy, selective laser trabeculoplasty (SLT), and trabeculotomy [1 study (4%) each]. The mean follow-up was 19.9 ± 11.6 months, with nearly half the studies ($n = 12$) having

only a 12-month follow-up, which may be too short for a glaucoma surgical procedure. IOP was measured by individuals not directly involved in patient care in only four studies (16%).

Only four studies (16%) utilized at least three diurnal IOP readings to establish the baseline. Washout baseline IOP measurements were used in eight RCTs (80%). Masked Goldmann applanation tonometry measurement by two readers was performed in only four RCTs (40%) and none of the non-RCTs. The primary IOP endpoint was defined as a combination of both an upper limit and percentage reduction in only four studies (16%): one RCT (10%) and three non-RCTs (20%; $P = 0.63$). An IOP-based survival curve was provided in seven studies (28%): none of the RCTs and seven non-RCTs. Two studies (8%) provided an IOP scatterplot: one RCT and one non-RCT. Twelve studies (48%) reported 95% confidence intervals.

In 64% of the studies ($n = 16$; 80% of RCTs and 53.3% of non-RCTs), at least one author reported an association with the industry. Among RCTs, 90% had industry funding, 80% had at least one author reporting industry association, 60% had at least one author being a shareholder, and 60% had at least one industry employee author. Overall, there was poor adherence (45.6%) to the WGA guidelines.

4.2. Economic Assessment

Economic assessment serves to provide patients, physicians, and policy makers with adequate information to evaluate the cost and associated benefit of a particular intervention (Shrime et al. 2017). The common types of economic assessments performed include cost-effectiveness analysis, benefit–cost analysis, and multicriteria decision analysis (Jit 2018). The majority of MIGS economic evaluation studies were benefit–cost analyses or cost-effectiveness analyses (Ngan et al. 2018, Ordóñez et al. 2019, Patel et al. 2019).

Ngan et al. (2018) performed an economic comparison among topical medications, cataract surgery combined with iStent, and SLT as first-line treatments for open-angle glaucoma, assuming equal efficacy for the three treatment modalities. The mean annual medication cost was NZD$144.81 (range NZD$42.25–NZD$485.11). The annual medication cost was compared to the iStent cost to obtain the time taken for iStent to break even with the medications, assuming equal efficacy and a 100% success rate. Three of 19 (15.8%) medications broke even within five years, nine of 19 (47.3%) within 10 years, and 12 of 19 (63.2%) within 15 years. In comparison, the time taken for SLT to break even when compared to medications was markedly less: 0.71 years for consultants and 0.67 years for registrars. In a five-year study comparing two iStents to Travoprost, Fechtner et al. (2019) reported that two iStents were equivalent to Travoprost in terms of IOP lowering. At five years postoperatively, 22.2% of cases needed additional medication. There is no data on the effectiveness of iStents at 10 and 15 years postoperatively. Ngan et al. (2018) did not consider direct nonhealth costs, indirect costs, costs related to postoperative complications and follow-up, and quality of life. This study also has the limitation shared by most economic analyses that its findings may not be generalized to other countries where the healthcare system and costs are different (Shrime et al. 2017).

Ordóñez et al. (2019) used a Markov model to perform a cost-effectiveness analysis, comparing iStent to medications. iStents were estimated to have 127,971 more discounted quality adjusted life years compared to laser trabeculoplasty, 405,982 compared to timolol + dorzolamide + brimonidine, and 378,287 compared to timolol + dorzolamide + latanoprost or timolol + dorzolamide + bimatoprost. At 40 years, the cumulative cost for iStents was $13,252,318, $6,403,534, $22,311,064, and $29,156,113 lower than laser trabeculoplasty, timolol + dorzolamide + brimonidine, timolol + dorzolamide + latanoprost, and timolol + dorzolamide + bimatoprost, respectively. These findings are based on assumptions made while evaluating external data

sources. Another limitation was that the model ran for 40 years, creating uncertainty, as the initial assumptions may not hold true for the follow-up period.

Iordanous et al. (2014) compared the direct costs of treating patients with Trabectome, iStent, and endoscopic cyclophotocoagulation, as per the Ontario Health Insurance Plan (Ontario, Canada). The costs were projected over a six-year period. At six years, treatment with the Trabectome, iStent, and endoscopic cyclophotocoagulation offered a per-patient cumulative cost savings of CAN$2424.71, CAN$2124.71, and CAN$2924.71, respectively, compared to tridrug therapy. This study did not consider the start-up costs involved and assumed that all devices and procedures remain effective for six years.

Patel et al. (2019) evaluated the cost utility of two iStents compared to standard of care in mild to moderate open-angle glaucoma patients in Canada. A Markov model was used in the evaluation of visual field deterioration over 15 years. A meta-analysis of RCTs was also conducted to calculate the pooled reduction in IOP and medication use in both groups. There was an additional reduction of 1.13 medications per patient in the iStent group, apart from an additional decrease in IOP of 1.10 mm Hg at three years. The time to dominance for iStent was 3.7 years. There was a decrease in total healthcare costs by CAN$2,908.3 per patient over 15 years. Efficacy was limited to 10 years despite there being no 10-year data on iStent. Costs of managing complications were not considered.

Berdahl et al. (2017) compared the direct costs of implanting two iStents, SLT, and medications only. A population-based cost-of-care model was used to estimate the costs over five years. The projected average cumulative costs at five years were $4,420, $4,730 and $6,217 for iStents, SLT, and medications only, respectively. However, the initial year-zero costs were $2,810, $842, and $996, respectively. This study was limited by its reliance on clinical expert panel opinion and lack of real-world data.

Economic analysis may be better conducted through microcosting studies, which include every input consumed in a patient's management. In contrast to gross-costing studies, which use averages and assumptions, thereby decreasing the transparency and ability to deliver consistent estimates, microcosting studies increase the precision and transparency in estimating costs and better reflect the use of resources (CADTH 2019, Gold et al. 1996).

4.3. Ethical Issues

In this section, we discuss issues related to industry funding, conflict of interest, extent of disclosure, reconcilability of conflict, and reporting transparency.

4.3.1. Industry funding. Industry funding for a study can include providing the device being investigated; funding any part of the study, including the writing process; and paying investigators or patients for involvement in the study. Industry funding has been strongly associated with proindustry conclusions (Ahn et al. 2017, Baker et al. 2003). This phenomenon has also been reported in industry-funded studies in ophthalmology (Alasbali et al. 2009). A Cochrane review reported that industry-sponsored drug and device studies show more favorable results and conclusions than studies funded by other sources. This industry bias could not be explained by standard risk of bias assessments (Lundh et al. 2017). On an individual level, industry payments were positively associated with increased use of intravitreal antivascular endothelial growth factor injections (Taylor et al. 2016). Industry funding has become more or less a requirement for conducting device or implant studies due to the high costs of conducting these studies and limited nonindustry or government research funding. Investigators frequently have financial ties to the specific industry of the device under study. Researchers with financial ties to industry have greater scholarly impact

in different fields of medicine than do researchers with no ties to industry. However, this finding does not represent a causal relationship (Eloy et al. 2017).

4.3.2. Conflicts of interest of authors. The Bayh-Dole Act of 1980 heralded an era of scientists, industry, and universities patenting inventions and discoveries and profiting financially from federally funded research (Markel 2013). A conflict of interest indicates the risk of an individual acting in a biased manner as a result of personal interests (Muth 2017). Negative findings are 10 to 20 times less likely to be reported by authors with conflicts of interest (Friedman & Richter 2004). This leads to growing mistrust between the public and the scientific community, as revealed by the lay press targeting scientific misadventures and unwanted attention from politicians (Schaefer et al. 2017). In 2013, stockholder academic leaders owned a median of 50,699 shares in healthcare companies and industry, which translated to a median compensation of $193,000. The share value is dependent on the performance of the product, thus potentially diminishing clinical trials to the level of product promotions (Anderson et al. 2015). A review of the literature found at least one shareholder author in 60% of comparative MIGS studies (Mathew et al. 2019).

MIGS journal articles have been authored by industry employee authors (Craven et al. 2012; Katz et al. 2015, 2018; Myers et al. 2018). Their role in research should definitely be acknowledged with transparent reporting of their specific roles in the study and complete declaration of the conflicts of interest (Smilowitz et al. 2018). The possibility of bias should be kept in mind while interpreting studies that have significant conflicts of interest (Godlee 2015). Useful scientific research thrives on academic freedom and the scientists' impartial work to uncover new knowledge. However, financial support from industry and for-profit organizations are significant sources of support for research, and rejecting such sources can jeopardize numerous research initiatives. Thus, transparency, rather than independence, may be the way forward (Cosgrove et al. 2017, Schaefer et al. 2017).

4.3.3. Disclosure: extent and implications. Conflicts of interest were declared completely in 11%, declared incompletely in 25%, and unreported in 64% of journal articles by the most productive authors in ophthalmology (Schaefer et al. 2017). The International Council for Journal Medical Editors' Declaration of Potential Conflicts of Interests has terminology that may be unclear to authors, resulting in incomplete disclosure (Liesegang & Bartley 2014a,b). A full disclosure is just a starting point to manage the conflict, rather than the solution. However, a full disclosure may influence clinicians to offer more biased advice to neutralize anticipated discounting, also known as strategic exaggeration (Loewenstein et al. 2012). Another issue with full disclosure is moral licensing, the feeling that biased advice is acceptable because the patient has been notified about the disclosure (Loewenstein et al. 2012). Early adopters of MIGS often make significant investments and spend time training, which may result in the ethical risk of personal investment affecting clinical judgement (Barnett & Katz 2015).

Institutional conflict of interest may occur when institutional processes for research are influenced or reasonably appear to be influenced by the financial interests of the institution, or of an institutional official who has authority to act on behalf of the institution (McKinney 2016, 2018). Institutions where innovative surgeries such as MIGS are performed often receive industry funding and seek a cutting-edge reputation by pursuing innovation (Johnson & Rogers 2012). Every research institution or university should have clearly laid out institutional conflict of interest policies (Cigarroa et al. 2018).

4.3.4. Reconcilability of conflict. Conflict of interest committees in universities find it difficult to manage complex conflicts of interest while safeguarding the integrity of the research process

(Boyd & Bero 2007). Most authors of MIGS studies reported financial support from industry, including fees for being a consultant or employee, honoraria, revenue from shares, provision of study devices by industry, and industry assistance in publication (Craven et al. 2012; Dorairaj et al. 2018a; Fea et al. 2014; Katz et al. 2015, 2018; Samuelson et al. 2011; Vold et al. 2016). Such financial conflicts may be regulated through a case-by-case review or via stringent institutional policies. Institutional committees face challenges in managing conflicts and should be given adequate authority to implement their decisions in managing the conflicts of academic leaders (Pisano et al. 2014). Some academic institutions have mitigated conflicts arising from directorships by limiting the payment of academic directors (Pisano et al. 2014). Financial benefits from owning stocks is directly related to the success of the company. This, coupled with the finding that academic leaders own a median of 50,699 shares, indicates the irreconcilability of the conflict. Such a conflict may be partly managed by prohibiting academic leaders involved in research from owning stock (Anderson et al. 2015). Complete prohibition of researchers with unmanageable conflicts has also been implemented as an extreme measure (Anderson et al. 2015, Cent. Medicare Medicaid Serv. 2013).

4.3.5. Steps to improve transparency. The first step to improving transparency is a complete disclosure of all conflicts (Loewenstein et al. 2012). A full disclosure can be ensured by a clear disclosure-of-conflicts statement administered by journals and by ensuring that authors, reviewers, and editors comply with it (Liesegang & Bartley 2014a,b). Dunn et al. (2016) recommended a global public registry of academic researchers' conflicts of interest. This record should be updated and periodically audited to ensure currency and accuracy. Sharing individual patient data from clinical trials is another means to enhance the transparency of a study by giving the reader access to all of the relevant data (Ohmann et al. 2017).

5. CONCLUSION

MIGS consist of a group of distinct devices and procedures aimed at reducing the IOP. Compared to traditional glaucoma surgeries, such as trabeculectomy and Ahmed, Baerveldt, and Molteno implants, MIGS have a lower incidence of vision-threatening complications. However, the IOP-reducing ability of MIGS, especially those that target the conventional trabecular meshwork outflow, is inferior to that of traditional glaucoma surgeries. At present, there is insufficient evidence to compare the efficacy and safety of the various MIGS. MIGS procedures need further study, including long-term studies to assess efficacy and late complications of implanted devices, better and more transparent reporting of results with meaningful endpoints, and microcosting of real-time economic evaluations. MIGS procedures and devices have a potential position in the glaucoma treatment paradigm, which may become more established with better evaluation of their safety and efficacy.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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