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ORIGINAL RESEARCH

Five-Year Outcomes of iStent *inject* Implantation With or Without Phacoemulsification in Eyes with Open-Angle Glaucoma

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ABSTRACT

Introduction: Minimally invasive glaucoma surgery (MIGS) has become more widespread in open-angle glaucoma (OAG) management. Broad evidence has shown a greater decrease in mean intraocular pressure (IOP) when cataract surgery is combined with MIGS, compared with cataract surgery alone. In this study, we evaluated the effectiveness and safety of second-generation trabecular micro-bypass implantation (iStent *inject*®) either in combination with cataract surgery (Combined subgroup) or as a standalone procedure (Standalone subgroup) in eyes with OAG. Our hypothesis was that implementing interventional glaucoma management would provide meaningful reductions in IOP and topical medication burden.

Methods: This long-term retrospective consecutive case series included patients with mild to moderate OAG who received the iStent *inject*® Trabecular Micro-bypass stent with or without phacoemulsification between 2018 and 2024. Eligible patients were ≥ 18 years of age with mild or moderate OAG, cataract requiring surgery (for the Combined subgroup), and the need for IOP and/or medication reduction. Study outcomes included mean and proportional analyses of IOP and medications over time. Analyses were completed for the overall population and for the Combined/Standalone and Mild/Moderate subgroups.

Results: The study included 271 eyes with mean age 69 years and a mean of 40 months of follow-up (range 10–79 months). In the overall population, mean IOP decreased from 16.4 mmHg at baseline to 13.7 mmHg at last follow-up ($p = 0.001$), while the mean number of medications decreased from 2.24 at baseline to 0.62 at last follow-up ($p = 0.001$). IOP reductions were also significant in the Combined/Standalone subgroups and in the Mild/Moderate subgroups ($p = 0.001$ for all), and all subgroups experienced increased proportions of eyes on no topical medications at last follow-up versus preoperative ($p = 0.001$ for all).

Conclusion: This 5-year real-world study showed significant and sustained reductions

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in IOP and topical medication burden following iStent *inject* trabecular micro-bypass with or without cataract surgery in eyes with mild and moderate open-angle glaucoma.

Keywords: Glaucoma; Minimally invasive glaucoma surgery (MIGS); iStent *inject*®; Cataract; Long-term; Intraocular pressure; Second-generation; Stent; Trabecular micro-bypass

Key Summary Points

Why carry out this study?

The management of open-angle glaucoma (OAG) utilizing minimally invasive glaucoma surgery (MIGS) has become more widespread as an effective way to control intraocular pressure (IOP) and mitigate the challenges of topical therapy.

In this retrospective study we assessed 5-year real-world outcomes following implantation of second-generation trabecular micro-bypass implantation (iStent *inject*®) either in combination with cataract surgery or as a standalone procedure in eyes with mild or moderate OAG.

The study hypothesis was that iStent *inject* implantation could effectively and safely reduce IOP and medication burden over the long term.

What was learned from this study?

The results of this real-world longitudinal study of patients who received iStent *inject* with or without cataract surgery showed favorable efficacy and safety across a 5-year period.

Meaningful reduction in IOP and medication were observed for the overall population and across subgroup analyses (combined/standalone and mild/moderate).

INTRODUCTION

Glaucoma is a leading cause of blindness globally, estimated to have caused permanent vision loss in 3.6 million individuals over the age of 50 years in 2020 [1]. With the anticipated growth of the aging population, it has been estimated that 111.8 million people will be affected by glaucoma by 2040 [2]. If untreated, glaucoma results in progressive, permanent and vision loss. The key objective in treatment is lowering intraocular pressure (IOP) as this has demonstrated efficacy in reducing progression in patients with ocular hypertension and open-angle glaucoma (OAG). Most often, topical pharmacotherapy to lower IOP has been the mainstay of treatment for decades, with the aim to delay progression of visual field loss, and this therapy has been shown to be effective and reasonably safe. The use of topical medications to treat glaucoma, however, can be associated with substantial side effects, damage to the ocular surface, ongoing financial burden, and limited effectiveness due to some degree of nonadherence in up to 90% of patients [3–10].

Recently, the management of OAG utilizing minimally invasive surgical interventions has become more widespread. Such interventions can include selective laser trabeculoplasty (SLT), minimally invasive glaucoma surgery (MIGS), and sustained-release procedural pharmaceuticals. Within the past two decades, MIGS procedures have become recognized as surgical interventions that both deliver improved outcomes and can be employed earlier in the disease process. This interventional management strategy has enhanced the surgeon's armamentarium for the treatment of mild to moderate glaucoma, and even severe glaucoma. A recent publication of data from the American Academy of Ophthalmology IRIS Registry reported that of > 200,000 eyes receiving glaucoma surgeries in the USA between 2013 and 2018, the iStent® implant (Glaukos Corp., San Clemente, CA, USA) was the most commonly performed MIGS, being used primarily for individuals with normal tension glaucoma (NTG) or primary OAG (POAG) [11].

The iStent® Trabecular Micro-Bypass Stent (containing one stent) was the first MIGS device to be approved by the United States Food and

Drug Administration (FDA) and, more recently, the second-generation iStent *inject*® (containing 2 stents) was also approved for use. Both iterations of the iStent create a patent pathway to bypass the trabecular meshwork and allow for direct aqueous flow into Schlemm's canal, thus decreasing IOP, and clinical studies conducted in a variety of settings have demonstrated significant reductions in IOP and medication burden and a favorable safety profile. Studies of up to 42 months duration have evaluated the impact on IOP and medication reduction after single and multiple stent placement, performed in a standalone procedure or combined with cataract surgery, and confirmed that although the majority of IOP reduction is the result of the first stent, each additional stent provides further reduction in IOP and medication use [12–14]. We previously completed a study in which we compared both iStent and iStent *inject* system and observed significant and safe IOP and medication reductions with both devices, with a trend toward greater efficacy and fewer adverse events with the iStent *inject* system compared to the iStent system [15].

In Brazil, the iStent *inject* procedure is approved to be performed in conjunction with cataract surgery or as a standalone procedure. Although it has been shown that cataract surgery may independently lower IOP among patients with co-existing cataract and glaucoma, broad evidence has shown a statistically significant greater decrease in mean IOP postoperatively when cataract surgery is combined with MIGS, compared with cataract surgery alone, and a 50% less likelihood of having to use one or more topical medications postoperatively with a combined procedure [16, 17]. Previous studies have also shown that when cataract surgery is combined with MIGS procedures, it is more cost effective [18, 19]. Specific to the iStent *inject* combined with cataract surgery compared to cataract surgery alone, Samuelson and colleagues reported the findings of a 2-year randomized multicenter trial, with the results showing that clinically and statistically greater reductions in medication-free IOP were achieved after iStent *inject* implantation with cataract surgery in eyes with mild to moderate POAG as compared to cataract surgery alone, with excellent safety through the 2-year study period [20]. More recently, Fan Gaskin et al. reported that in their similarly designed 2-year, randomized single-center trial of eyes with mild to moderate POAG, 57% of those undergoing the combined procedure were on no medications at 2 years, compared to 36% of those who had only cataract surgery [21].

Several studies have also demonstrated longer-term safety and preservation of structure and function following iStent *inject* implantation with phacoemulsification. In a study conducted in Canada, Salimi and colleagues reported that significant and sustained reductions in IOP and medication burden were achieved across 3 years in their real-world cohort of 124 eyes with different subtypes of glaucoma, ranging from mild to severe, while structural and functional parameters remained stable [22]. Clement et al. also reported similar findings in a 3-year-long multicenter study in 273 eyes from Australia. In addition, Hengerer and colleagues confirmed favorable efficacy and safety over a 7-year period in their 125-eye study, which is the longest follow-up of any iStent *inject* implantation published to date [24].

Here, we report the efficacy and safety outcomes of iStent *inject* implantation with and without combined phacoemulsification over a 5-year follow-up period in eyes with mild to moderate OAG. Our hypothesis was that this intervention would provide meaningful reductions in IOP and topical medication burden, and that these reductions would be seen across all subgroups. This study is current one of the longest-term iStent *inject* studies available, and the longest-term study performed outside of Europe or North America to date.

METHODS

This was a retrospective case series of consecutive patients with mild to moderate OAG who received the iStent *inject* Trabecular Micro-bypass either as the sole procedure (Standalone subgroup) or in combination with phacoemulsification (Combined subgroup). All cases were performed from January 2018 to January 2024 in a

single tertiary ophthalmology center in Brazil. The local Institutional Review Board approved the study (Ethics in Research Committee under the number CAAE: 21327319.5.0000.5139), and all data accessed complied with relevant data protection and privacy regulations. The research methods comply with the Declaration of Helsinki. All patients gave informed consent prior to undergoing the procedure. Separate consent for data analysis was not needed due to the study's retrospective design and non-interventional review of medical records from the surgeon's existing practice.

Main study outcomes included the changes versus baseline in mean IOP and number of medications used over time. Additional outcomes included the proportion of eyes achieving IOP ≤ 12 mmHg, ≤ 15 mmHg, and ≤ 18 mmHg over the study period and the proportion of eyes using zero, one, two, three, or more topical medications over the same study period.

Eligible patients in the Combined subgroup were ≥ 18 years of age and had mild or moderate OAG, cataract requiring surgery, and the need for IOP and/or medication reduction. The only difference between the Combined subgroup and Standalone subgroup was that those in the Standalone subgroup were already pseudophakic in the study eye. Any eyes presenting with significant coexisting ocular diagnoses that could confound the outcomes of the surgery were excluded. The staging of glaucoma was classified using the Hodapp–Parrish–Anderson visual field criteria that are commonly used in clinical studies, with mild glaucome defined as mean deviation [MD] no worse than – 6 dB; moderate glaucome as MD worse than – 6 dB but no worse than – 12 dB; and severe glaucome as MD worse than – 12 dB [25].

Each patient in the Combined subgroup underwent phacoemulsification and intraocular lens implantation using the standard technique through a clear corneal incision. Prior to proceeding to the iStent *inject* procedure, and for those receiving iStent *inject* as the sole procedure, the patient's head and surgical microscope were positioned to confirm an appropriate gonioscopic view of the trabecular meshwork and nasal angle. Viscoelastic with or without intracameral miotic was injected into the anterior chamber to deepen the angle, enhance visualization of Schlemm's canal and maintain the anterior chamber. The iStent *inject* inserter was inserted through the existing temporal corneal incision used for phacoemulsification, then advanced across the anterior chamber to the nasal angle, where the first stent was implanted into Schlemm's canal. Then, without withdrawing the inserter from the eye, the surgeon laterally repositioned the injector tip to implant the second stent, approximately 2 to 3 clock hours away from the first stent. Following confirmation of proper stent placement and seating after implantation, viscoelastic was removed and proper sealing of the corneal incision was ensured [27].

All procedures were performed under local anesthesia. Patients were prescribed postoperative topical antibacterial medication (moxifloxacin 4 times/day for 10 days) and topical anti-inflammatory medication (dexamethasone 4 time/day for 10 days, with tapering to 3 time/day for 5 days, 2 time /day for 5 days, 1 time/day for 5 days, then stop), as per the surgeon's standard practice.

Data were analyzed preoperatively and at annual time points following the procedure. Data collected included IOP, number of medications, visual fields, adverse events, and secondary glaucoma procedures. Statistical analysis was performed using SPSS statistical software (SPSS IBM Corp., Armonk, NY, USA) and a p value of 0.05 was defined as the threshold for statistical significance. Four analysis populations were assessed: (1) the 'Observed cohort' of all eyes at each time point ($n = 271$ at baseline, $n = 102$ at 5 years); (2) 'Last-follow-up analysis' (LFU), including data from all visits, regardless of patients' length of follow-up ($n = 271$ at baseline, $n = 271$ at last follow-up); (3) Mild/Moderate glaucoma subgroups; (4) and Combined/Standalone subgroups. Analyses of mean IOP and medications were performed across the 5 years of follow-up in the Observed cohort and in the Mild/Moderate and Combined/Standalone subgroups. LFU analyses of mean and proportional outcomes of IOP and medications were performed in the Observed cohort, Mild/Moderate subgroups, and Combined/Standalone subgroups. As this was a retrospective study, sample size was determined

empirically, rather than via formal sample size calculation. The number of cases was determined by the number of iStent inject surgeries completed over a given time period (January 2018 to January 2024).

RESULTS

The study enrolled 271 eyes of 271 subjects (Observed cohort $n=271$) and the mean follow-up period was 40 months (range 10–79 months). At baseline, the mean age was 69 (range 27–88) years, 55% were female, and most subjects were of European or Hispanic descent (83%). Subject characteristics are summarized in Table 1.

The majority of eyes in the cohort were diagnosed with POAG (93%), and the mean (± SD) number of medications at baseline was 2.24 ± 0.90. The stage of glaucoma at baseline was mild for 86% of eyes and moderate for 14%, with a mean preoperative Humphrey Visual Field mean deviation (HVF MD) of −3.49 ± 2.18 dB. Overall, at baseline the mean IOP was 16.4 ± 3.4 mmHg, including those eyes in the Mild subgroup with a mean IOP of 16.2 ± 3.4 mmHg, and 17.8 ± 3.2 mmHg for those in the Moderate subgroup (Table 1).

The majority of eyes ($n=214$, 79%) received iStent *inject* in combination with cataract surgery (Combined subgroup), while 21% of eyes ($n=57$) underwent iStent *inject* implantation alone (Standalone subgroup). The preoperative mean IOP was 16.0 ± 3.3 mmHg in the Combined subgroup and 17.8 ± 3.4 mmHg in the Standalone subgroup.

IOP outcomes

The mean annual IOPs at years 1 through 5 postoperatively were compared to those at baseline.

In the Observed cohort, statistically significant reductions in IOP were achieved in all available eyes from baseline at each annual visit: baseline 16.4 mmHg; year 1 time point 13.4 mmHg; year 5 time point 14.1 mmHg (all $p<0.05$) (Fig. 1). In the LFU population, the final mean (± SD) IOP was 13.7 ± 1.9 mmHg, which is significantly lower than the mean baseline IOP of 16.4 ± 3.4 mmHg ($p=0.001$) (Fig. 2). A statistically significantly higher proportion of eyes achieved thresholds of mean IOP ≤ 12 mmHg, ≤ 15 mmHg, and ≤ 18 mmHg, respectively, at their last follow-up visit, when compared to baseline. Notably, a high proportion of eyes (82.7%) achieved an IOP of ≤ 15 mmHg at their last follow-up visit, compared to 43.9% preoperatively (Fig. 3).

Subgroup Analyses

Stratification by procedure type (Combined/Standalone subgroups) For eyes in the Combined subgroup ($n=214$), the mean (± SD) IOP at baseline was 16.0 ± 3.3 mmHg, which had decreased significantly at last follow-up (13.6 ± 1.1 mmHg, $p=0.001$). In the Standalone subgroup ($n=57$), the mean preoperative IOP was 17.8 ± 3.4 mmHg, which had significantly declined at last follow-up to 14.2 ± 2.3 mmHg ($p=0.001$). In addition to this last follow-up analysis, the mean IOP and number of medications at the annual visits across the 5 years of follow-up were calculated (see Table 2 for the Combined and Standalone subgroups).

Stratification by glaucoma severity (Mild/Moderate) For eyes with mild glaucoma ($n=234$), the mean (± SD) baseline IOP of 16.2 ± 3.4 mmHg significantly decreased to 13.6 ± 1.9 mmHg ($p=0.001$) at the last follow-up. In eyes with moderate glaucoma ($n=37$), the mean baseline IOP of 17.8 ± 3.2 mmHg at baseline significantly decreased to 14.4 ± 2.1 mmHg at the last follow-up ($p=0.001$). The vast majority of eyes in both the Mild and Moderate subgroups achieved an IOP of ≤ 18 mmHg at their last follow-up visit (99.1% and 94.6%, respectively; $p=0.001$). Improvements to the ≤ 12 mmHg and ≤ 15 mmHg thresholds were similarly significant for the Mild subgroup (32.1% and 83.8% for each threshold, respectively; $p=0.001$).The difference in IOP in eyes in the Moderate subgroup did not achieve statistical significance in comparison to baseline, with 21.6% and 75.7% of eyes achieving the ≤ 12

Table 1 Summary of baseline characteristics of overall patient cohort

Parameter	Total (*N* = 271 eyes of 271 subjects)
Age (years)	
Mean (SD)	69 (10)
Min, Max	27, 88
Gender, n subjects (%)	
Male	122 (45%)
Female	149 (55%)
Race, n (%)	
European or Hispanic descent	226 (83%)
African descent	11 (4.1%)
Mixed	34 (13%)
Glaucoma subtype, n (%)	
Primary open-angle glaucoma	252 (93%)
Other	19 (7%)
Glaucoma stage n (%)	
Mild	234 (86%)
Moderate	37 (14%)
Humphrey Visual Field mean deviation, dB	
Mean (SD)	-3.49 (2.18)
Min, Max	-11.88, -0.34
Preoperative intraocular pressure, mmHg	
Mean (SD)	16.4 (3.4)
Min, Max	10, 30
Number of medications at baseline, n	
Mean (SD)	2.24 (0.9)
Min, Max	0, 5
Procedure, n (%)	
iStent *inject* in combination with phacoemulsification (Combined subgroup)	214 (79%)
iStent *inject*, alone (Standalone subgroup)	57 (21%)
Subgroup parameters	
Preoperative IOP by glaucoma stage, mmHg, mean (SD)	

Table 1 continued

Parameter	Total ($N = 271$ eyes of 271 subjects)
Mild ($n = 234$ eyes)	16.2 (3.4)
Moderate ($n = 37$ eyes)	17.8 (3.2)
Preoperative IOP by procedure, mmHg, mean (SD)	
iStent *inject* in combination with phacoemulsification ($n = 214$ eyes) (Combined subgroup)	16.0 (3.3)
iStent *inject*, alone ($n = 57$ eyes) (Standalone subgroup)	17.8 (3.4)

dB Decibels, *HVF* Humphrey Visual Field, *IOP* intraocular pressure, *Max* maximum, *MD* mean deviation, *Min* minimum, *SD* Standard deviation

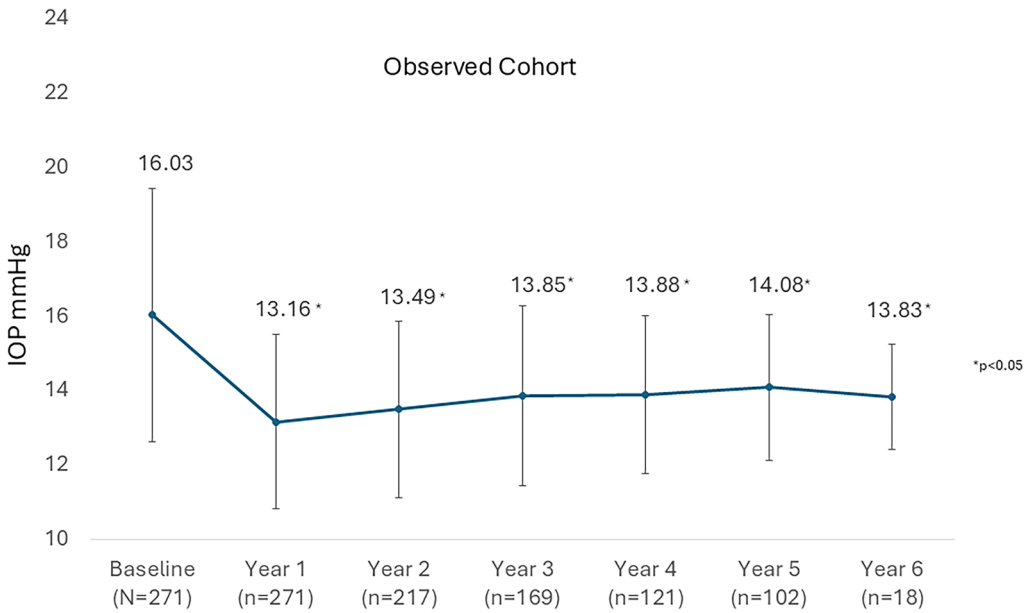

Fig. 1 Mean intraocular pressure (*IOP*) for the Observed cohort of all available eyes at each time point. Asterisk indicates a significant difference from baseline at $^*p < 0.05$

mmHg and ≤ 15mmHg thresholds, respectively. In addition to these last follow-up analyses, the mean IOP and medications at annual visits across the 5 years were calculated, as shown in Table 3 for the Mild and Moderate subgroups.

Number of Glaucoma Medications

In the Observed cohort, statistically significant reductions in the mean (± SD) number of medications were achieved from baseline to each annual visit: baseline: 2.24 ± 0.90 medications; year 1 time point 0.55 ± 0.88 medications; year 5 time point 0.76 ± 1.05 medications (all $p < 0.05$) (Fig. 4). There was a significant decrease in the number of glaucoma medications required by the time patients reached their last follow-up visit. At last follow-up, the mean number of medications was 0.62 ± 0.95 compared to 2.24 ± 0.90 at baseline ($p = 0.001$). (Fig. 5) At baseline, no medications at all were being used in

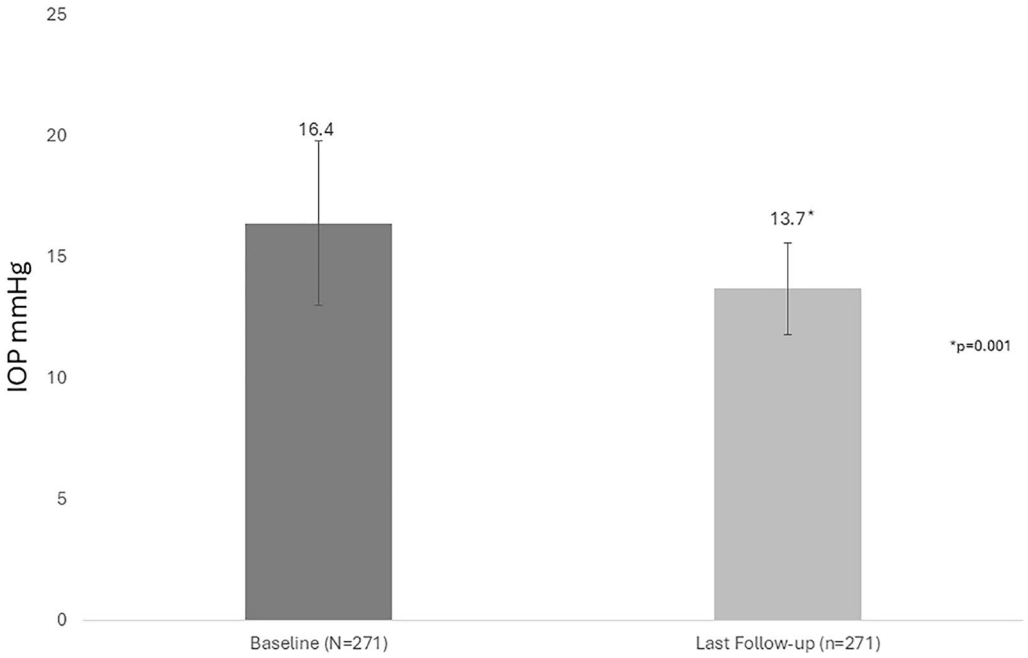

Fig. 2 Mean intraocular pressure (*IOP*) at baseline and last follow-up ($n = 271$ at both time points). Asterisk indicates a significant difference from baseline at $^*p < 0.05$

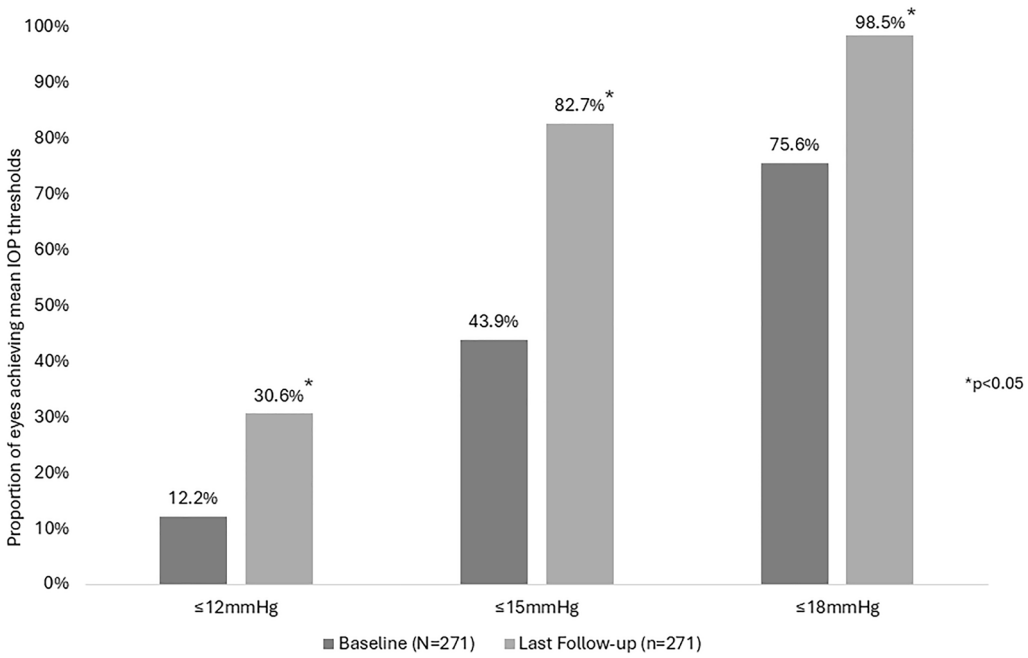

Fig. 3 Proportions of eyes achieving intraocular pressure (*IOP*) thresholds at baseline and last follow-up ($n = 271$ at both time points). Asterisk indicates a significant difference from baseline at $^*p < 0.05$

Table 2 Mean intraocular pressure and number of medications over time in the Combined and Standalone subgroups

Parameters	Study time point					
	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
	Mean IOP, Combined subgroup					
n	214	214	166	127	86	73
Mean	16.0	13.2	13.4	13.8	13.8	14.0
SD	3.3	2.1	2.3	2.5	2.0	1.9
p-value		0.001	0.001	0.001	0.001	0.001
	Mean IOP, Standalone subgroup					
n	57	57	51	42	35	29
Mean	17.8	14.1	13.8	14.0	14.0	14.3
SD	3.4	2.9	2.6	2.3	2.4	2.3
p-value		0.001	0.001	0.001	0.001	0.001
	Mean number of medications, Combined subgroup					
n	214	214	166	127	86	73
Mean	2.14	0.35	0.42	0.44	0.41	0.38
SD	0.91	0.71	0.81	0.85	0.82	0.78
p-value		0.001	0.001	0.001	0.001	0.001
	Mean number of medications, Standalone subgroup					
n	57	57	51	42	35	29
Mean	2.60	1.32	1.53	1.67	1.69	1.72
SD	0.78	1.02	1.08	1.00	1.05	1.07
p-value		0.001	0.001	0.001	0.001	0.001

IOP Intraocular pressure, *SD* standard deviation

1.8% of eyes, which significantly increased to 66.4% at last follow-up ($p=0.001$). Conversely, 42.8% of patients were using ≥ 3 medications at baseline, which declines to 5.5% at the last visit ($p<0.001$) (Fig. 6).

Subgroup Analyses

Stratification by procedure type (Combined/Standalone) The mean (± SD) number of medications used at baseline for those in the Combined subgroup was 2.14 ± 0.91 and was 2.60 ± 0.78 for those in the Standalone subgroup. At the last follow-up, mean medication use was reduced to 0.39 ± 0.78 for the Combined subgroup ($p=0.001$) and 1.46 ± 1.09 for the Standalone subgroup ($p=0.0925$). Notably, 76.2% of eyes that received the Combined procedure and 30.0% of eyes having the Standalone procedure required no medications at the last visit, compared to 2.3% and 0% of eyes in the respective subgroups preoperatively (both $p=0.001$). In addition to this last follow-up analysis, the mean IOP and medications at annual visits across the 5 years of the follow-upwere calculated, as shown in Table 2 for the Combined and Standalone subgroups.

Table 3 Mean intraocular pressure and number of medications over time in the Mild and Moderate subgroups

Parameter	Study time point					
	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
	Mean IOP, eyes with mild glaucoma					
n	234	234	182	138	92	81
Mean	16.2	13.2	13.4	13.8	13.7	14.0
SD	3.4	2.3	2.3	2.5	2.2	1.9
p-value		0.001	0.001	0.001	0.001	0.001
	Mean IOP, eyes with moderate glaucoma					
n	37	37	35	31	29	21
Mean	17.8	14.1	14.1	14.0	14.3	14.5
SD	3.2	2.3	2.4	2.2	1.9	2.2
p-value		0.001	0.001	0.001	0.001	0.001
	Mean number of medications, eyes with mild glaucoma					
n	234	234	182	138	92	81
Mean	2.17	0.46	0.53	0.59	0.54	0.59
SD	0.92	0.82	0.88	0.93	0.89	0.92
p-value		0.001	0.001	0.001	0.001	0.001
	Mean number of medications, eyes with moderate glaucoma					
n	37	37	35	31	29	21
Mean	2.68	1.11	1.43	1.42	1.52	1.43
SD	0.67	1.02	1.22	1.23	1.21	1.29
p-value		0.001	0.001	0.001	0.001	0.001

IOP Intraocular pressure, *SD* standard deviation

Stratification by glaucoma severity (Mild/Moderate) The mean (± SD) number of medications used at baseline in eyes with mild and moderate glaucoma was 2.17 ± 0.92 and 2.68 ± 0.67, respectively. At the last follow-up, the mean number of medications had declined to 0.51 ± 0.87 for those eyes with mild glaucoma ($p = 0.001$) and to 1.30 ± 1.20 for those with moderate glaucoma ($p = 0.0446$). At last follow-up, 71.0% of the eyes in the Mild subgroup (vs. 2.1% preoperatively, $p = 0.001$) and 37.8% of eyes in the Moderate subgroup (vs. 0% preoperatively, $p = 0.001$) were not using any medications. In addition to these last follow-up analyses, the mean IOP and medications at annual visits across 5 years were calculated; these are shown in Table 3 for the Mild and Moderate subgroups.

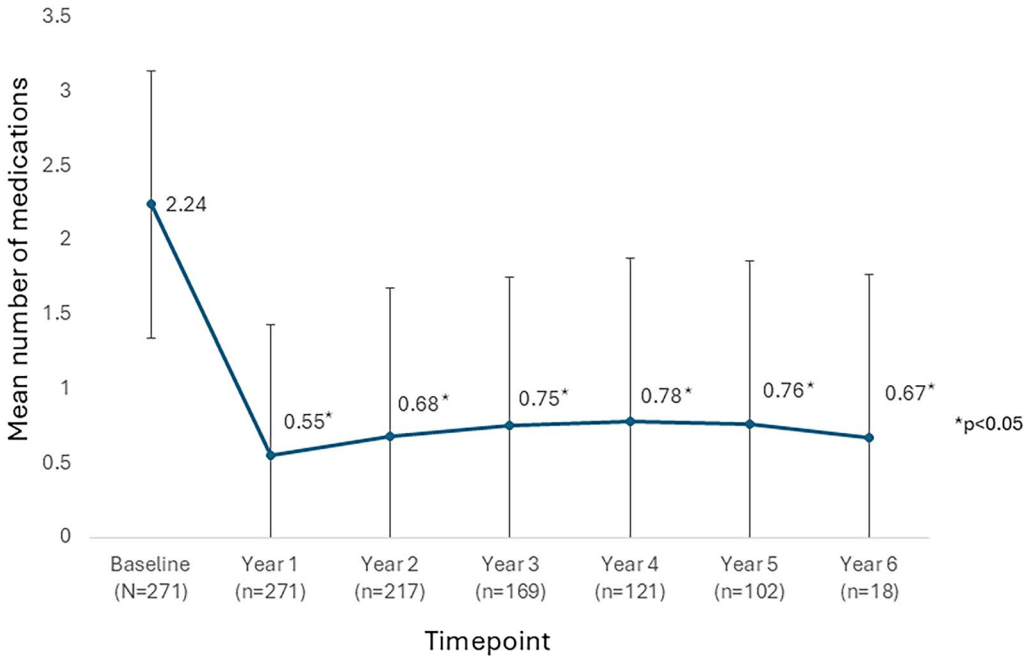

Fig. 4 Mean number of medications in the Observed cohort of all available eyes at each time point. Asterisk indicates a significant difference from baseline at $^*p < 0.05$

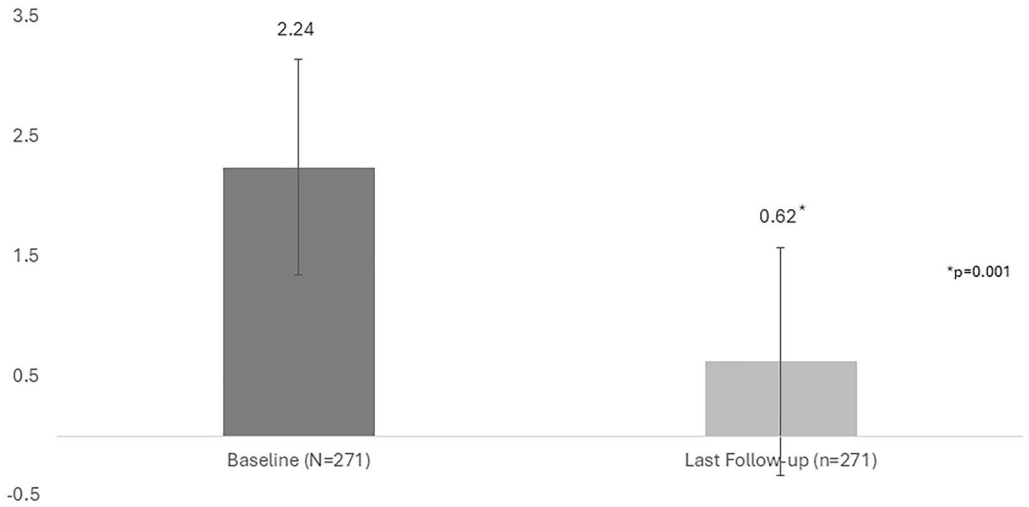

Fig. 5 Mean number of medications at baseline and last follow-up ($n = 271$ at both time points). Asterisk indicates a significant difference from baseline at $^*p < 0.05$

Safety

Intraoperative adverse events included intraoperative bleeding in 3 cases (1.1%); these cases were controlled with viscoelastic injection into the anterior chamber. Postoperative adverse events included one case of peripheral anterior synechiae into the implant ostium, which

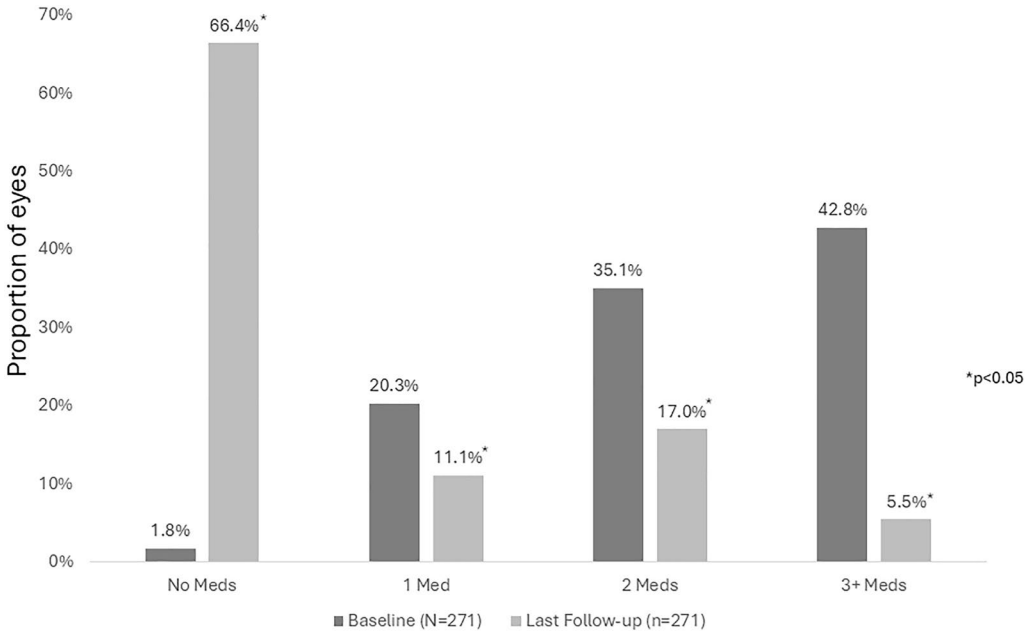

Fig. 6 Proportions of eyes using 0, 1, 2, and 3+ medications at baseline and last follow-up ($n = 271$ at both time points). Asterisk indicates a significant difference from baseline at $^*p < 0.05$

was treated with a peripheral iridotomy using Nd:YAG laser under gonioscopic visualization.

Over the 5-year follow-up period, four eyes underwent a secondary procedure due to IOP and/or medication above target: two eyes had trabeculectomy (at 1 month and 8 months, respectively), and two eyes had SLT (at 7 months and 9 months, respectively). The two eyes undergoing trabeculectomy had an IOP above target despite the use of three topical antiglaucoma medications. The two eyes undergoing SLT presented an above-target IOP that could not be treated with topical medications due to ocular allergies and poor tolerability.

Visual Fields

A small but consistent improvement in visual field was detected in the overall Observed cohort. Average (± SD) visual field MD at the final post-operative visit was − 3.41 ± 2.21 dB, compared to − 3.49 ± 2.18 dB preoperatively ($p = 0.015$). The difference was statistically but not clinically significant. In the Combined subgroup, the average visual field MD at last follow-up was − 3.18 ± 1.89 dB, compared to − 3.25 ± 1.85 dB preoperatively ($p = 0.062$). In the Standalone subgroup, the average visual field MD at the last follow-up was − 4.25 ± 2.99 dB, compared to − 4.38 ± 2.98 dB preoperatively ($p = 0.108$).

DISCUSSION

This real-world longitudinal study of patients who received the iStent *inject* stent with or without cataract surgery showed favorable efficacy and safety for up to 5 years. Statistically significant reductions in IOP and the number of medications were observed for the entire cohort for the duration of the study period, and these reductions were observed across the subgroup analyses (Combined/Standalone and Mild/Moderate) and in the last follow-up analysis. Safety was favorable, including relatively few adverse events or secondary procedures. Visual field MD improved slightly, although this could have been due to cataract extraction and/or increased familiarity with the test. The findings

of this study (e.g., 16.5% IOP reduction and 72.3% reduction in number of medications at the last follow-up) are relatively consistent with prior literature on the iStent *inject*® system. For example, in the Canadian 3-year study by Salimi et al., mean IOP was reduced by 22%, mean medication burden was reduced by 51%, and favorable safety included stable best-corrected visual acuity (BCVA), visual field (VF), retinal nerve fiber layer (RNFL) thickness, and ganglion cell inner plexiform layer (GCIPL) thickness after iStent inject implantation with cataract surgery [22]. The 3-year Australian multicenter study by Clement et al., which also included concomitant cataract surgery, reported a mean IOP reduction of 15.5% and a mean medication reduction of 68.5%, with 71.4% of eyes being fee of medication at 3 years [23]. In that study, safety was favorable across glaucoma subtypes, severities, and surgeons, with few adverse events, stable VF, RNFL, and central corneal thickness (CCT); and over the 3-year period, filtering surgery was required in only 2.9% of eyes [23].

In terms of study design, among all previously published studies, our study is most similar to the 7-year study by Hengerer and colleagues, which examined outcomes of iStent *inject* implantation with or without phacoemulsification in eyes with relatively high preoperative disease burden [24]. In these eyes, iStent *inject* implantation with or without phacoemulsification resulted in significant and durable reductions in IOP (up to 44%) and medication burden (up to 76%) over the 7-year period. No filtration surgeries were required over the follow-up period, and only 4.84% of eyes experienced clinically significant VF loss. In comparison, the present study, completed in a patient population with a relatively lower disease burden at baseline, exhibited a lower percentage reduction in IOP (16.5% at last follow-up) and a similar percentage reduction in medications (72.3%). The lesser IOP reduction can be attributed to the well-recognized pattern of higher preoperative IOP yielding greater absolute and percentage reductions in IOP postoperatively. Safety in the current study was similarly favorable as that in the Hengerer et al. study [24], with filtering surgery in only two eyes (< 1% of total) and stable visual fields through last follow-up.

Reduction in mean medication use was particularly noteworthy in the present study, with two thirds of eyes not requiring any topical medication at their last follow-up compared to only 1.8% preoperatively. Adherence to a daily topical treatment regimen can be very challenging and complex for patients as they are required to successfully self-administer one or more medications, potentially several times per day, for a lifetime. Studies have demonstrated that nonadherence is a key risk factor for glaucoma progression and poor functional outcomes [27, 28]. Beyond adherence, identified challenges of topical therapy include associated costs, inadequate penetration of the corneal surface, ocular surface disease, fluctuations in IOP, and diminished quality of life [29]. Additionally, some patients are unable to use topical medications due to certain comorbidities or dangerous interactions with systemic medications [30].

The broader use of an interventional glaucoma approach to glaucoma management to reduce or eliminate medication burden in patients with glaucoma, especially at earlier stages of the disease, has a range of well-recognized benefits, both clinically and for the patient [29–35]. These include more consistent IOP control and prevention of disease progression, reduced long-term costs, reduced incidence of medication-related side-effects, and reduction or elimination of the need for patient adherence [29, 36]. Additionally, IOP fluctuations can occur with topical therapies, and they have been identified as a significant and independent risk factor for glaucomatous progression, but are reduced with interventional management [37, 38]. Studies have also documented significant improvement in quality of life with reduced topical medication use, associated with freedom from strict and complex medication regimens, reduced side effects, and significant improvement in ocular surface health [26, 39].

The majority of patients in the present study received the combined phacoemulsification and iStent *inject* procedure. Other studies of iStent *inject* used in combination with cataract surgery in the treatment of mild to moderate POAG have similarly shown good efficacy and safety profiles and limited postoperative sequelae [15, 22–24, 40–53]. These studies have consistently

demonstrated clinically important reductions in IOP and medication burden, with follow-up duration ranging from 6 months to 7 years. The current study reports on patients with a follow-up of 5 years post-procedure, allowing for assessment of the durability of iStent *inject* in reducing IOP and medication burden. This is particularly important due to the increasing longevity of the population and the chronic nature of glaucoma.

Certain limitations should be discussed in this study. The study was retrospective, occurred at a single center, had no medication washout period, and was limited to mild/moderate glaucoma. Additionally, reported medication use was based on routine clinical practice, rather than on a controlled protocol, and diurnal IOP measurements were not assessed, as these were not done in normal clinical care. Although VFs were measured and analyzed, RNFL thickness was not, so this could be the subject of future analyses. An additional subject of future research could be a prospective study comparing iStent inject and cataract surgery versus cataract surgery alone. These limitations notwithstanding, we believe this population to be highly representative of those patients presenting to real-world practice.

CONCLUSION

In conclusion, these long-term real-world results demonstrate significant reductions in IOP and in the number of topical glaucoma medications required following iStent *inject* Trabecular Microbypass implantation with or without cataract surgery. This study represents one of the longest-term follow-up periods for iStent *inject*, providing 5 years of safety and efficacy results in both combined and standalone surgical settings, and in eyes of both mild and moderate glaucoma severities.

The present study also could be a promising springboard for future research. For example, further studies could include a detailed analysis of VF outcomes, inclusion of RNFL measurements, and completion of diurnal IOP measurements. A prospective study comparing iStent inject implantation with cataract surgery versus cataract surgery alone also may be informative.

Implementing interventional glaucoma management in eyes with mild and moderate glaucoma provides the opportunity to provide more consistent IOP control, helping to slow disease progression and also limit or remove the challenges associated with patient adherence. Importantly, reducing topical medication use decreases the incidence of local and systemic medication-related side-effects and maintains ocular surface health. Achieving these long-term durability and safety results of iStent *inject* combined with phacoemulsification in a real-world, consecutive cohort, followed for up to 5 years, supports the generalizability of these findings to ophthalmic practice.

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Declarations

Conflict of Interest. Ricardo Augusto Paletta Guedes: Abbvie (consultant, speaker); Alcon (consultant); Baush Lomb (consultant, speaker); Cristalia (consultant, speaker); Glaukos (consultant, speaker); OftaVision (consultant, speaker). Daniela Marcelo Gravina: None. Vanessa Maria Paletta Guedes: None. Daniel Augusto Guedes Moraes: None. Alfredo Chaoubah: None.

Ethical Approval. The local Institutional Review Board approved the study (Ethics in Research Committee under the number CAAE: 21327319.5.0000.5139), and all data accessed complied with relevant data protection and privacy regulations. The research methods comply with the Declaration of Helsinki. All patients gave informed consent prior to undergoing the procedure. Separate consent for data analysis was not needed due to the study's retrospective design and non-interventional review of medical records from the surgeon's existing practice.

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