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ORIGINAL RESEARCH

# Standalone Implantation of 2–3 Trabecular Micro-Bypass Stents (iStent *inject* ± iStent) as an Alternative to Trabeculectomy for Moderate-to-Severe Glaucoma

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## ABSTRACT

***Introduction***: This retrospective consecutive study compared standalone implantation of multiple (2–3) trabecular micro-bypass stents (iStent *inject* ± iStent) (Multi-Stent group) vs trabeculectomy + mitomycin C (Trab group) in moderate to severe open-angle glaucoma (OAG).

***Methods***: Eligible patients underwent Multi-Stent or Trab surgery from 2018 to 2020 and had at least 3-month follow-up; visual field mean deviation (VF MD) − 6 dB or worse; inadequate prior response to maximum medications ± laser procedures; and had trabeculectomy as their next planned intervention. Primary effectiveness, safety-adjusted treatment success, was defined as ≥ 20% intraocular pressure (IOP) reduction on the same or fewer medications, without clinically significant safety events (severe complications, secondary surgeries, reinterventions). Secondary effectiveness included mean IOP and medications; qualified and complete attainment of target IOP (≤ 21/18/15/12 mmHg and > 6 mmHg); health-economic and quality-of-life (QoL) measures; and 2-vs-3-stent subgroup analysis.

***Results***: The baseline groups ($n$ = 70 Multi-Stent/40 Trab) were similar: mean IOP (21.1 mmHg/22.3 mmHg); medications (2.87/3.10 medications); disease stage (30%/35% severe); VF MD (− 10.1 dB/− 10.4 dB); and mean last follow-up (LFU, 13.1 months/15.7 months) (all differences non-significant). Primary effectiveness: treatment success at LFU was 62.9% vs 30.0% in Multi-Stent vs Trab eyes, respectively ($p$ = 0.001). Secondary effectiveness: At LFU in Multi-Stent vs Trab groups, respectively: mean IOP decreased by 31% to 14.2 mmHg ($p < 0.001$) vs by 43% to 12.5 mmHg ($p < 0.001$); mean medications decreased by 51% to 1.31 medications ($p < 0.001$) vs by 84% to 0.43 medications ($p < 0.001$). Multi-Stent eyes, compared to Trab eyes, had fewer visits ± reinterventions within 3 months (3.6 vs 6.1, $p < 0.001$); longer time to first reintervention (12.2 months vs 4.5 months, $p$ = 0.01); fewer total reinterventions (0.26 vs 0.75, $p$ = 0.006); and earlier lifting of postoperative restrictions (12.6 vs 32.1 days, $p < 0.001$). In 2-vs-3-stent analysis, there was a trend toward more 3-stent eyes achieving target IOP than 2-stent eyes. Visual fields remained stable in both Multi-Stent and Trab eyes.

***Conclusion***: Implanting 2–3 trabecular micro-bypass stents was a viable alternative to trabeculectomy for moderate-to-severe OAG, with clinically appropriate IOP/medication

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reductions and higher safety-adjusted treatment success vs trabeculectomy.

**Keywords:** Intraocular pressure; iStent; iStent *inject*; Micro-invasive glaucoma surgery (MIGS); Safety; Severe; Trabecular micro-bypass; Trabeculectomy

**Key Summary Points**

***Why carry out this study?***

There is continued need for glaucoma treatment options with improved safety profiles alongside clinically sufficient IOP lowering, particularly in patients with more advanced disease severity who otherwise might necessitate filtration surgery.

This novel comparative cohort study contributes some of the first head-to-head data comparing a standalone trabecular micro-invasive glaucoma surgery (MIGS) device with standard trabeculectomy–mitomycin C (MMC) in the treatment of moderate and severe glaucoma.

This retrospective study examined whether implantation of 2–3 trabecular micro-bypass stents (iStent *inject* ± iStent) could indeed offer a viable lower-risk alternative to trabeculectomy.

***What was learned from the study?***

Multi-Stent implantation produced clinically appropriate IOP and medication reductions in eyes with moderate to severe glaucoma, with significantly higher rates of safety-adjusted treatment success than trabeculectomy–MMC. These findings show that this Multi-Stent intervention indeed is a viable alternative to filtration surgery.

Multi-Stent eyes also outperformed Trab eyes in health-economic and quality-of-life (QoL) endpoints; 2-vs-3-stent subgroup analysis showed a clear trend toward more 3-stent eyes achieving target IOP than 2-stent eyes.

## INTRODUCTION

Known in literary works as the "silent thief of sight," glaucoma has always been a top cause of human blindness, with patients ranging from historical luminaries like Galileo to present-day readers of this article. All currently available glaucoma treatments revolve around lowering intraocular pressure (IOP), whether by medical, laser, or surgical means. These interventions are typically employed in a stepwise fashion, using the least invasive treatment possible to effect the necessary IOP reduction. A longstanding mainstay of glaucoma surgical options is trabeculectomy, which significantly lowers IOP and is often considered a reference standard against which other surgical modalities may be compared. Although effective in reducing IOP, trabeculectomy is also associated with considerable short-term safety risks and long-term morbidity [1–3].

Over the past decade, the range of glaucoma surgical options has expanded considerably, most notably because of the advent and increasing utilization of micro-invasive glaucoma surgery (MIGS) [4]. MIGS procedures and devices are characterized by a minimally invasive (usually *ab interno*) surgical approach, shortened recovery time, and minimal tissue manipulation. They are designed to have a better safety profile than traditional trabeculectomy, while still yielding clinically meaningful (though comparatively smaller) IOP reduction [5].

To date, the MIGS devices with the largest and longest-term evidence base are the iStent and iStent *inject* trabecular micro-bypass stents. As cited in a recent press release [6], there are now over 200 peer-reviewed scientific publications supporting the effectiveness and safety of

iStent and iStent *inject*. These include studies in combined or standalone usage, single or multiple-stent placement, different racial groups, various glaucoma subtypes (e.g., pseudoexfoliative, pigmentary, narrow-angle, normal-tension), and different glaucoma severities (from ocular hypertensive to severe) [7–38]. The literature also includes studies on the cost-effectiveness, cost–utility, and QoL benefits of iStent and iStent *inject* [39–46]. And recently, a number of wholly independent, investigator-initiated studies showed superior efficacy and safety with iStent or iStent *inject* than with other MIGS devices [47–51]. Meanwhile, as traditional filtration surgeries such as trabeculectomy have long been a central part of glaucoma treatment, the literature is replete with studies evaluating them.

Despite the wealth of evidence on either side, minimal comparative data exist regarding the outcomes of trabeculectomy versus a MIGS device; most of these MIGS-vs-trabeculectomy studies have been completed with the subconjunctival XEN gelatin microstent (Allergan, Dublin, Ireland) [53–55]. Like trabeculectomy, the XEN stent provides a conduit between the anterior chamber and the subconjunctival space, and requires concomitant application of mitomycin C to prevent fibrosis (MMC) [52]. These comparative studies have generally shown smaller IOP and medication reductions after XEN implantation than after trabeculectomy, but with relatively fewer complications [53–55]. Unfortunately, the incidence of adverse events and procedure-related reinterventions (such as bleb needling) after XEN is still appreciable, so most surgeons reserve it for their more advanced or refractory patients, whose disease severity warrants the potential risks of the intervention.

The present retrospective comparative study analyzed the ability of multiple (2–3) trabecular micro-bypass stents vs trabeculectomy to achieve significant IOP and medication reductions while preserving favorable safety and avoiding sight-threatening complications. As such, it marks one of the first direct comparisons of a standard filtration procedure vs a trabecular MIGS procedure, completed by a single surgeon in a single location and drawing from the same population of glaucomatous eyes with comparable baseline characteristics and surgical goals.

## METHODS

### Study Design and Participants

This retrospective cohort study compared outcomes of consecutive patients with moderate to severe OAG [including primary OAG (POAG), pigmentary glaucoma (PG), and pseudoexfoliative glaucoma (PXG)] who underwent either standalone implantation of 2 or 3 trabecular micro-bypass stents (iStent *inject* with/without concomitant iStent) (Multi-Stent group) or standalone trabeculectomy with mitomycin C application (Trab group). Surgeries were performed from January 2018 to December 2020 by a single glaucoma surgeon in Brazil (R.G.).

A standalone antiglaucoma procedure was offered to all patients. The benefits and risks, advantages and disadvantages, and patient-specific suitability (e.g., duration of surgery, individual ability to complete postoperative care, complications, cost, personal preference, caregiver support) of multiple stents and trabeculectomy were discussed with each patient. Since trabecular micro-bypass stents are an *ab interno*, tissue-preserving intervention, Multi-Stent patients retained the option of undergoing trabeculectomy in the future, should their IOP reduction not be sufficient to prevent VF progression. Once consensus was reached, the patient gave written informed consent prior to undergoing surgery. Anonymized retrospective data analysis was undertaken in accordance with the Tenets of the Declaration of Helsinki and with the approval of the Ethics Committee of Santa Casa de Misericórdia Hospital (approval number 21327319.5.0000.5139). Clinical trial registration was not required because of the retrospective design of the study, as patients had already received treatment. iStent and iStent *inject* are approved for standalone implantation in Brazil.

All charts of patients who underwent either standalone implantation of 2 or 3 trabecular micro-bypass stents or standalone

trabeculectomy with mitomycin C application and who had a minimum 3 months of follow-up were reviewed for potential inclusion. Eligibility criteria at the preoperative visit were as follows: minimum of 18 years old; diagnosis of OAG (including POAG, PG, or PXG); phakic or pseudophakic; on oral and/or topical glaucoma medications; at risk for filtration surgery (i.e., patients would otherwise be scheduled for trabeculectomy); and inadequate prior response to maximum tolerated medical therapy and/or glaucoma laser procedures. Patients were required to have moderate or severe glaucoma stage per standard visual field criteria, defined as follows: mild, mean deviation (MD) no worse than − 6 dB; moderate, MD worse than − 6 dB but no worse than − 12 dB; severe, MD worse than − 12 dB [56]. Eyes were excluded if they had undergone prior incisional glaucoma surgery; had active ocular inflammation; or had clinical characteristics making them ineligible for either procedure (e.g., angle closure, corneal pathology precluding stent visualization, conjunctival erosion precluding bleb formation), prior to treatment with trabecular micro-bypass stents or trabeculectomy.

### *Ab Interno* Trabecular Micro-Bypass Stent Implantation

The iStent and iStent *inject* devices and implantation procedures have been described in detail previously [7, 25]. In brief, for either device, the respective injector is advanced under direct gonioscopy through a temporal peripheral clear corneal incision and across to the nasal trabecular meshwork. The stent is implanted through the meshwork into Schlemm's canal, via a slightly diagonal approach (iStent) or via a direct/*en face* approach (iStent *inject*). With iStent *inject*, a second stent is implanted approximately 60–90° (2–3 clock hours) away from the first without exiting the eye. The stents and their implantation location are depicted in Fig. 1a, b. In this particular study, some patients received three stents; in these patients, the surgeon first implanted the two iStent *inject* stents, then re-entered through the same incision to implant a single iStent. Following insertion of two (or three) stents, proper placement and seating in the trabecular meshwork were confirmed under intraoperative gonioscopy. Figure 2a, b shows in vivo gonioscopic images of 2 or 3 implanted stents. Viscoelastic was then removed and sealing of the corneal incision was ensured.

### Trabeculectomy

Before dissecting a fornix-based conjunctival flap, the surgeon completed a subconjunctival injection at the area of the future bleb of a mixed solution of 0.1 ml of 2% lidocaine + 0.1 ml of 0.2 mg/ml mitomycin C. A slight cauterization was then performed. A partial-thickness 4 mm × 4 mm scleral flap was prepared, followed by creation of a temporal paracentesis, sclerostomy, and peripheral iridectomy. The scleral flap was closed using four 10-0 nylon sutures in a manner allowing aqueous humor to exit posteriorly [57], and the conjunctiva was closed using the standard method for fornix-based flaps [58]. The presence and patency of the bleb were confirmed.

### Postoperative Management

No medication washout was completed prior to surgery, as this would not have been appropriate within the surgeon's standard practice. Postoperatively, eyes undergoing multi-stent implantation were prescribed topical antibiotic (moxifloxacin 4 times daily for 1 week) and topical anti-inflammatory medication (dexamethasone 4 times daily tapered over 4 weeks); eyes undergoing trabeculectomy were prescribed topical antibiotic (moxifloxacin 4 times daily for 1 week) and topical anti-inflammatory medication (dexamethasone 6 times daily tapered over 8 weeks). Per surgeon custom, postoperative restrictions in both groups were comprehensive and cautious. They included the following: (a) avoid compressing the eye globe (may include use of a shield while sleeping), (b) avoid exercise and heavy lifting, and (c) avoid crowded places such as malls, schools, and large gatherings. Restrictions were lifted incrementally as the patient recovered, until all

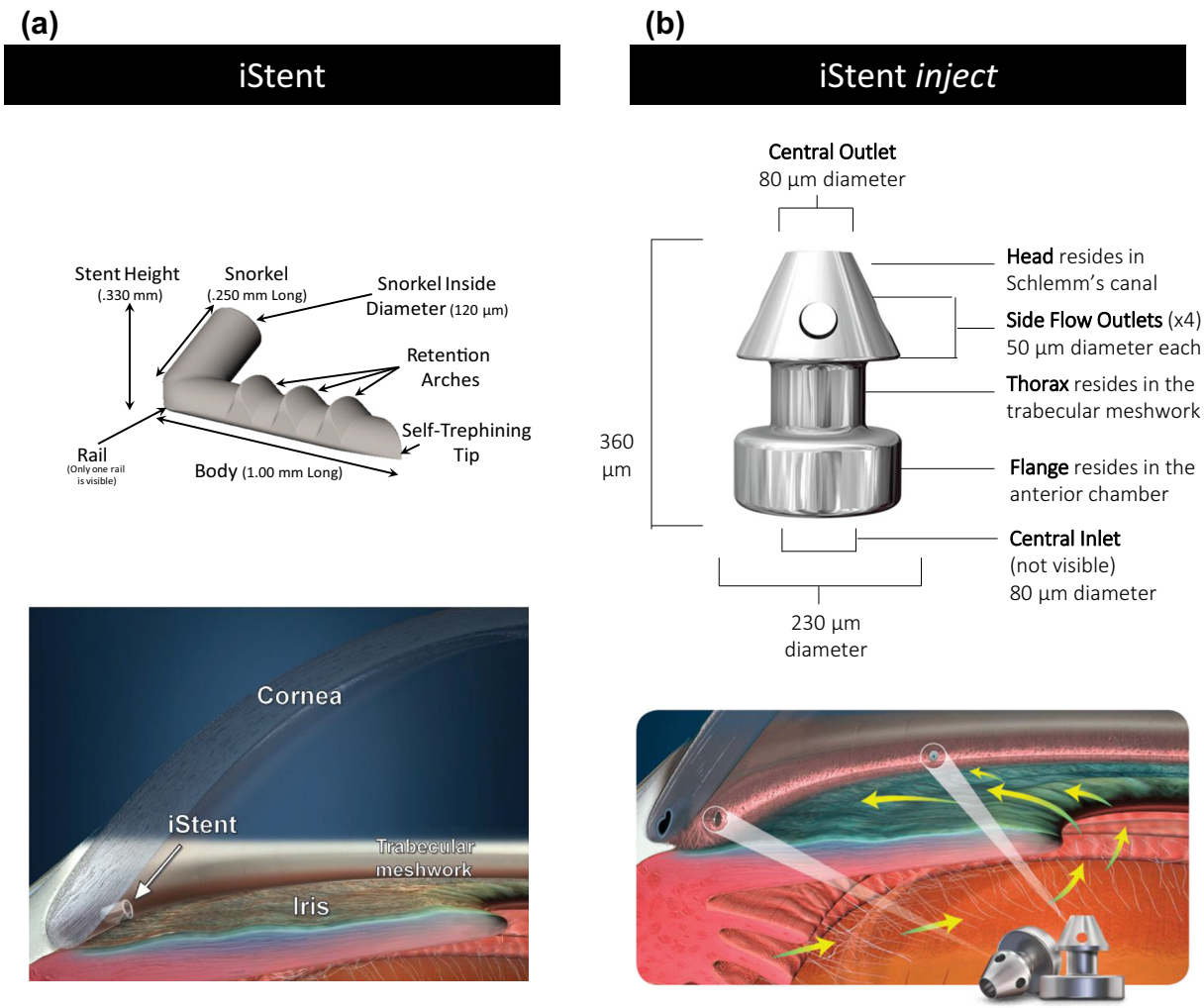



**Fig. 1** **a** iStent device and implantation location. **b** iStent *inject* device and implantation location

restrictions had been removed (this time point was recorded as the "time to lifting all postoperative restrictions").

### Effectiveness Outcomes: Primary, Secondary, and Subgroup Analyses

The *primary effectiveness* outcome was the proportion of eyes achieving safety-adjusted treatment success after standalone multi-stent or trab surgery. Safety-adjusted treatment success was defined as a 20% or greater IOP reduction from baseline on the same or fewer medications, and without clinically significant safety events (comprising severe complications, secondary glaucoma surgery, or procedure-related reinterventions; Table 1). These criteria for treatment success and failure are consistent with the criteria used in the US Food and Drug Administration (FDA) product-registration trials for the XEN gel stent [52] and for the three-stented iStent infinite trabecular micro-bypass device [59]. These are the two MIGS devices that address a patient population with similarly advanced glaucoma severity as the present cohort. As such, they were considered the most directly relevant MIGS comparators to help guide the design of the present MIGS-vs-trabeculectomy study.

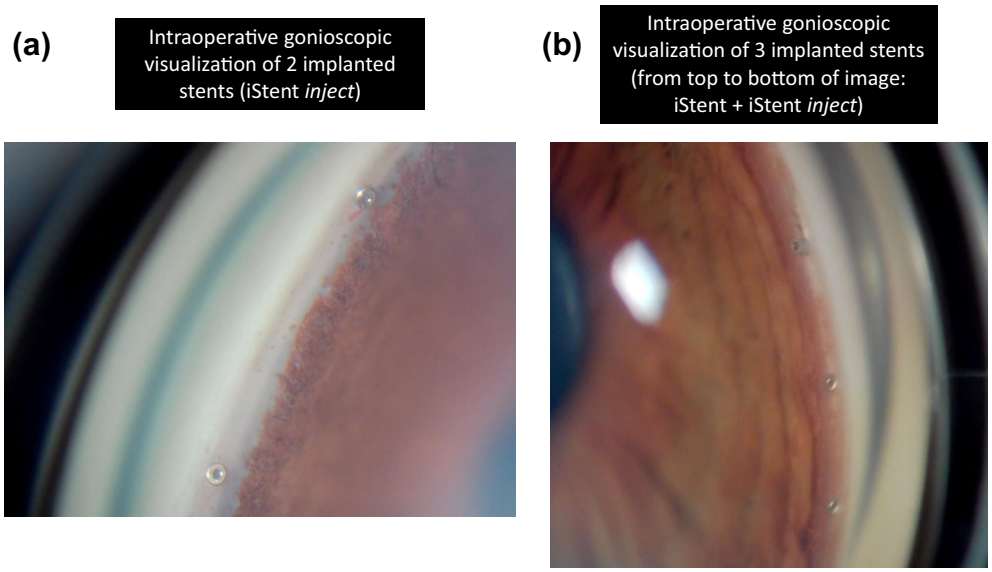



**Fig. 2** **a** Intraoperative gonioscopic visualization of 2 implanted stents (iStent *inject*). **b** Intraoperative gonioscopic visualization of 3 implanted stents (from top to bottom of image: iStent *inject* + iStent)

**Table 1** Clinically significant safety events

| |
|---|
| (a) Severe safety complications |
| IOP < 6 mmHg occurring at 1 month postoperative or later |
| Clinically significant hypotony at any time point (hypotony associated with consequent surgical intervention, maculopathy, flat anterior chamber requiring reformation, corneal folds, choroidal effusions requiring drainage, choroidal detachment, suprachoroidal hemorrhage) |
| Diplopia |
| BCVA loss ≥ 2 lines vs preoperative BCVA |
| Bleb leak |
| Blebitis or endophthalmitis |
| (b) Secondary glaucoma surgery or laser procedure (e.g., tube shunt, selective laser trabeculoplasty, etc.) |
| (c) Procedure-related reinterventions (e.g., suture lysis, bleb needling, goniosynechiolysis) |

The occurrence of one or more of these events constituted a treatment failure
*BCVA* best-corrected visual acuity

*Secondary effectiveness* outcomes included mean IOP, mean medication burden, and success rates according to traditional World Glaucoma Association (WGA) guidelines advised for glaucoma clinical trials, which have minimal to no adjustment for different safety profiles between procedures [60]. These endpoints included the percentage of eyes with qualified or complete attainment of various upper IOP limits (IOP ≤ 21 mmHg, ≤ 18 mmHg, ≤ 15 mmHg, or ≤ 12 mmHg) and one lower

limit (IOP < 6 mmHg), without adjusting for safety.

Additionally, given increasing awareness and appreciation of cost- and patient-centric outcomes in the ophthalmic community, proxy measures relating to health economics and quality of life (QoL) were incorporated. Specifically, we measured the mean time to lifting all postoperative restrictions, which may be thought to represent the potential number of days of diminished wages, additional caregiver costs, and/or decreased QoL. Other outcomes included the mean number of clinic visits and reinterventions within the first 3 months postoperative; mean total number of reinterventions throughout follow-up; and mean time to first reintervention. These outcomes were considered by the surgeon to be informative and responsive indicators of overall cost–benefit and QoL of patients during the months following their surgery.

*Subgroup analyses* were completed for eyes receiving 2 stents or 3 stents, in order to discern potential differences in performance. Specifically, we measured the rates of qualified or complete attainment of IOP $\leq$ 18 mmHg, $\leq$ 15 mmHg, or $\leq$ 12 mmHg in the two subgroups. These three targets were evaluated (rather than the single safety-adjusted treatment success endpoint), to allow for more sensitive detection of potential differences between the subgroups.

### Safety Outcomes

Safety data included visual field testing, best-corrected visual acuity (BCVA), slit-lamp and fundus examinations, gonioscopy, pachymetry, and documentation of adverse events (AEs), secondary surgeries, and reinterventions. Assessments were completed according to the surgeon's standard postoperative schedule, which generally included visits at the following time points: preoperative, day 1, week 1, week 2, and months 1, 3, 6, 9, 12, 18, and 24.

### Statistical Analysis

Subjects' preoperative demographic and ocular characteristics were described by mean and standard deviation for continuous (numerical) variables, and by absolute and relative frequencies for categorical variables. For between-group comparisons, continuous variables were first assessed with Levene's test for equality of variances, followed by analysis via a two-tailed Student's *t* test (if equal variances) or a non-parametric test such as Kruskal–Wallis or Mann–Whitney (if unequal variances). The chi-square test (either Pearson chi-square or Fisher's exact) was used for the analysis of categorical variables. Changes from baseline in mean IOP and medications were calculated for each group using a paired *t* test.

Kaplan–Meier survival analyses were constructed to illustrate the time to treatment failure, according to the aforementioned safety-adjusted failure definition. Comparisons of the survival curves were performed with the log-rank (Mantel–Cox) test. Additionally, although sample sizes were small, an exploratory subgroup analysis was completed to compare effectiveness outcomes of the 2-stent vs 3-stent subgroups. Either the test of proportions or the Fisher's exact test was used for these comparisons.

Statistical analysis was performed using SPSS or Stata, with the significance threshold set at a *p* value under 0.05. No sample size calculations were indicated in this retrospective analysis.

## RESULTS

### Study Population

A total of 110 eyes (70 Multi-Stent, 40 Trab) were included in this study. Follow-up duration ranged from 3 to 24 months postoperative (mean follow-up 13.1 months and 15.7 months for Multi-Stent and Trab eyes, respectively; $p = 0.112$). The baseline demographic and ocular characteristics were reflective of a moderate to severe glaucoma population, and were very similar between groups (Table 2). This included mean medicated IOP (21.1 and 22.3 mmHg,

**Table 2** Demographic and baseline ocular characteristics, Multi-Stent and Trab groups

| Characteristics | Multi-Stent ($n$ = 70) | Trab–MMC ($n$ = 40) | $p$ value (between-group comparison)[a] |
|---|---|---|---|
| Demographic | | | |
| Age (years) | | | |
| Mean ± SD | 69.3 ± 14.2 | 66.9 ± 14.1 | 0.395 |
| Follow-up (months) | | | |
| Mean ± SD (range) | 13.1 ± 8.3 (3 to 24) | 15.7 ± 7.3 (6 to 24) | 0.112 |
| Gender | | | |
| Male | 21 (30.0%) | 17 (42.5%) | 0.185 |
| Female | 49 (70.0%) | 23 (57.5%) | |
| Race | | | |
| Caucasian | 57 (81.4%) | 33 (82.5%) | 1.00 |
| African descent | 8 (11.4%) | 4 (10.0%) | |
| Other | 5 (7.1%) | 3 (7.5%) | |
| Ocular | | | |
| Glaucoma type | | | |
| POAG | 65 (92.9%) | 36 (90.0%) | 0.772 |
| Pigmentary | 3 (4.3%) | 3 (7.5%) | |
| Pseudoexfoliative | 2 (2.9%) | 1 (2.5%) | |
| Glaucoma stage[b] | | | |
| Moderate | 49 (70%) | 26 (65%) | 0.588 |
| Severe | 21 (30%) | 14 (35%) | |
| Prior glaucoma procedure | | | |
| Yes | 11 (15.7%) | 4 (10.0%) | 0.401 |
| No | 59 (84.3%) | 36 (90.0%) | |
| Filtration surgery (trab or tube shunt) | 0 (0%) | 0 (0%) | |
| Selective laser trabeculoplasty | 11 (15.7%) | 4 (10.0%) | |
| Duration of med use | | | |
| Fewer than 5 years | 34 (48.6%) | 16 (40.0%) | 0.386 |
| 5–10 years | 24 (34.3%) | 19 (47.5%) | |
| More than 10 years | 12 (17.1%) | 5 (12.5%) | |
| Diamox use | | | |

**Table 2** continued

| Characteristics | Multi-Stent ($n$ = 70) | Trab–MMC ($n$ = 40) | $p$ value (between-group comparison)[a] |
|---|---|---|---|
| Yes | 1 (1.4%) | 2 (5.0%) | 0.299 |
| No | 69 (98.6%) | 38 (95.0%) | |
| Lens status | | | |
| Phakic, $n$ (%) | 14 (20.0%) | 18 (45.0%) | 0.005 |
| Pseudophakic, $n$ (%) | 56 (80.0%) | 22 (55.0%) | |
| Visual field mean deviation, dB | | | |
| Mean ± SD | − 10.13 ± 2.94 | − 10.47 ± 3.28 | 0.575 |
| Baseline IOP, mmHg | | | |
| Mean ± SD | 21.1 ± 3.0 | 22.3 ± 3.8 | 0.073 |
| Baseline # meds | | | |
| Mean ± SD | 2.87 ± 0.80 | 3.10 ± 0.63 | 0.123 |

*Multi-Stent* multiple stents [eyes implanted with 2–3 trabecular micro-bypass stents (iStent inject ± iStent)], *Trab–MMC* trabeculectomy with mitomycin C, *SD* standard deviation, *IOP* intraocular pressure, *Med* medication

[a]Via Student's $t$ test for continuous variables; or chi-square test (Pearson chi-square or Fisher's exact) for categorical variables

[b]Per standard Hodapp–Parrish–Anderson visual field criteria: mild, mean deviation (MD) no worse than − 6 dB; moderate, MD worse than − 6 dB but no worse than − 12 dB; severe, MD worse than − 12 dB [56]

respectively); number of medications (2.87 and 3.10 medications); glaucoma type (primary OAG in > 90% of eyes); glaucoma severity (30% and 35% with severe disease); and visual field mean deviation (− 10.1 and − 10.4 dB) (all differences not significant). The only baseline ocular parameter differing between groups was lens status (higher percentage of pseudophakic eyes in Multi-Stent group than in Trab group).

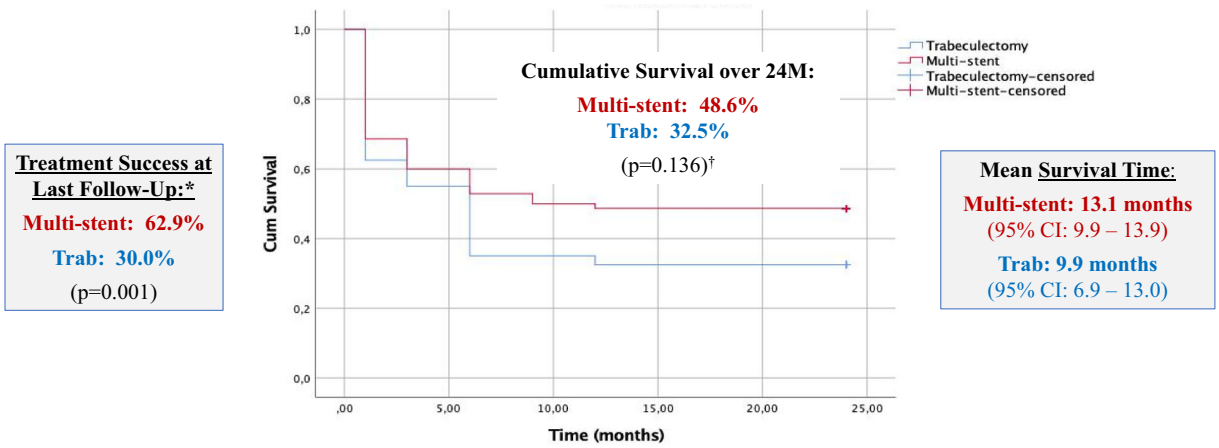
## Primary Effectiveness Outcome: Safety-Adjusted Treatment Success

By the time of last follow-up, safety-adjusted treatment success was 62.9% in the Multi-Stent group and 30.0% in the Trab group ($p$ = 0.001). In Kaplan–Meier survival analysis, the probability of treatment success through 24-month follow-up was observationally higher in the Multi-Stent group (48.6%) than in the Trab group (32.5%) [log-rank (Mantel–Cox) $p$ = 0.136] (Fig. 3). The mean survival time was 13.1 months in the Multi-Stent group [95% confidence interval (CI) 9.9–13.9 months] and 9.9 months in the Trab group (95% CI 6.9–13.0 months).

## Secondary Effectiveness Outcomes

### *Mean Intraocular Pressure*

There was no significant difference between the Multi-Stent and Trab groups in the percentage of eyes achieving IOP reduction ≥ 20% vs baseline on the same or fewer medications (72.9% and 82.5%, respectively; $p$ = 0.252). Preoperatively, mean IOP was 21.1 and 22.3 mmHg in the Multi-Stent and Trab groups, respectively. After surgery, mean IOP from 1 to 24 months of follow-up ranged from 13.4 to 15.0 mmHg in Multi-Stent eyes, reflecting a reduction of 6.1–7.7 mmHg versus preoperative (29–36%, based on means; $p < 0.001$ at all time points). In Trab eyes, mean IOP from 1 to 24 months ranged from 11.4 to 12.6 mmHg, a




**Defined as a 20% or greater IOP reduction from baseline on the same or fewer medications, without clinically significant safety events (listed in Table 2). Last follow-up duration =15.7 months (Multi-Stent) or 13.1 months (Trab)*
*† Log-Rank (Mantel-Cox)*
*M, month.*

**Fig. 3** Kaplan–Meier survival analysis of safety-adjusted treatment success through 24 months, Multi-Stent and Trab groups

reduction of 9.7–10.9 mmHg versus preoperative (43–49%, based on means; $p < 0.001$ at all time points) (Fig. 4a). At the last follow-up, mean IOP was 14.2 mmHg in Multi-Stent eyes (31% reduction, based on patients' individual paired IOPs; $p < 0.001$) and 12.5 mmHg in Trab eyes (43% reduction, based on patients' individual paired IOPs; $p < 0.001$) (between-group comparison of percentage reduction, $p = 0.006$) (Fig. 4b).

### *Mean Medication Burden*

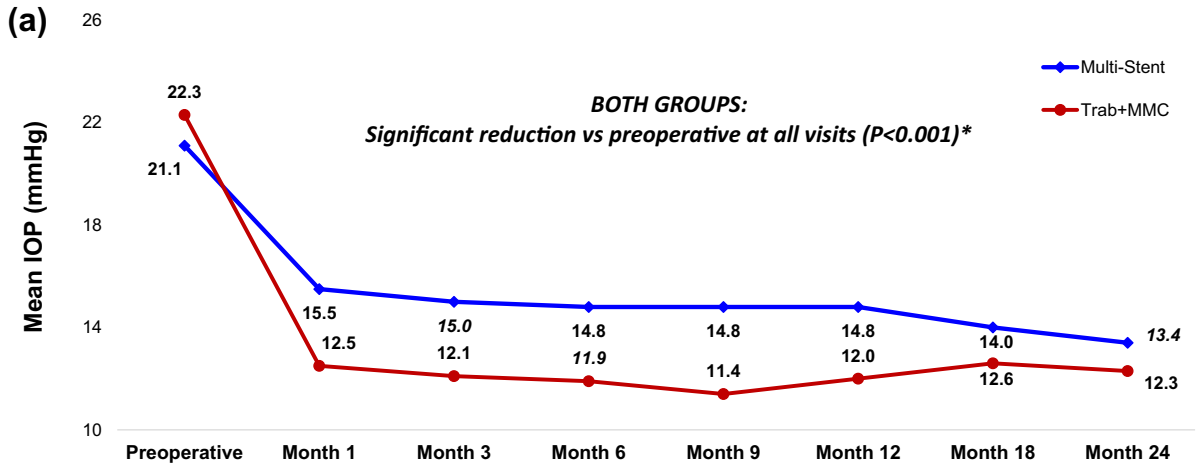
Preoperatively, the mean number of medications was 2.87 and 3.10 medications in the Multi-Stent and Trab groups, respectively. After surgery, mean number of medications from 3 to 24 months of follow-up ranged from 1.24 to 1.62 medications in Multi-Stent eyes, reflecting a reduction of 1.25–1.63 medications versus preoperative (44–57%, based on means; $p < 0.001$ at all time points); in Trab eyes, mean postoperative medication number ranged from 0.15 to 0.95 medications, a reduction of 2.15–2.95 medications versus preoperative (69–95%, based on means; $p < 0.001$ at all time points) (Fig. 5a). At the last follow-up, the mean medication burden was 1.31 medications in Multi-Stent eyes (51% reduction based on patients' individual paired medications, $p < 0.001$) and 0.43 medications in Trab eyes (84% reduction based on patients' individual paired medications, $p < 0.001$) (between-group comparison of percentage reduction, $p < 0.001$) (Fig. 5b).

### *Traditional (Unadjusted) WGA IOP Endpoints*

The proportions of eyes with qualified or complete attainment of target IOP $\leq$ 21 mmHg, $\leq$ 18 mmHg, $\leq$ 15 mmHg, and $\leq$ 12 mmHg, without adjusting for complications and reinterventions, are given in Table 3. There was no significant difference between the Multi-Stent and Trab groups in the proportion of eyes with qualified attainment of target IOP $\leq$ 21 mmHg, $\leq$ 18 mmHg, or $\leq$ 15 mmHg; the remaining upper-limit thresholds were attained by more Trab than Multi-Stent eyes.

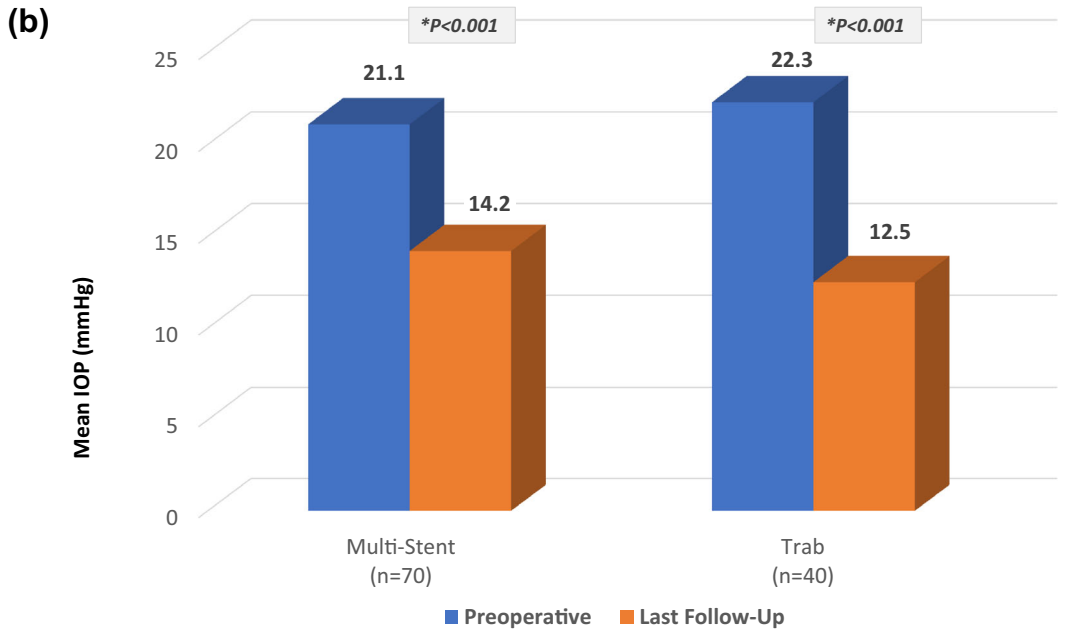
### *Health Economics and QoL*

Additional effectiveness outcomes were measured to serve as proxy outcomes related to health economics and QoL. These included the mean number of clinic visits and/or reinterventions within the first 3 months postoperative; mean total number of reinterventions throughout follow-up; mean time to first




| Visit (# months) | Preop | 1M | 3M | 6M | 9M | 12M | 18M | 24M |
|---|---|---|---|---|---|---|---|---|
| n, Multi-Stent | 70 | 70 | 70 | 61 | 58 | 54 | 26 | 17 |
| n, Trab | 40 | 40 | 40 | 40 | 30 | 30 | 20 | 14 |

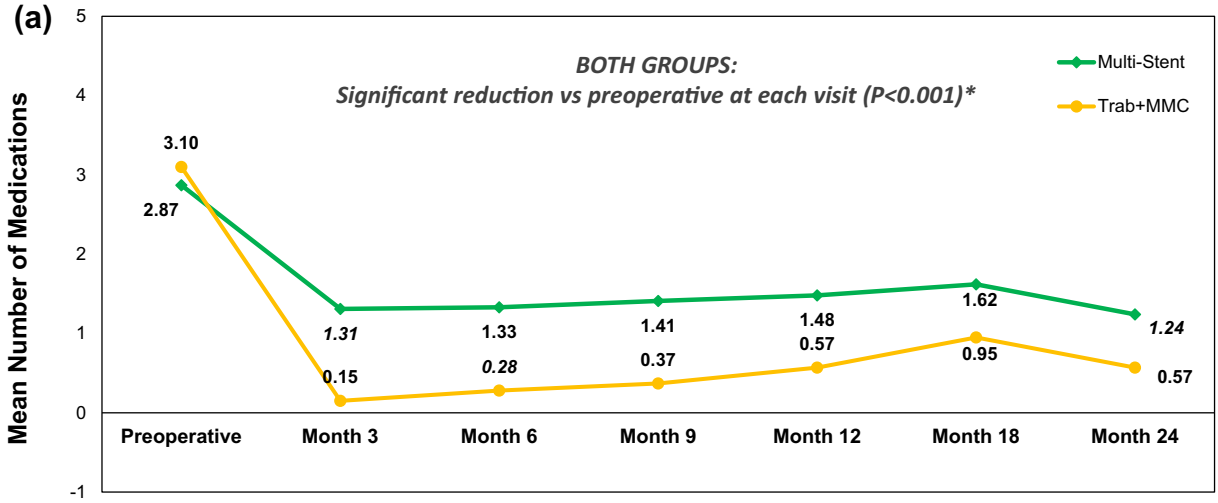
*IOP, intraocular pressure; Trab, trabeculectomy + mitomycin C; M, month*
**Statistical analysis based on means; analysis completed for visits from 1 to 24 months.*




*IOP, intraocular pressure; Trab, trabeculectomy + mitomycin C*
**Statistical analysis based on patients' paired individual IOP's*

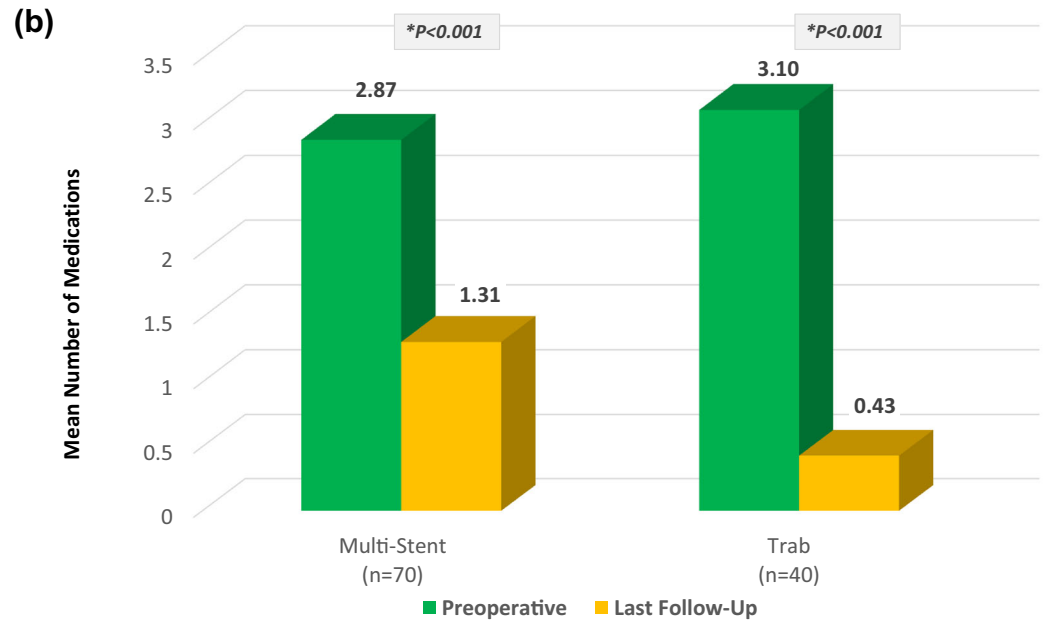
**Fig. 4** **a** Mean IOP over time in Multi-Stent and Trab groups, all available eyes at each visit. **b** Mean IOP at last follow-up vs preoperative in Multi-Stent and Trab groups

reintervention; and mean time to lifting all postoperative restrictions. During the first 3 months postoperative, an average of 3.6 visits were needed for Multi-Stent eyes vs 6.1 visits for




| Visit (# months) | Preop | 3M | 6M | 9M | 12M | 18M | 24M |
|---|---|---|---|---|---|---|---|
| n, Multi-Stent | 70 | 70 | 61 | 58 | 54 | 26 | 17 |
| n, Trab | 40 | 40 | 40 | 30 | 30 | 20 | 14 |

*Trab+MMC, trabeculectomy + mitomycin C; M, month*
**Statistical analysis based on means; analysis completed for visits from 3 to 24 months*




*Trab, trabeculectomy + mitomycin C*
**Statistical analysis based on patients' paired individual medication burdens*

**Fig. 5** **a** Mean number of medications over time in Multi-Stent and Trab groups, all available eyes at each visit. **b** Mean number of medications at last follow-up vs preoperative in Multi-Stent and Trab groups

Trab eyes ($p < 0.001$). Multi-Stent eyes had approximately threefold longer time before first reintervention than Trab eyes (12.2 vs 4.5 months, respectively, $p = 0.01$) and

**Table 3** Traditional (unadjusted) WGA IOP endpoints at last follow-up, Multi-Stent and Trab groups

| IOP outcome | Multi-Stent ($n$ = 70) | Trab–MMC ($n$ = 40) | $p$ value (between-group comparison)[a] |
|---|---|---|---|
| Qualified IOP (± medication), upper limits | | | |
| ≤ 21 mmHg | 69 (98.6%) | 38 (95.0%) | 0.269 |
| ≤ 18 mmHg | 64 (91.4%) | 36 (90.0%) | 0.802 |
| ≤ 15 mmHg | 52 (74.3%) | 34 (85.0%) | 0.191 |
| ≤ 12 mmHg | 24 (34.3%) | 25 (62.5%) | 0.004 |
| Complete IOP (medication-free), upper limits | | | |
| ≤ 21 mmHg | 20 (28.6%) | 29 (72.5%) | < 0.001 |
| ≤ 18 mmHg | 19 (27.1%) | 29 (72.5%) | < 0.001 |
| ≤ 15 mmHg | 18 (25.7%) | 27 (67.5%) | < 0.001 |
| ≤ 12 mmHg | 9 (12.9%) | 21 (52.5%) | < 0.001 |
| IOP lower limit, < 6 mmHg | | | |
| < 6 mmHg | 0 (0.0%) | 1 (2.5%) | 0.184 |

Unadjusted for safety; outcomes according to World Glaucoma Association (WGA) guidelines [60]
*WGA* World Glaucoma Association
[a]Via Student's $t$ test for continuous variables; or chi-square test (Pearson chi-square or Fisher's exact) for categorical variables

**Table 4** Outcomes related to health economics and quality of life

| Outcome | Multi-Stent ($n$ = 70) | Trab–MMC ($n$ = 40) | $p$ value (between-group comparison)[b] |
|---|---|---|---|
| Time to first reintervention (months) | | | |
| $n$ (%) of eyes affected | 9 (12.9%) | 22 (55.0%) | |
| Mean (SD) | 12.2 (6.0) | 4.5 (7.5) | 0.01 |
| Average number of reinterventions per eye, mean (SD) | 0.26 (0.81) | 0.75 (1.01) | 0.006 |
| Number of visits during the first 3 months, mean (SD) | 3.6 (0.7) | 6.1 (1.6) | < 0.001 |
| Time to removal of all postoperative restrictions (days)[a], mean (SD) | 12.6 (3.8) | 32.1 (7.1) | < 0.001 |

[a]Defined as the point at which the patient is no longer under instructions to (a) avoid compressing the eye globe (includes use of a shield while sleeping), (b) avoid exercise and heavy lifting, and/or (c) avoid crowded places such as malls, schools, large gatherings, etc.
[b]Via Student's $t$ test for continuous variables; or chi-square test (Pearson chi-square or Fisher's exact) for categorical variables

threefold lower total number of reinterventions during follow-up (0.26 vs 0.75 mean reinterventions, respectively; $p = 0.006$). The mean time to lifting all postoperative restrictions was 12.6 days for Multi-Stent eyes vs 32.1 days for Trab eyes ($p < 0.001$). Table 4 summarizes these findings.

### *2-Stent vs 3-Stent Subgroup Analysis*

An exploratory subgroup analysis was completed to compare the ability of 2-stent ($n = 34$) vs 3-stent ($n = 36$) eyes to achieve qualified or complete IOP endpoints (IOP $\leq$ 18 mmHg, $\leq$ 15 mmHg, or $\leq$ 12 mmHg). For all three IOP targets, and for both qualified and complete definitions of success, the rates of target IOP attainment were higher in 3-stent than in 2-stent eyes. The difference was apparent in all between-group comparisons; statistical significance was reached in two. Table 5 shows the results of all comparisons with statistical testing.

## Safety Outcomes

Safety data included visual field testing, BCVA, slit-lamp and fundus examinations, gonioscopy, pachymetry, and documentation of adverse events (AEs), secondary surgeries, and procedure-related reinterventions. Assessments were recorded at the following visits: preoperative, operative, day 1, week 1, week 2, and months 1, 3, 6, 9, 12, 18, and 24.

Average VF MD was compared between the preoperative and postoperative visits in both groups. No significant decline was observed in either group: − 10.13 dB preoperative vs − 10.09 dB postoperative in Multi-Stent eyes, and − 10.47 dB preoperative vs − 10.23 dB postoperative in Trab eyes. Likewise, patients' glaucoma severity (i.e., moderate or severe, based on standard VF MD criteria [56]) was unchanged between preoperative and postoperative measurements. These outcomes are provided in Table 6.

**Table 5** 2-Stent vs 3-Stent subgroup analysis: qualified (medicated) and complete (medication-free) attainment of IOP targets ($\leq$ 18, $\leq$ 15, $\leq$ 12 mmHg) at last follow-up

| IOP outcome | 2 Stents ($n = 34$) *n* (%) of eyes | 3 Stents ($n = 36$) *n* (%) of eyes | Two-sided *p* value (between-group comparison)[a] |
|---|---|---|---|
| Qualified IOP attainment ($\pm$ medication) | | | |
| $\leq$ 18 mmHg | 30 (88.2%) | 34 (94.4%) | NS |
| $\leq$ 15 mmHg | 21 (61.8%) | 31 (86.1%) | 0.0198* |
| $\leq$ 12 mmHg | 10 (29.4%) | 14 (38.9%) | NS |
| Complete IOP attainment (medication-free) | | | |
| $\leq$ 18 mmHg | 7 (20.6%) | 12 (33.3%) | NS |
| $\leq$ 15 mmHg | 6 (17.6%) | 12 (33.3%) | NS |
| $\leq$ 12 mmHg | 1 (2.9%) | 8 (22.2%) | 0.028^ |

*NS* not significant ($p \geq 0.05$)
[a]Chi-square test (Pearson chi-square or Fisher's exact) for categorical variables
*Test of proportions
^Fisher's exact test

**Table 6** Visual field mean deviation and glaucoma severity, preoperative vs last follow-up (LFU)

| Visual field mean deviation | | | Glaucoma severity | | | | |
|---|---|---|---|---|---|---|---|
| VF MD | Preop | LFU | | Preop (*n*) | Preop (%) | LFU (*n*) | LFU (%) |
| Multi-Stent ($n$ = 70) | | | | | | | |
| Mean | − 10.13 | − 10.09 | Moderate | 49 | 0.7 | 49 | 0.7 |
| SD | 2.94 | 2.97 | Advanced | 21 | 0.3 | 21 | 0.3 |
| $p$ value | | 0.6776825 | | | | | |
| Trabeculectomy + MMC ($n$ = 40) | | | | | | | |
| Mean | − 10.47 | − 10.23 | Moderate | 26 | 0.65 | 26 | 0.65 |
| SD | 3.28 | 3.22 | Advanced | 14 | 0.35 | 14 | 0.35 |
| $p$ value | | 0.0061175 | | | | | |

*LFU* last follow-up (mean 15.7 months in Multi-Stent group, 13.1 months in Trab group)

***Intraoperative Complications***

Intraoperative complications in Multi-Stent eyes consisted of 3 cases of stent over-implantation. No interventions were undertaken, and no sequelae ensued. Intraoperative complications in Trab eyes included 2 cases of perforated ("buttonholed") conjunctiva, which were remedied intraoperatively with sutures.

***Early Postoperative Complications (< 1 Month Postoperative)***

Early complications were reported in 0 Multi-Stent eyes (0%) vs 12 Trab eyes (30%) ($p < 0.001$). Events included IOP elevation > 10 mmHg vs preoperative (5 cases), bleb failure (3 cases), bleb leak (2 cases), suture dehiscence (1 case), and shallow anterior chamber (1 case).

***Mid-Range Postoperative Complications (1–3 Months Postoperative)***

Complications occurring from 1 to 3 months postoperative were reported in 0 Multi-Stent eyes (0%) vs 7 Trab eyes (17.5%) ($p = 0.011$). Events included 1 case each of bleb leak, suture dehiscence, and IOP < 6 mmHg, and 4 cases of bleb failure.

***Late Postoperative Complications (> 3 Months Postoperative)***

Later-stage complications were reported in 4 Multi-Stent eyes (6%) vs 13 Trab eyes (33%) ($p < 0.001$). In Multi-Stent eyes, this included 3 cases of peripheral anterior synechiae and 1 case of IOP elevation > 10 mmHg vs preoperative. In Trab eyes, cases included bleb failure (9 cases), peripheral corneal thinning (dellen; 2 cases), blebitis (1 case), and clinically significant hypotony (1 case). The complete listing of reported safety events is provided in Table 7.

## DISCUSSION

This retrospective comparative cohort study contributes some of the first data evaluating a trabecular MIGS device vs standard trabeculectomy–MMC in the treatment of moderate and severe glaucoma. The cohort consisted of consecutive patients who came from the same clinical population, had similar baseline characteristics, and underwent either procedure by the same surgeon at a single site; all eyes would have been scheduled for standard filtration surgery if a MIGS option had not been offered as well. This uniformity across groups decreases possible confounding and allows for a consistent comparison between treatment interventions. Given the ongoing need for options that

**Table 7** Intraoperative and postoperative adverse events

| Safety event | Multi-Stent ($n$ = 70) | Trab–MMC ($n$ = 40) | $p$ value (between-group comparison)[a] |
|---|---|---|---|
| Intraoperative | | | |
| Yes | 3 (10.0%) | 2 (5.0%) | NS |
| No | 67 (90.0%) | 38 (95.0%) | |
| Stent over-implantation | 3 (4.3%) | N/A | |
| Conjunctival perforation ("buttonhole") | 0 (0%) | 2 (5.0%) | |
| Early postoperative (< 1 month) | | | |
| Yes | 0 (0%) | 12 (30.0%) | < 0.001 |
| No | 70 (100%) | 28 (70.0%) | |
| IOP spike > 10 mmHg vs preop | 0 (0%) | 5 (12.0%) | |
| Significant bleb leak | N/A | 2 (5.0%) | |
| Bleb failure | N/A | 3 (7.5%) | |
| Suture dehiscence | 0 (0%) | 1 (2.5%) | |
| Shallow AC | 0 (0%) | 1 (2.5%) | |
| Mid-postoperative (1–3 months) | | | |
| Yes | 0 (0%) | 7 (17.5%) | 0.011 |
| No | 70 (100%) | 33 (82.5%) | |
| Significant bleb leak | N/A | 1 (2.5%) | |
| Bleb failure | N/A | 4 (10.0%) | |
| Suture dehiscence | 0 (0%) | 1 (2.5%) | |
| IOP < 6 mmHg | 0 (0%) | 1 (2.5%) | |
| Late postoperative (> 3 months) | | | |
| Yes | 4 (5.7%) | 13 (32.5%) | < 0.001 |
| No | 66 (94.3%) | 27 (67.5%) | |
| IOP spike > 10 mmHg vs preop | 1 (1.4%) | 0 (0%) | |
| Bleb failure | N/A | 9 (22.5%) | |
| Clinically significant hypotony | 0 (0%) | 1 (2.5%) | |
| Peripheral anterior synechiae | 3 (4.3%) | 0 (0%) | |
| Peripheral corneal thinning (dellen) | 0 (0%) | 2 (5.0%) | |

**Table 7** continued

| Safety event | Multi-Stent ($n$ = 70) | Trab–MMC ($n$ = 40) | $p$ value (between-group comparison)[a] |
|---|---|---|---|
| Blebitis | 0 (0%) | 1 (2.5%) | |

Refers to number of eyes affected. If an eye had more than one complication during a given period, the most significant, sight-threatening, or causative/root-origin event was designated
*NS* not significant
[a]Pearson chi-square

have improved safety profiles alongside clinically sufficient IOP lowering, the potential of a viable MIGS option for more advanced glaucoma is highly relevant. In this comparative analysis of multiple-stent implantation (iStent and/or iStent *inject*) vs trabeculectomy, outcomes through up to 2 years postoperative suggest that such a MIGS treatment option may be viable, and that it warrants further investigation.

Specifically, the data showed significantly higher rates of safety-adjusted treatment success in Multi-Stent eyes than in Trab eyes. Mean IOP at LFU reduced significantly in both groups, with the post-stent reduction (31%, $p < 0.001$) being slightly less marked than the post-trab reduction (43%; $p < 0.001$). This IOP difference may be expected given that trabecular bypass does not circumvent the lower floor of episcleral venous pressure. Multi-Stent eyes also were on approximately one more postoperative medication at last follow-up (1.31 vs 0.43 medications, respectively). However, the mean medication number in Multi-Stent eyes still decreased by 51% compared to preoperative values, so from a patient's standpoint, a tangible postoperative-vs-preoperative improvement is still experienced for both IOP and medication burden. Additionally, given the greater number of safety-related visits, complications, and reinterventions in the Trab group, many doctors and patients may consider it a reasonable trade-off to have one additional eyedrop and marginally higher (though still adequately controlled) IOP in exchange for a superior safety profile and QoL.

In order to verify whether IOP was indeed adequately controlled, postoperative visual field outcomes were compared against preoperative fields. The comparison showed stable VF MD, as well as unchanged grading of glaucoma severity, between postoperative and preoperative time points in both groups. Further, if at some point any progression were detected in a Multi-Stent patient, they would still retain the option of more invasive surgery given that the original stent surgery is *ab interno*, conjunctival-sparing, and leaves approximately 97–98% of the angle undisturbed [61].

In addition to the first-in-kind comparative nature of this study, a particularly novel aspect of the data is the inclusion of proxy measures for health economics and quality of life. Of particular economic importance is the total number of visits during the early, middle, and late postoperative periods (before and after 3 months, respectively), as each visit incurs expense to both patients and the healthcare system [42–46]. Many of these extra visits may have been associated with clinically significant safety complications and/or interventions (as evidenced by the significantly higher total number of reinterventions in the Trab group), adding to the potential additional financial burden of Trab surgery over Multi-Stent surgery. Further, the time to lifting all postoperative restrictions was significantly longer in Trab eyes than in Multi-Stent eyes. This difference could have direct economic implications, as it may be thought to roughly approximate the potential number of days a patient is unable to participate fully in work or personal responsibilities.

Furthermore, the study included a subgroup analysis comparing outcomes of 2 vs 3 stents. At all three IOP levels ($\leq$ 18/15/12 mmHg), a higher proportion of 3-stent than 2-stent eyes achieved their target. This difference was apparent, either as a clear trend or with statistical significance, for both qualified and complete IOP outcomes. This is not entirely surprising, as there is existing evidence supporting the benefit of additional stents [20–24].

Certain limitations must be noted in this single-site comparative study. Given the retrospective nature of data collection, it was not possible to perfectly match baseline characteristics of the two groups; and we cannot rule out the possibility of non-quantifiable patient differences between the two groups. Despite this constraint, the groups were well matched for baseline characteristics, including for the most clinically relevant measures such as preoperative IOP, medication burden, glaucoma type, disease severity, and visual field. The only data point differing between the groups was lens status, with more pseudophakic eyes in the Multi-Stent group than in the Trab group. The authors acknowledge that their standard protocol for postoperative restrictions is cautious and comprehensive, and that some clinicians may advocate earlier resumption of unrestricted activity. However, the same restrictions were applied to both groups in this study, so the significant between-group differences are still meaningful. There were no preoperative or postoperative medication washouts, as these would not be appropriate in this real-world clinical population. And finally, visual field outcomes were stable in both groups through up to 24 months postoperative; however, longer monitoring will be necessary to confirm that patients' glaucoma remains controlled.

## CONCLUSIONS

This study provides an informative window on the potential viability of implanting multiple trabecular micro-bypass stents (2 or 3 iStent or iStent *inject* stents) in a standalone surgery to treat moderate and severe treatment-resistant glaucoma. To our knowledge, this is the first study to date that compares multi-stent vs trab surgery, performed in patients from the same clinical population and in the hands of the same surgeon at the same clinical site. As could be expected given the level of invasiveness of filtration surgeries, many of the traditional (unadjusted) WGA IOP endpoints were higher in the Trab group. However, the primary effectiveness outcome, safety-adjusted treatment success, was significantly higher in Multi-Stent eyes.

Given that glaucoma is a permanent condition and patients must live with any surgery-induced complications over their lifetimes, an improved safety profile may outweigh a comparatively smaller IOP reduction vs trabeculectomy in many patients, as captured in the safety-adjusted treatment success endpoint. The improved safety profile also may have direct ramifications for health economics and QoL, as captured in those respective metrics in the dataset. Furthermore, there was a consistent strong trend toward better IOP outcomes with 3 vs 2 stents, aligning with prior research [20–24]. Together these findings indicate a highly favorable benefit–risk balance. They show that standalone implantation of 2 or 3 trabecular bypass stents (iStent or iStent *inject*) may be a viable and safe treatment option for patients with moderate to severe treatment-resistant glaucoma.

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***Author Contributions.*** RG concept and design, completion of surgeries, preoperative/postoperative management, data collection, statistical analysis, manuscript drafting. DMG concept and design, preoperative/postoperative management, manuscript drafting. VMPG concept and design, preoperative/postoperative management, manuscript drafting. AC preoperative and postoperative management, data collection.

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***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.



## REFERENCES

1. Gedde SJ, Herndon LW, Brandt JD, et al. Postoperative complications in the tube versus trabeculectomy (TVT) study during five years of follow-up. Am J Ophthalmol. 2012;153:804–14.

2. Rulli E, Biagioli E, Riva I, et al. Efficacy and safety of trabeculectomy vs nonpenetrating surgical procedures: a systematic review and meta-analysis. JAMA Ophthalmol. 2013;131(12):1573–82.

3. Jampel HD, Musch DC, Gillespie BW, et al. Perioperative complications of trabeculectomy in the collaborative initial glaucoma treatment study (CIGTS). Am J Ophthalmol. 2005;140(1):16–22.

4. Boland MV, Corcoran KJ, Lee AY. Changes in performance of glaucoma surgeries 1994 through 2017 based on claims and payment data for United States Medicare Beneficiaries. Ophthalmol Glaucoma. 2021;S2589–4196(21):00032–6. https://doi.org/10.1016/j.ogla.2021.01.004.

5. Saheb H, Ahmed II. Micro-invasive glaucoma surgery: current perspectives and future directions. Curr Opin ophthalmol. 2012;23:96–104.

6. Businesswire.com. Glaukos announces market-leading clinical milestone of 200 peer-reviewed publications on iStent Technologies. Press Release August 23, 2021. https://www.businesswire.com/news/home/20210823005049/en/Glaukos-Announces-Market-Leading-Clinical-Milestone-of-200-Peer-Reviewed-Publications-on-iStent%C2%AE-Technologies.

7. Samuelson TW, Katz LJ, Wells JM, et al. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmol. 2011;118:459–67.

8. Ferguson TJ, Swan RJ, Bleeker A, et al. Trabecular microbypass stent implantation in

pseudoexfoliative glaucoma: long-term results. J Cataract Refract Surg. 2020;46(9):1284–9.

9. Ferguson TJ, Mechels KB, Dockter Z, et al. iStent trabecular microbypass stent implantation with phacoemulsification in patients with open-angle glaucoma: 6-year outcomes. Clin Ophthalmol. 2020;14:1859–66. https://doi.org/10.2147/OPTH.S247910.

10. Ferguson T, Swan R, Ibach M, Schweitzer J, Sudhagoni R, Berdahl JP. Evaluation of a trabecular microbypass stent with cataract extraction in severe primary open-angle glaucoma. J Glaucoma. 2018;27(1):71–6.

11. Ferguson TJ, Ibach M, Schweitzer J, Karpuk KL, Stephens JD, Berdahl JP. Trabecular microbypass stent implantation with cataract extraction in pigmentary glaucoma. Clin Exp Ophthalmol. 2020;48(1):37–43.

12. Gallardo MJ, Supnet RA. Three-year outcomes of combined trabecular micro-bypass and phacoemulsification in a predominantly Hispanic population with primary open-angle glaucoma. Clin Ophthalmol. 2019;13:869–79.

13. Bargoud AR, Lira J, An S, Walsman SM, Herndon LW, Khouri AS. Trabecular microbypass stent and phacoemulsification in African American patients with open-angle glaucoma: outcomes and effect of prior laser trabeculoplasty. J Glaucoma. 2021;30(1):89–93.

14. Neuhann TH, Hornbeak DM, Neuhann RT, Giamporcaro JE. Long-term effectiveness and safety of trabecular micro-bypass stent implantation with cataract surgery in patients with glaucoma or ocular hypertension: 5-year outcomes. J Cataract Refract Surg. 2019;45(3):312–20.

15. Nitta K, Yamada Y, Morokado S, Sugiyama K. iStent trabecular micro-bypass stent implantation with cataract surgery in a Japanese glaucoma population. Clin Ophthalmol. 2020;15(14):3381–91.

16. Ferguson TJ, Ibach M, Schweitzer J, et al. Trabecular microbypass stent implantation in pseudophakic eyes with open-angle glaucoma: long-term results. J Cataract Refract Surg. 2019;45(4):414–20.

17. Ziaei H, Au L. Manchester iStent study: long-term 7-year outcomes. Eye (Lond). 2020. https://doi.org/10.1038/s41433-020-01255-6.

18. Fechtner RD, Voskanyan L, Vold SD, et al. Five-year, prospective, randomized, multi-surgeon trial of two trabecular bypass stents versus prostaglandin for newly-diagnosed open-angle glaucoma. Ophthalmol Glaucoma. 2019;2(3):156–66.

19. Saheb H, Donnenfeld ED, Solomon KD, et al. Five-year outcomes prospective study of two first-generation trabecular micro-bypass stents (iStent®) in open-angle glaucoma. Curr Eye Res. 2020;46(2):224–31.

20. Katz LJ, Erb C, Carceller Guillamet A, et al. Long-term tirated IOP control with one, two or three trabecular micro-bypass stents in open-angle glaucoma subjetcs on topical hypotensive medication: 42-month outcomes. Clin Ophthalmol. 2018;12:255–62.

21. Belovay GW, Naqi A, Chan BJ, Rateb M, Ahmed II. Using multiple trabecular micro-bypass stents in cataract patients to treat open-angle glaucoma. J Cataract Refract Surg. 2012;38(11):1911–7.

22. El Wardani M, Bergin C, Achache F, Sharkawi E. Evaluating the trabecular micro-bypass stent combined with phacoemulsification compared to phacoemulsification alone. Klin Monatsbl Augenheilkd. 2015;232:442–5.

23. Hunter K, Fjield T, Heitzmann H, Shandas R, Kahook M. Characterization of micro-invasive trabecular bypass stents by ex vivo perfusion and computational flow modeling. Clin Ophthalmol. 2014;8:499–506.

24. Bahler C, Hann C, Fjield T, Haffner D, Heitzmann H, Fautsch MP. Second-generation trabecular meshwork bypass stent (iStent inject) increases outflow facility in cultured human anterior segments. Am J Ophthal. 2012;153(6):1206–13.

25. Samuelson TW, Sarkisian SR Jr, Lubeck DM, et al. Prospective, randomized, controlled pivotal trial of iStent inject trabecular micro-bypass in primary open-angle glaucoma and cataract: two-year results. Ophthalmology. 2019;126(6):811–21.

26. Clement C, Howes F, Ioannidis AS, et al. Two-year multicenter outcomes of iStent inject trabecular micro-bypass stents combined with phacoemulsification in various types of glaucoma and ocular hypertension. Clin Ophthalmol. 2020;14:3507–17.

27. Ferguson TJ, Dockter Z, Bleeker A, et al. iStent inject trabecular microbypass stent implantation with cataract extraction in open-angle glaucoma: early clinical experience. Eye Vis (Lond). 2020;20(7):28.

28. Guedes RAP, Gravina DM, Paletta Guedes VM, Chaoubah A. Two-year comparative outcomes of first- and second-generation trabecular micro-bypass stents with cataract surgery. Clin Ophthalmol. 2021;5(15):1861–73.

29. Hengerer FH, Auffarth GU, Riffel C, Conrad-Hengerer I. Prospective, non-randomized, 36-month study of second-generation trabecular micro-bypass

stents with phacoemulsification in various types of glaucoma. Ophthalmol Ther. 2018;7(2):405–15.

30. Hengerer FH, Auffarth GU, Riffel C, Conrad-Hengerer I. Second-generation trabecular micro-bypass stents as standalone treatment for glaucoma: a 36-month prospective study. Adv Ther. 2019;36(7):1606–17.

31. Huang AS, Penteado RC, Papoyan V, Voskanyan L, Weinreb RN. Aqueous angiographic outflow improvement after trabecular micro-bypass in glaucoma patients. Ophthalmol Glaucoma. 2019;2:11–21.

32. Neuhann R, Neuhann T. Second-generation trabecular micro-bypass stent implantation: retrospective analysis after 12- and 24-month follow-up. Eye Vis (Lond). 2020;10(7):1.

33. Salimi A, Abu-Nada M, Harasymowycz P. Matched cohort study of cataract surgery with and without trabecular micro-bypass stent implantation in primary angle-closure glaucoma. Am J Ophthalmol. 2021. https://doi.org/10.1016/j.ajo.2020.12.032.

34. Salimi A, Watt H, Harasymowycz P. Three-year outcomes of second-generation trabecular microbypass stents (iStent inject) with phacoemulsification in various glaucoma subtypes and severities. J Glaucoma. 2021;30(3):266–75.

35. Salimi A, Clement C, Shiu M, Harasymowycz P. Second-generation trabecular micro-bypass (iStent inject) with cataract surgery in eyes with normal-tension glaucoma: one-year outcomes of a multicentre study. Ophthalmol Ther. 2020;9(3):585–96.

36. Berdahl J, Voskanyan L, Myers JS, Katz LJ, Samuelson TW. iStent inject trabecular micro-bypass stents with topical prostaglandin as standalone treatment for open-angle glaucoma: 4-year outcomes. Clin Exp Ophthalmol. 2020;48(6):767–74.

37. Lindstrom R, Sarkisian SR, Lewis R, Hovanesian J, Voskanyan L. Four-year outcomes of two second-generation trabecular micro-bypass stents in patients with open-angle glaucoma on one medication. Clin Ophthalmol. 2020;14:71–80.

38. Healey PR, Clement CI, Kerr NM, Tilden D, Aghajanian L. Standalone iStent trabecular micro-bypass glaucoma surgery: a systemic review and meta-analysis. J Glaucoma. 2021. https://doi.org/10.1097/IJG.0000000000001805.

39. Samuelson TW, Singh IP, Williamson BK, et al. Quality of life in primary open-angle glaucoma and cataract: an analysis of VFQ-25 and OSDI from the iStent inject® pivotal trial. Am J Ophthalmol. 2021. https://doi.org/10.1016/j.ajo.2021.03.007.

40. Schweitzer JA, Hauser WH, Ibach M, et al. Prospective interventional cohort study of ocular surface disease changes in eyes after trabecular micro-bypass stent(s) implantation (iStent or iStent inject) with phacoemulsification. Ophthalmol Ther. 2020;9(4):941–53.

41. Al Habash A, Nagshbandi AA. Quality of life after combined cataract and minimally invasive glaucoma surgery in glaucoma patients. Clin Ophthalmol. 2020;14:3049–56.

42. Berdahl JP, Khatana AK, Katz LJ, et al. Cost-comparison of two trabecular micro-bypass stents versus selective laser trabeculoplasty or medications only for intraocular pressure control for patients with open-angle glaucoma. J Med Econ. 2017;20(7):760–6.

43. Ahmed IIK, Podbielski DW, Patel V, et al. A Canadian cost-utility analysis of 2 trabecular microbypass stents at time of cataract surgery in patients with mild to moderate open-angle glaucoma. Ophthalmol Glaucoma. 2020;3(2):103–13.

44. Bartelt-Hofer J, Flessa S. Comparative efficacy and cost-utility of combined cataract and minimally invasive glaucoma surgery in primary open-angle glaucoma. Int Ophthalmol. 2020;40(6):1469–79.

45. Wang SY, Singh K, Stein JD, Chang RT. Ocular antihypertensive medication use after iStent implantation concurrent with cataract surgery vs cataract surgery alone in a large US Health Care Claims Database. JAMA Ophthalmol. 2019;137(1):21–7.

46. Teus M, Belda J, Lavín C, et al. Cost-effectiveness analysis of iStent Inject® implantation during cataract surgery compared to cataract surgery alone for mild to moderate open-angle glaucoma patients in Spain. Expert Rev Ophthalmol. 2021;16(4):319–28.

47. Favre H, Sherry E, Waldman C, Foster A. Comparison of iStent inject, Hydrus Microstent, and Kahook dual blade in a predominantly Hispanic population with primary open angle glaucoma. In: Poster presented at the annual meeting of the association for research in vision and ophthalmology (ARVO), Virtual/San Francisco, May 2–6, 2021.

48. Chen S, Raju L, Goyal H. Evaluation of three minimally invasive glaucoma surgeries (MIGS) combined with phacoemulsification for treatment of open-angle glaucoma and visually significant cataract. In: Poster presented at the annual meeting of the association for research in vision and ophthalmology (ARVO), Virtual/San Francisco, May 2–6, 2021.

49. David JA, Tran JA, Grenier CP, Al-Dujaili LJ, Fang Z, Morgan MG. Outcomes of cataract extraction with

Kahook dual blade goniotomy versus iStent trabecular micro-bypass device with minimum two-year follow up. In: Poster presented at the annual meeting of the association for research in vision and ophthalmology (ARVO), Virtual/San Francisco, May 2–6, 2021.

50. Bechay J, Patel S, Lam S, et al. Hemorrhagic complications following trabecular bypass microstent surgery in the setting of antithrombotic therapy. In: Poster presented at the annual meeting of the association for research in vision and ophthalmology (ARVO), Virtual/San Francisco, May 2–6, 2021.

51. Holmes DP, Clement CI, Nguyen V, et al. A comparative study of 2-year outcomes for Hydrus or iStent inject microinvasive glaucoma surgery implants with cataract surgery. In: Paper presented at the World Glaucoma e-Congress, June 30–July 3, 2021.

52. Grover DS, Flynn WJ, Bashford KP, et al. Performance and safety of a new ab interno gelatin stent in refractory glaucoma at 12 months. Am J Ophthalmol. 2017;183:25–36.

53. Schlenker MB, Gulamhusein H, Conrad-Hengerer I, et al. Efficacy, safety, and risk factors for failure of standalone ab interno gelatin microstent implantation versus standalone trabeculectomy. Ophthalmology. 2017;124(11):1579–88.

54. Marcos Parra MT, Salinas López JA, López Grau NS, Ceausescu AM, Pérez Santonja JJ. XEN implant device versus trabeculectomy, either alone or in combination with phacoemulsification, in open-angle glaucoma patients. Graefes Arch Clin Exp Ophthalmol. 2019;257(8):1741–50.

55. Wagner FM, Schuster AK, Emmerich J, Chronopoulos P, Hoffmann EM. Efficacy and safety of XEN®-Implantation vs. trabeculectomy: data of a "real-world" setting. PLoS ONE. 2020;15(4): e0231614. https://doi.org/10.1371/journal.pone.0231614.

56. Hodapp E, Parrish RK II, Anderson DR. Clinical decisions in glaucoma. St Louis: Mosby; 1993.

57. Wasielica-Poslednik J, Schmeisser J, Hoffmann EM, et al. Fluctuation of intraocular pressure in glaucoma patients before and after trabeculectomy with mitomycin C. PLoS ONE. 2017;12(10): e0185246. https://doi.org/10.1371/journal.pone.0185246.

58. Pfeiffer N, Grehn F. Improved suture for fornix-based conjunctival flap in filtering surgery. Int Ophthalmol. 1992;16(4–5):391–6. https://doi.org/10.1007/bf00917998.

59. United States clinicaltrials.gov database. Investigation of the Glaukos® Trabecular Micro-Bypass System, Model iS3, in Subjects With Refractory Glaucoma. Accessed Aug 30, 2021. https://clinicaltrials.gov/ct2/show/NCT03639870.

60. Shaarawy TM, Sherwood MB, Grehn F, editors. World Glaucoma Association guidelines on design and reporting of glaucoma surgical trials. Amsterdam: Kugler; 2009.

61. Samuelson TW, on behalf of the iStent inject Pivotal Trial Study Team. Three-year effectiveness and safety of 2nd-generation trabecular micro-bypass (iStent inject). In: Paper at the annual meeting of the American Academy of Ophthalmology (AAO), Virtual Meeting, November 13–15, 2020.