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ORIGINAL RESEARCH

Two-Year Multicenter Outcomes of iStent *inject* Trabecular Micro-Bypass Stents Combined with Phacoemulsification in Various Types of Glaucoma and Ocular Hypertension

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Purpose: This multicenter study evaluated 2-year effectiveness and safety following implantation of two second-generation trabecular micro-bypass stents (iStent *inject*®) with phacoemulsification.

Materials and Methods: This was a retrospective study of iStent *inject* implantation with phacoemulsification by nine surgeons across Australia. Eyes had mild to advanced glaucoma (predominantly primary open-angle/POAG, appositional angle-closure/ACG, or normal-tension /NTG) or ocular hypertension (OHT), and cataract. Evaluations included intraocular pressure (IOP); medications; proportions of eyes with 0 or ≥2 medications, reduced/stable medications versus preoperative, and IOP ≤15 mmHg; visual acuity; cup-to-disc ratio (CDR); visual fields (VF); adverse events; and secondary surgery.

Results: A total of 340 eyes underwent surgery and had 24-month follow-up data. At 24 months, mean IOP decreased by 16% from 16.4±4.7 mmHg preoperatively to 13.7±3.1 mmHg ($p<0.001$), and 77% of eyes achieved IOP of ≤15 mmHg versus 49% preoperatively ($p<0.001$). Mean number of medications decreased by 67% to 0.49±0.95 versus 1.49±1.20 preoperatively ($p<0.001$), with 74% of eyes medication-free versus 25% preoperatively ($p<0.001$), and 14% of eyes on ≥2 medications versus 46% preoperatively ($p<0.001$). Medication burden was reduced or stable in 98% of eyes versus preoperative. Stratified analyses showed significant IOP and medication reductions across glaucoma subtypes (POAG, ACG, NTG, OHT): 13–22% for IOP ($p<0.01$ for all) and 62–100% for medication ($p<0.001$ for all). Favorable safety included few adverse events; stable CDR, VF, and visual acuity; and filtering surgery in only 8 eyes (2.4%) over 2 years.

Conclusion: This 340-eye multicenter dataset provides robust evidence of the safety and efficacy of iStent *inject* implantation with phacoemulsification, with significant and sustained IOP and medication reductions through 2 years. Results were similarly favorable across glaucoma subtypes (including POAG, ACG, NTG, OHT) and were attained across various glaucoma severities, clinical sites, and surgeons, highlighting the real-world versatility and utility of this treatment modality.

Keywords: microinvasive glaucoma surgery, MIGS, glaucoma, iStent *inject*, intraocular pressure, second-generation, multicenter

Introduction

As the leading cause of irreversible blindness worldwide, glaucoma is expected to increase in prevalence even further in coming years, expanding from 76 million patients affected in 2020 to 95.4 million patients in 2030.[1] Glaucoma treatment focuses on decreasing intraocular pressure (IOP), which is typically achieved

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through ocular hypotensive medication, laser therapy, micro-invasive glaucoma surgery (MIGS), and/or traditional filtering surgeries such as trabeculectomy or tube shunt.[2]

For a given patient, the choice of treatment often depends on numerous factors, such as disease severity, rate of progression, treatment compliance, medication hypersensitivities, or surgical and medical history. Along the spectrum of treatment options, MIGS procedures have increasingly filled a critical gap that previously existed between more conservative therapies (such as medications) and higher-risk filtering surgeries. The IOP reduction achieved with MIGS devices is expected to be more modest than that of filtering surgery, and MIGS procedures are typically employed earlier in the glaucoma treatment algorithm than filtering surgery. However, in an overall risk-benefit calculation for a given patient, it is important to consider the risks of filtering surgery (eg, endophthalmitis, hypotony, blebitis, choroidal hemorrhage or effusion)[3–5] as well as its five-year failure rates (~50%).[3]

The iStent® trabecular micro-bypass stent (Glaukos Corporation, San Clemente, CA, USA) was the first MIGS device approved by the US Food and Drug Administration (FDA). It has been the subject of some of the most broad-ranging research to-date of the MIGS devices, with outcomes through seven years in a variety of glaucoma subtypes, and in both standalone usage or combined with cataract surgery.[6–22] The more recently introduced iStent *inject* trabecular micro-bypass, containing two stents with second-generation design, has quickly gained traction as well, with outcomes reported through four years postoperative.[23–39] The evidence for both devices has consistently shown sustained IOP and medication reductions alongside a favorable safety profile.

A prior publication[23] reported 1-year multicenter outcomes of iStent *inject* implantation with cataract surgery in 165 eyes from five surgeons in Australia. The cohort included various subtypes of glaucoma, with the most predominant diagnoses being primary open-angle glaucoma (POAG), appositional angle-closure glaucoma (ACG), pseudoexfoliative glaucoma (PXG), and ocular hypertension (OHT). The results showed a 23.2% IOP reduction and 71.5% medication reduction from preoperative, with over three-fourths of patients medication-free (on zero medications) at 12 months (vs 17.6% preoperatively). The present report shows 2-year outcomes from these five surgeons as well as from four additional surgeons, for a total of 340 eyes from nine surgeons across Australia.

Materials and Methods

Study Population

This study was a retrospective outcome assessment of pooled data from nine surgeons across Australia. Records were reviewed to identify eyes implanted with iStent *inject* in the setting of cataract surgery between January 2016 and February 2018. Allowed diagnoses included primary open-angle glaucoma, pseudoexfoliative glaucoma, normal-tension glaucoma, pigmentary glaucoma, combined-mechanism glaucoma, appositional angle-closure glaucoma (ACG) and ACG suspects, or ocular hypertension. Consistent with clinical and regulatory guidelines, all eyes were eligible for cataract surgery and needed additional glaucoma intervention due to inadequate IOP control, visual field progression, heavy medication burden, and/or nonadherence with topical therapy; eyes were not eligible for iStent *inject* surgery if they had significant ocular comorbidities, active ocular inflammation, or synechial angle closure. Efficacy was quantified by mean IOP and number of medications; and proportional analyses of eyes on zero medications, eyes on ≥2 medications, eyes with the same or decreased medication burden versus preoperative, and eyes with IOP ≤15 mmHg. Safety outcomes included corrected distance visual acuity (CDVA), cup-to-disc ratio (CDR), visual field (VF), surgical complications, postoperative adverse events, and secondary surgical interventions.

iStent *inject* Device and Implantation Technique

The iStent *inject* trabecular micro-bypass system contains two biocompatible heparin-coated titanium stents, each with four lateral outlet lumens to allow for multidirectional aqueous egress from the anterior chamber. The stents are pre-loaded in a single-use sterile injector that is advanced ab internally under gonioscopic guidance through the phacoemulsification incision at the close of cataract surgery. After advancing the injector to the nasal angle, the stents are implanted two clock hours apart through two separate regions of the trabecular meshwork into Schlemm's canal. This placement, completed in a single intraocular entry, allows access to up to six clock hours of collector channels for aqueous outflow.[39] The viscoelastic is then removed, the eye is irrigated with balanced salt solution, and the

wound is confirmed to be patent. Following surgery, patients were prescribed each surgeon's standard post-operative medication regimen, which usually included a topical antibiotic for 1–2 weeks and a topical steroid (typically a prednisolone formulation such as prednefrin forte) tapered over 4 weeks.

All patients signed an informed consent to allow for the retrospective evaluation of their de-identified clinical data. All data were collected in accordance with the tenets of the Declaration of Helsinki, and the study received ethics committee approval from the Royal Australian and New Zealand College of Ophthalmology Human Research Ethics Committee. Descriptive statistics were used to summarize pre- and postoperative data, including means (± standard deviation) and proportional analyses. Paired t-tests were used to compare pre- and postoperative mean IOP and medication values. The McNemar test was used to compare the proportions of eyes with IOP ≤15 mmHg or ≤18 mmHg, and the proportions of eyes on 0 medications or on ≥2 medications. Results were considered significant for p-values <0.05. Patients have been followed for 24 months, and follow-up continues.

Results

Patient Population

Of 421 total eyes that underwent cataract surgery with iStent *inject* trabecular micro-bypass stent implantation, 340 eyes of 230 patients reached 24 months of follow-up by the time of data collection; these eyes constitute the consistent cohort analyzed in this report. Preoperative demographic and ocular characteristics are summarized in Table 1. Most patients were Caucasian, and the most common diagnoses were POAG (67%), appositional ACG or ACG suspects (10%), ocular hypertension or glaucoma suspects (8%), and normal-tension glaucoma (NTG, 6%). Approximately 35% of eyes (119/340) had a history of prior glaucoma procedure(s), most commonly a laser trabeculoplasty and/or laser peripheral iridotomy; 2 eyes had undergone prior trabeculectomy, which was non-functioning at the time of iStent *inject* surgery. Approximately 76% of eyes had mild glaucoma based on visual field criteria (Hodapp-Anderson-Parrish grading scale).[40]

IOP and Medications

Figures 1 and 2 depict the mean and proportional analysis of IOP from preoperative to 24 months postoperative. At 24 months, mean IOP decreased by 16% from 16.4±4.7 mmHg preoperatively to 13.7±3.1 mmHg (p<0.001); 77% of eyes achieved IOP ≤15 mmHg versus 49% preoperatively (p<0.001); and 93% of eyes had IOP ≤18 mmHg versus 77% preoperatively (p<0.001). Figures 3 and 4 display the mean and proportional analysis of medication burden from preoperative to 24 months postoperative. At 24 months, the mean number of medications decreased by 67% to 0.49±0.95 versus 1.49±1.20 preoperatively (p<0.001), with 74% of eyes medication-free versus 25% preoperatively (p<0.001), and only 14% of eyes on ≥2 medications versus 46% preoperatively (p<0.001). Patients' medication regimen decreased or remained the same in all but 98% of eyes (332/340) versus preoperative.

Outcomes were stratified by glaucoma subtype for the four most prevalent diagnoses in the cohort (POAG n=227, ACG n=35, OHT n=28, NTG n=20). Within these analyses, significant reductions in IOP and medications were achieved across all glaucoma subtypes. At 24 months versus baseline, mean IOP reduced by 14% in POAG eyes (p<0.001), 19% in ACG eyes (p<0.001), 22% in OHT eyes (p<0.001), and 13% in NTG eyes (p=0.007) [Figure 5]. At 24 months, medication reductions versus baseline were 65% in POAG eyes, 74% in ACG eyes, 100% in OHT eyes, and 62% in NTG eyes (p<0.001 for all) [Figure 6].

Safety

Successful implantation of two stents was achieved in all but 2 eyes (338/340 or 99.4%); in those 2 eyes, only 1 stent was implanted but meaningful reductions in IOP and medication were still observed through two years (one eye had final IOP 13 mmHg on 1 medication vs baseline IOP 18 mmHg on 2 medications; the other eye had final IOP 20 mmHg on 1 medication vs baseline IOP 26 mmHg on 3 medications). Over two years of follow-up, there were no adverse events occurring at a rate of 2% or greater, a threshold frequently used in MIGS clinical studies.[24,41] The adverse events that did occur were mild, transient, and resolved with minimal to no intervention and without incurring sequelae. Nearly all eyes (96%) achieved CDVA of 20/40 or better at two years, up from 90% preoperatively. Mean CDR remained stable at 24 months (0.71 ± 0.16) versus baseline (0.69 ± 0.17) (p=0.263). The average visual field mean deviation also was stable at 24 months (−4.90 ± 5.56 dB) versus preoperative (−4.60 ± 4.93 dB) (p=0.191) [Table 2].

Table 1 Demographic and Preoperative Ocular Characteristics

		N = 340 Eyes of 230 Patients		
Age (years) (data from 339 eyes)	Mean ± SD	73.0	±	7.7
	Range	42	–	90
Gender (data from 340 eyes)	Male/Female	43%/57%		
Race/Ethnicity (data from 308 eyes)	White	95.5%		
	Asian	3.2%		
	Hispanic	0.6%		
	Arabic	0.6%		
Type of Glaucoma (data from 340 eyes)		n %		
	POAG	227		66.76%
	Appositional ACG or ACG suspects	35		10.29%
	OHT/glaucoma suspect	28		8.24%
	NTG	20		5.88%
	PXG	10		2.94%
	CMG	5		1.47%
	PG	10		2.94%
	Uveitic	3		0.88%
	Neovascular	1		0.29%
	Angle recession	1		0.29%
Eyes with prior glaucoma surgical or laser procedures (data from 340 eyes)	No	221		65.0%
	Yes[a]	119		35.0%
C:D ratio (data from 310 eyes)	Mean ± SD	0.70	±	0.17
CDVA 20/40 or better (data from 340 eyes)	% (n/N)	89.7% (305/340)		
VF MD (dB) (data from 299 eyes)	Mean ± SD	−4.619	±	4.998
Central Corneal Thickness (μm) (data from 267 eyes)	Mean ± SD	537	±	37
Glaucoma Severity[b]	Mild	227		75.9%
	Moderate	50		16.7%
	Severe	22		7.4%
IOP (mmHg) (data from 340 eyes)	Mean ± SD	16.4	±	4.7
Number of medications (data from 340 eyes)	Mean ± SD	1.49	±	1.20
	Range	0	–	5

Notes: Not all preoperative measurements were available for all eyes. [a]Includes 117 eyes with prior laser procedures [laser peripheral iridotomy and/or laser trabeculoplasty] and 2 eyes with prior trabeculectomy that was no longer functioning; some eyes had more than one prior procedure. [b]Consistent with Hodapp–Anderson–Parrish visual field criteria. Mild: VF MD no worse than −6 dB, moderate: VF MD worse than −6 dB but no worse than −12 dB, severe: VF MD worse than −12 dB.
Abbreviations: POAG, primary open-angle glaucoma; ACG, appositional angle-closure glaucoma; OHT, ocular hypertension; NTG, normal-tension glaucoma; PXG, pseudoexfoliative glaucoma; CMG, combined-mechanism glaucoma; PG, pigmentary glaucoma; IOP, intraocular pressure; SD, standard deviation; CDVA, corrected distance visual acuity; MD, mean deviation; VF, visual field; C:D, cup-to-disc.

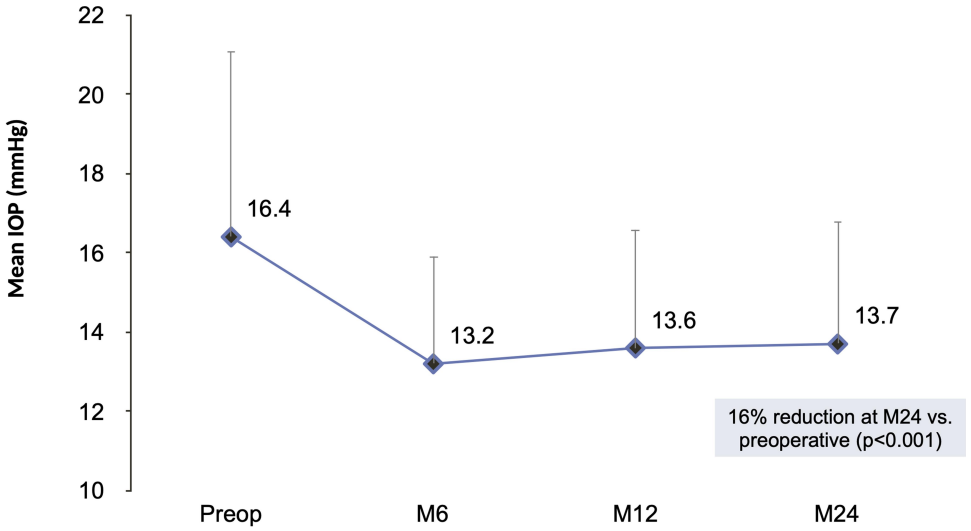

Figure 1 Mean IOP through 24 months postoperative, all eyes (n=340).
Abbreviations: IOP, intraocular pressure; M, month; Preop, preoperative.

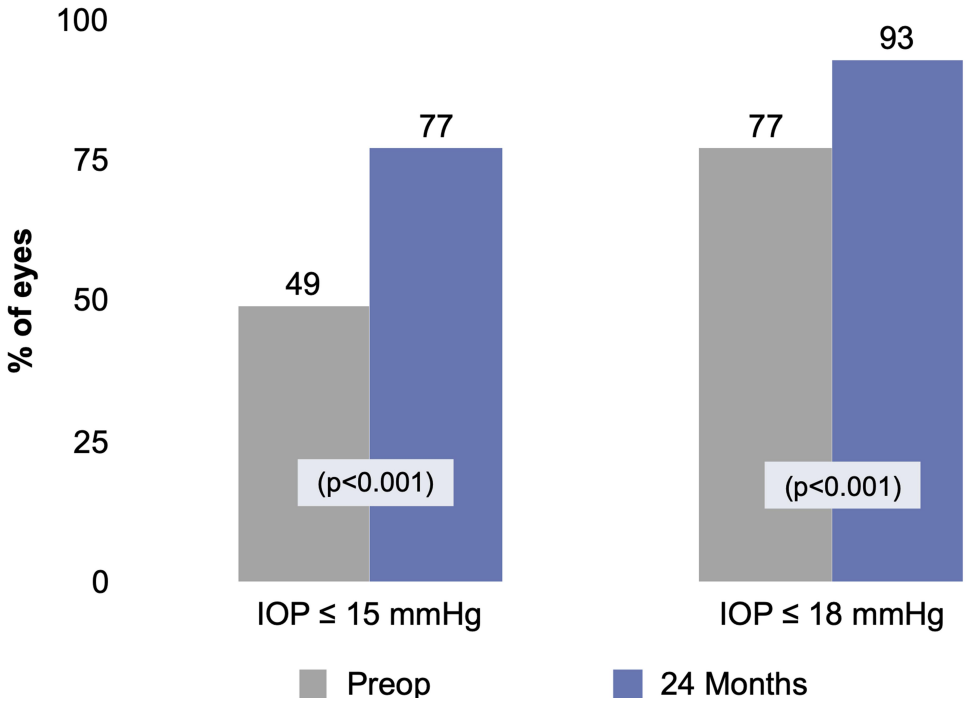

Figure 2 Proportional analysis of IOP at 24 months vs preoperative, all eyes (n=340).
Abbreviations: IOP, intraocular pressure; Preop, preoperative.

Secondary glaucoma procedures were infrequent, with the majority noted to be unrelated to the stent and/or due to disease progression despite good IOP control. Over two years of follow-up, a total of 6 eyes had filtration surgery alone, 5 eyes had selective laser trabeculoplasty (SLT) alone, and 2 eyes had both filtration surgery and SLT (hence 8 total filtration surgeries and 7 total SLT procedures in a total of 13 eyes); in addition, 2 eyes underwent implantation of a second iStent *inject*. Final IOP at two years in eyes receiving secondary interventions ranged from 5 to 17 mmHg on a range of 0 to 4 medications. In the eyes receiving a second iStent *inject* specifically, final IOP at two years was 7 mmHg on 0 medications and 14 mmHg on 0 medications, respectively;

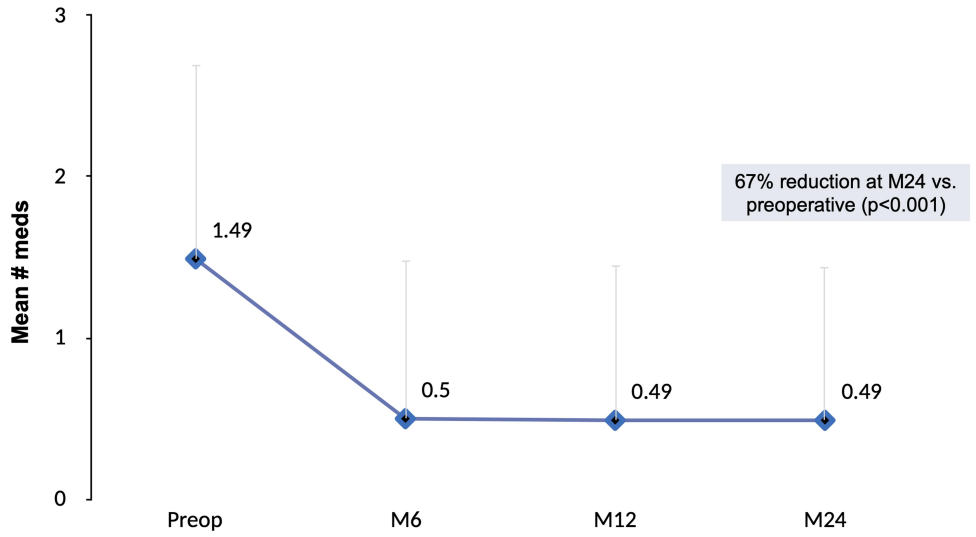

Figure 3 Mean number of medications through 24 months postoperative, all eyes (n=340).
Abbreviations: M, month; Preop, preoperative; Meds, medications.

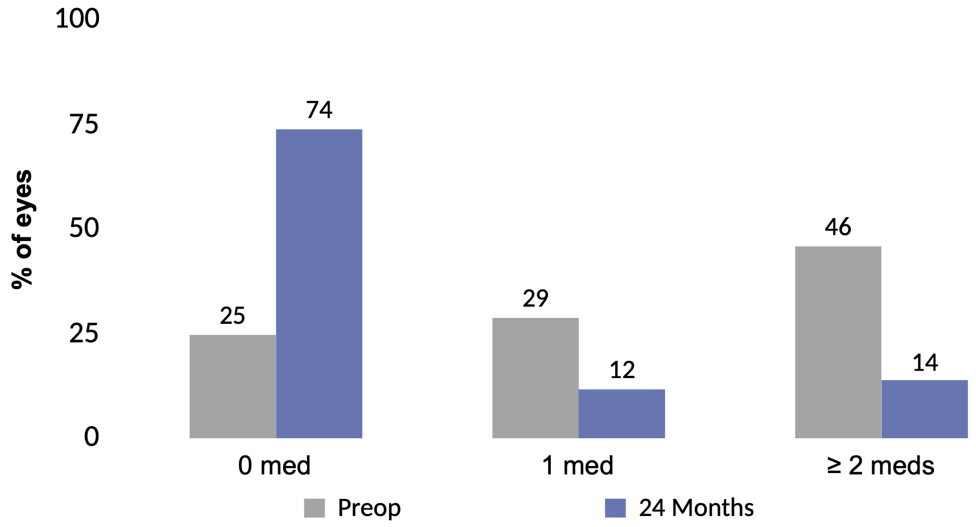

Figure 4 Proportional analysis of medications at 24 months vs preoperative, all eyes (n=340).
Abbreviations: Preop, preoperative; Meds, medications.

no stent-related adverse events or anomalies were reported for either eye.

Discussion

This large multicenter real-world case series presents sustained safety and effectiveness outcomes through 2 years postoperative following iStent *inject* implantation with concomitant cataract surgery. The cohort includes various glaucoma subtypes and severities, as well as data from various surgeons and sites across Australia, thereby increasing its clinical applicability and generalizability to other populations. Within this environment of real-world clinical practices and patient populations, iStent *inject* implantation with phacoemulsification resulted in significant and sustained reductions in IOP and medications through 2 years postoperative. Results were similarly favorable regardless of glaucoma subtype (including POAG, ACG, OHT, NTG). To our awareness, this report represents one of the largest multicenter multi-surgeon real-world studies of iStent *inject* to-date in the literature.

The observed 2.7 mmHg IOP reduction should be appreciated in the context of the cohort's relatively low mean starting IOP, given that lower starting IOP usually results in smaller postoperative IOP reductions.[16,17,29,42,43]

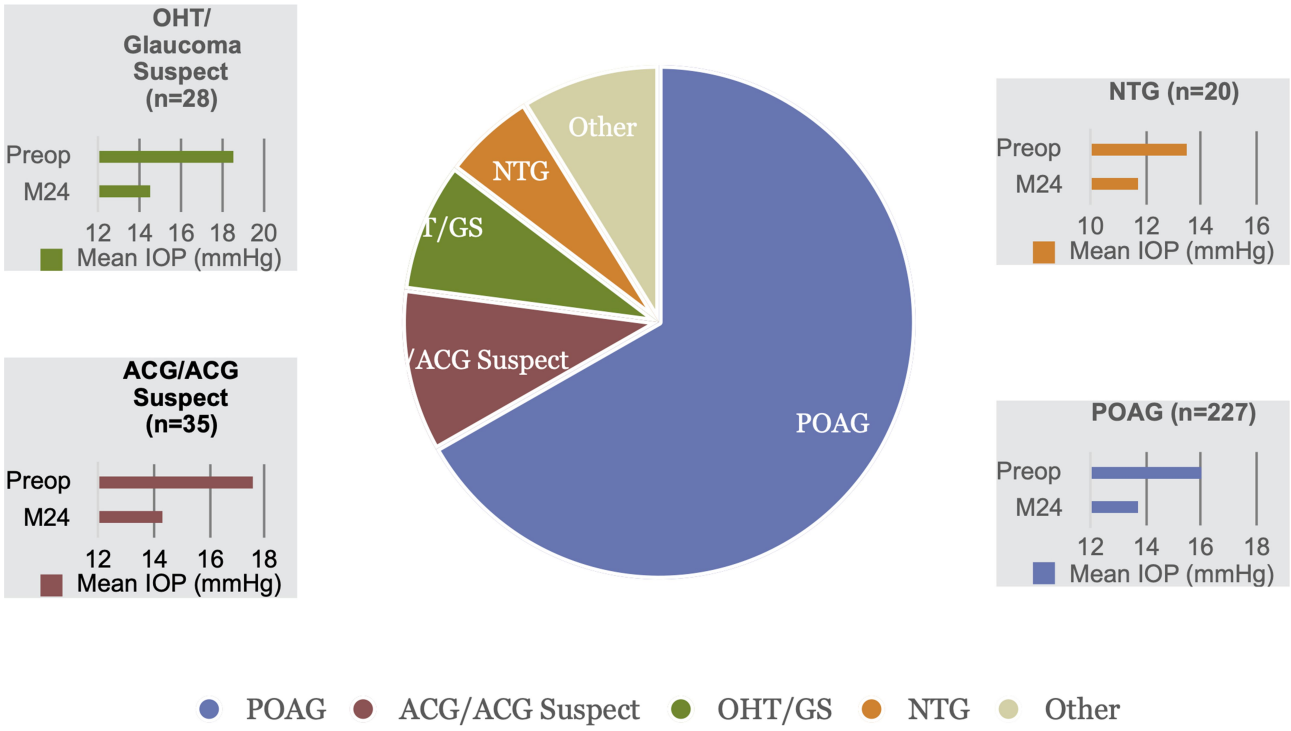

Figure 5 IOP reduction by glaucoma subtype (p<0.01 for all).
Abbreviations: IOP, intraocular pressure; POAG, primary open-angle glaucoma; ACG, appositional angle-closure glaucoma; OHT/GS, ocular hypertension/glaucoma suspect; NTG, normal-tension glaucoma; M, month.

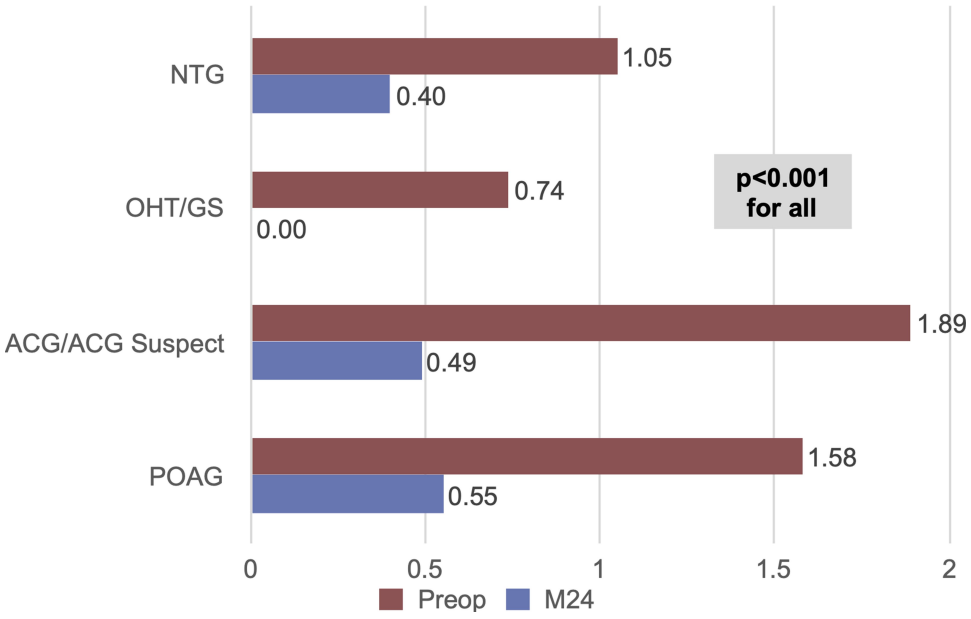

Figure 6 Medication reduction by glaucoma subtype (p<0.001 for all).
Abbreviations: POAG, primary open-angle glaucoma; ACG, appositional angle-closure glaucoma; OHT/GS, ocular hypertension/glaucoma suspect; NTG, normal-tension glaucoma; M, month.

The IOP target of ≤15 mmHg was achieved in half-again more eyes at two years versus preoperative (77% vs 49%, p<0.001). Coinciding with this IOP reduction, there was a threefold decrease in mean medication burden (0.49 versus 1.49 medications, p<0.001). In terms of per-patient medication usage, there was a threefold decline in the proportion of eyes on ≥2 medications versus preoperative (14% versus 46%, p<0.001), as well as a tripling of

Table 2 Preoperative and Month 24 CDR, VF MD, and CDVA Consistent Sets of Eyes with Data at Both Time Points

	Preoperative	Year 2
	n (%)	n (%)
No. of eyes with CDVA recorded at both time points	335	
CDVA 20/40 or better	301 (89.9%)	323 (96.4%)
No. of eyes with CDR recorded at both time points	213	
Mean ± SD	0.70 ± 0.17	0.71 ± 0.16
p-value		0.263
No. of eyes with VF MD recorded at both time points	226	
Mean ± SD	−4.60 ± 4.93	−4.90 ± 5.56
p-value		0.191

Abbreviations: SD, standard deviation; CDR, cup-to-disc ratio; CDVA, corrected distance visual acuity; VF MD, visual field mean deviation.

the proportion of eyes able to come off medications entirely (74% versus 25%, p<0.001). Nearly all eyes were able to lower or maintain their medication regimen versus preoperative.

The IOP and medication reductions observed in this study were in line with what has been reported in the literature, supporting the veracity of the findings. By significantly reducing both IOP and medications, patients can experience a tangible positive shift in their overall disease state. For a given patient, for example, this could take the form of using fewer drops per day, having fewer drop-related side effects, attaining more consistent IOP control at clinic visits, and/or needing fewer subsequent glaucoma procedures. Regardless of a patient's preoperative goal or postoperative benefit, all patients needed cataract surgery, thereby providing a unique opportunity for stent implantation without adding appreciable safety risks above cataract surgery alone.

The medication reduction observed in this study is particularly impressive given that a full quarter of patients in the cohort were on no medications preoperatively. This patient makeup led to a relatively low baseline medication burden, which conceivably could make it more difficult to achieve postoperative reduction. In addition, approximately a quarter of eyes had moderate or severe glaucoma at baseline (VF MD worse than −6 dB); it is possible that these patients were instructed to continue medication in order to maximize IOP reduction regardless of their surgical outcome, due to their more tenuous optic nerve condition.

Reducing a patient's medication burden carries wide-ranging benefits, given that medications are well-known to worsen treatment adherence, ocular surface disease, and patient quality of life, as well as to incur financial and caregiving ramifications of repeated drop instillation.[44–50] Treatment adherence is known to decrease dramatically when patients increase from single to multiple eye drops,[44] placing particular value on the study's finding of a threefold reduction in eyes on 2 or more medications. In addition, the sheer presence of medication can predispose to ocular surface deterioration,[46] adding further weight to the study's finding of a threefold increase in eyes becoming medication-free.

Alongside this medication reduction, the avoidance of filtration surgeries in nearly all eyes can be highlighted, given the short- and long-term complications and reoperations known to occur with such surgeries.[3–5] We do acknowledge that this patient population was generally less advanced than patients who would typically be undergoing filtering surgery; however, the rare incidence of such surgery in our cohort (2.4% over two years) is still likely lower than would be expected without stent implantation (projected to be ~3.1–4.6% per year in the broader glaucoma population).[51]

Stratified analyses were completed for the four most common diagnoses in the cohort (POAG, ACG, OHT, and NTG). Outcomes revealed significant reductions in IOP and medication burden regardless of glaucoma subtype, with IOP reducing 13–22% and medications reducing 62–100% (statistically significant for all). The data in the ACG, OHT, and NTG subgroups are especially valuable

given that these subtypes are less well represented in clinical research. The observed IOP and mediation reductions are consistent with prior work evaluating iStent or iStent *inject* implantation in these subtypes,[11,12,20,25,27] and they contribute some of the first long-term analyses on the use of the second-generation iStent *inject* specifically in these groups.

The reductions in OHT eyes are particularly remarkable, with 100% of eyes becoming medication-free alongside a 22% IOP reduction at 2 years postoperative. This possibly reflects the value of restoring trabecular flow while there is still an intact downstream outflow system in an earlier stage of the disease. In such eyes, the data suggest that earlier intervention with a tissue-sparing, minimally-invasive surgical procedure such as iStent *inject* potentially could alter the trajectory of disease progression before Schlemm's canal and aqueous collector channels are affected by loss of outflow.

The safety profile was highly favorable, as is characteristic of the iStent *inject* device. Postoperative adverse events were uncommon, mild, and transient; post-phacoemulsification improvements in CDVA were maintained over 2 years; and CDR and VF remained stable.

Certain limitations may be discussed in this study. Given that this was a real-world patient population from the surgeons' clinical practices, preoperative medication washout was not completed, as this could pose a risk of IOP elevation in participating eyes. The surgeons managed patients' medications according to their standard practice rather than formal codified guidelines. However, these choices were generally similar across surgeons; also, any differences would be expected to have negligible impact, since the same effectiveness outcomes were evaluated in the same patients and by the same clinicians throughout follow-up, meaning that changes over time still would be apparent. There was no formal control group of phacoemulsification alone, and thus it was not possible to isolate the effects of the stents versus those of cataract surgery. However, other comparative trials of stent-phaco or iStent *inject*-phaco versus phaco alone[8,11,15,21,22,24] can be used as a reference point, and the IOP-lowering effect of cataract surgery would be unlikely to persist to the same degree through 2 years postoperative.[52] Regression to the mean could have been possible, since diurnal IOP measurements and repeated-day evaluations were not employed; however, this would be expected to have minimal to no impact due to the robust sample size.

Conclusion

This report constitutes one of the largest multicenter datasets to-date of iStent *inject* with cataract surgery, and it presents outcomes in patients with a variety of glaucoma subtypes and severities, including those that are less frequently addressed in the research. Results were achieved in real-world settings and clinical populations, and thus are readily applicable to practicing clinicians. The outcomes showed that iStent *inject* plus phacoemulsification can significantly, safely, and sustainably reduce IOP and medication burden through two years postoperative in real-world clinical usage. These gains were similarly favorable across glaucoma subtypes, indicating the viability and adaptability of this treatment modality in managing glaucoma.

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Disclosure

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