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ORIGINAL PAPER

Outcomes of iStent inject combined with cataract surgery in Asian eyes: Australian data from the Fight Glaucoma Blindness international registry

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Abstract

Purpose To analyse real-world outcomes in Asian eyes of iStent inject, a second-generation trabecular micro-bypass stent, combined with phacoemulsification.

Methods This is a multi-centre, observational study of glaucomatous Asian eyes that have undergone iStent inject implantation combined with cataract surgery. Patient data were extracted from the Fight Glaucoma Blindness! Registry. Outcome measures included those of IOP reduction, glaucoma medication reduction, and adverse events including the need for secondary surgery.

Results 123 eyes of 86 patients with a mean age of 68.4 ± 9.3 years underwent iStent *inject* implantation with phacoemulsification. At baseline, the mean ± SD

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preoperative intraocular pressure (IOP) was 16.0 ± 4.4 mmHg, and the mean preoperative number of topical glaucoma medications was 1.9 ± 1.4. At 12 months 30.8% of eyes demonstrated a reduction in IOP greater than 20%, the mean IOP reduction was 12.5% with an additional reduction of 0.7 glaucoma medications. 40% of eyes were using no medications at 12 months compared to 16.3% preoperatively. 8.2% of eyes required a subsequent procedure within the 12-month follow-up window.

Conclusion iStent *inject* implantation combined with phacoemulsification in Asian eyes showed a reduction of IOP and glaucoma medication use in a real-world clinical setting. The safety profile of the device is good with minimal adverse outcomes, however, a subset of patients required secondary procedures within the 12 month follow up.

Keywords Glaucoma · Minimally invasive glaucoma surgery · Intraocular pressure · iStent inject

Introduction

Glaucoma is a progressive optic neuropathy that is the leading cause of irreversible blindness worldwide [14, 21]; over 110 million people are projected to have the condition by 2040 [21]. Intraocular pressure (IOP) is the only known modifiable risk factor in the development of glaucoma and lowering IOP remains the only proven treatment to slow or prevent disease progression [5, 20].

Trabecular micro-bypass stents now have robust RCT evidence of additional efficacy over that of cataract surgery alone [17, 18]. The second generation iStent inject® (Glaukos Corporation, San Clemente, CA, USA), implants two devices ab-interno into the trabecular meshwork and creates a bypass from the anterior chamber into Schlemm's canal.

Race is known to be a risk factor for glaucoma [12]; individuals of African descent have a higher prevalence of primary open angle glaucoma (POAG) than those of European descent, while Asian populations have an increased incidence of normal tension glaucoma (NTG) and primary angle-closure glaucoma (PACG) [21]. Asia alone accounts for almost 60% of the world's total glaucoma cases [4, 14, 24], however this population has been underrepresented in publications investigating safety and efficacy of trans-trabecular devices with cataract surgery [1, 2, 7, 8, 15].

We therefore investigated outcomes of this surgery in Asian eyes that are being tracked within the Fight Glaucoma Blindness registry [10]. This report presents the 12-month real-world outcomes of efficacy and safety of combined phacoemulsification with iStent inject in Asian eyes across a large group of Australian and New Zealand surgeons.

Methods

Study design

Data were collected from the Fight Glaucoma Blindness! (FGB) registry to describe outcomes of iStent inject combined with phacoemulsification and intra-ocular lens implant in a cohort of Asian eyes. The FGB is an international web-based audit and research tool used mostly in Australia and New Zealand that ensures the collection of accurate, comprehensive, and complete data on routine clinical care. The registry allows clinicians to audit the outcomes of their glaucoma treatments using dedicated web-based registry software. Aggregated anonymised data from the registry is then available for analysis and publication. The FGB registry has research ethics approval from the Royal Australian and New Zealand College of Ophthalmology Human Research Ethics Committee, and a detailed description of the registry has been previously published [11].

Patients and outcome measurements

Patients who self-identified as "Asian" as their ethnicity were examined in this study. Other possible ethnicity categories included "Fijian Indian", "Indian", "Middle Eastern", and "Mixed". Data were extracted on Asian eyes that had a diagnosis of either open-angle glaucoma (primary or secondary), primary angle closure spectrum disease, ocular hypertension, or glaucoma suspects and who had undergone iStent inject implantation combined with cataract surgery. Glaucoma suspects were cases identified by the surgeon with clinical suspicion of glaucoma which has not yet been confirmed or high risk of progressing glaucoma including those with

elevated intraocular pressure. Other inclusion criteria were at least six months of follow-up after surgery and all relevant IOP measurements taken with Goldman applanation tonometry. Patients who had any prior incisional glaucoma surgery were excluded. Cases where iStent insertion was unsuccessful were not included.

Due to the real-world nature of this study, the precise surgical technique was not prescribed. Each individual clinician operated according to their preferences, but all were a single procedure injecting 2 pre-loaded iStent inject devices into the trabecular meshwork either before or after performing phacoemulsification with lens implantation. Intracameral antibiotics following completion of surgery and postoperative topical antibiotics and steroids with or without a topical non-steroidal were given according to each surgeon's standard of care.

The primary outcomes were percentage of eyes achieving > 20% IOP reduction from baseline, change in mean IOP, and change in number of topical ocular hypotensive medications at 12 months. A range of secondary outcomes were investigated included adverse events such as VA loss of ≥ 10 letters, hypotony, hyphaema, and number of subsequent procedures. For interstudy comparability we also report outcomes as recommended by the WGA guidelines on reporting for clinical trials [19], including reporting complete (CS) and qualified success (QS) rates of > 20% IOP reduction and an IOP level less than or equal to 15, 18, or 21 mmHg. CS was defined as patients meeting the IOP criteria and not requiring any topical glaucoma medications while QS was defined as patients meeting the IOP criteria but still requiring medical therapy.

We also analysed according to some modified success criteria that more accurately reflects different clinical scenarios in which ab-interno trabecular by-pass stents are used in combination with phacoemulsification. These were any reduction in IOP from baseline with the same or fewer medications (anyIOP group), any reduction in medications from baseline with the same or lower IOP (anyMed group) or any reduction in both IOP and medications from baseline (IOPMed group).

Data analyses

The number and percentages of eyes and patients and means with standard deviations or medians with interquartile range for continuous data were reported.

Any patient requiring a secondary surgical or laser procedure within the follow-up window was considered a failure. Visits after the second procedure were censored using the 'last observation carried forward' analysis for IOP and medication values.

Cox proportional hazards model [9] was used to analyse the association between baseline parameters (baseline IOP, medications, age, and gender) and IOP and medication reduction. Random effects were also included to account for heterogeneity of outcomes among clinicians and patients treated by the same surgeon. $P = 0.05$ was used for level of significance.

All analyses were conducted using R software version 4.2.1. using the survival package (V 3.4-0) [22] for Kaplan–Meier survival analysis and the coxme package (V 2.2.17) [23] for the mixed effects Cox proportional hazards models.

Results

A total of 123 eyes from 86 patients had undergone phacoemulsification with iStent inject and were eligible for assessment. Table 1 presents the demographic and baseline characteristics, with over half (55.8%) of the study participants being female and the mean age of patients overall being 68.4 ± 9.3 years. The most common diagnosis was primary open-angle glaucoma (POAG) at 57.7%, followed by normal tension glaucoma (21.1%) and glaucoma suspects (9.8%).

The percentage of eyes on no glaucoma medications was 16.3% at baseline and this increased to 40% of eyes at 12 months. There was a reduction in intraocular pressure (IOP) of 13.5%, 12.5%, and 16.6% at 6, 12, and 36 months, respectively. Similarly, there was a mean reduction in medications of 0.6, 0.7, and 0.4 at the respective time points. For the small subgroup of eyes that have reach 36-month follow-up 42.3% of eyes maintained an IOP reduction of > 20%. Among eyes with a baseline intraocular pressure (IOP) greater than 21 mmHg, the proportion of eyes achieving a reduction in IOP of more than 20%

Table 1 Demographic and baseline characteristics of Asian eyes meeting the selection criteria

	All eligible procedures	6-Month completers	12-Month completers	24-Month completers	36-Month completers
Eyes	123	87	65	45	26
Patients	86	65	49	35	19
Procedures	123	87	65	45	26
Gender, % patients female	55.8%	50.8%	51%	45.7%	31.6%
Age, mean (SD)	68.4 (9.3)	67.3 (9.2)	68.1 (9.9)	67.7 (9.3)	65.9 (7.9)
IOP, mean (SD)	16 (4.4)	16.4 (4.2)	15.9 (4.3)	15.2 (3.4)	15.1 (2.7)
Medications, mean (SD)	1.9 (1.4)	1.8 (1.4)	2 (1.3)	1.7 (1.4)	1.5 (1.2)
Visual field MD, mean (SD)*	− 5.6 (5.2)	− 6.4 (5.6)	− 5.7 (4.8)	− 6 (5)	− 5.4 (3.8)

MD, mean deviation; NTG, normal tension glaucoma; POAG, primary open angle glaucoma; SD, standard deviation

*Data available for 1559 of the 2051 eligible procedures

Table 2 Intraocular pressure and medication outcomes at 6, 12, 24 and 36 months for all eligible procedures

All procedures	6 Months	12 Months	24 Months	36 Months
Procedures	87	65	45	26
IOP outcomes				
Pre-operative, mean (SD)	16.4 (4.2)	15.9 (4.3)	15.2 (3.4)	15.1 (2.7)
Final, mean (SD)	14.5 (5.5)	15 (6.3)	15.3 (6.8)	13.3 (3)
Change, mean (95% CI)	− 1.9 (5.6)	− 1 (5.8)	0.1 (5.9)	− 1.8 (2.5)
% Change, median (Q1, Q3)	− 13.5% (− 23.5, 0)	− 12.5% (− 25, 3.7)	− 6.7% (− 18.8, 17.6)	− 16.6% (− 22.2, 6.4)
> 20% reduction, n (%)	28 (32.2%)	20 (30.8%)	11 (24.4%)	11 (42.3%)
Medication outcomes				
Pre-operative, mean (SD)	1.8 (1.4)	2 (1.3)	1.7 (1.4)	1.5 (1.2)
Final, mean (SD)	1.2 (1.3)	1.3 (1.3)	1.1 (1.4)	1.1 (1.6)
Change, mean (95% CI)	− 0.6 (1.3)	− 0.7 (1.3)	− 0.6 (1.4)	− 0.4 (1.5)
Number of medications, n (%)				
0	42 (48.3%)	26 (40%)	21 (46.7%)	15 (57.7%)
1	9 (10.3%)	12 (18.5%)	11 (24.4%)	4 (15.4%)
2	16 (18.4%)	10 (15.4%)	4 (8.9%)	2 (7.7%)
> 2	20 (23%)	17 (26.2%)	9 (20%)	5 (19.2%)
Qualified success, n (%)				
IOP ≤ 15 mmHg	24 (27.6%)	18 (27.7%)	10 (22.2%)	11 (42.3%)
IOP ≤ 18 mmHg	26 (29.9%)	20 (30.8%)	11 (24.4%)	11 (42.3%)
IOP ≤ 21 mmHg	28 (32.2%)	20 (30.8%)	11 (24.4%)	11 (42.3%)
Complete success, n (%)				
IOP ≤ 15 mmHg	9 (10.3%)	7 (10.8%)	3 (6.7%)	7 (26.9%)
IOP ≤ 18 mmHg	9 (10.3%)	9 (13.8%)	4 (8.9%)	7 (26.9%)
IOP ≤ 21 mmHg	11 (12.6%)	9 (13.8%)	4 (8.9%)	7 (26.9%)

IOP, intraocular pressure; SD, standard deviation

was 70.0% at 6 months and 50.0% at both 12 and 24 months of follow-up (Table 2).

Percentage of eyes achieving qualified success (QS) and complete success (CS) with IOP thresholds

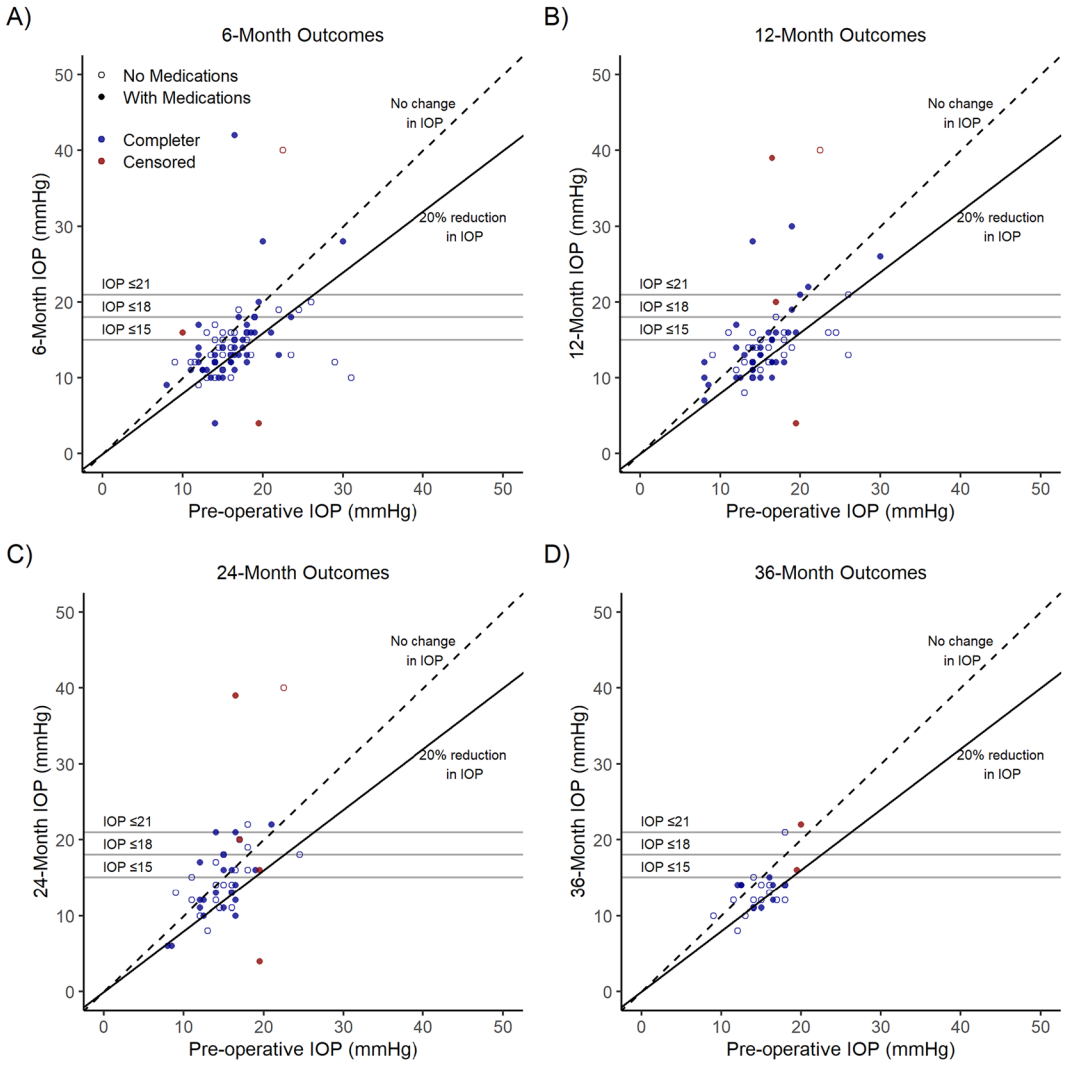

Fig. 1 Pre- versus post-operative IOP at **A** 6 months, **B** 12 months, **C** 24 months and **D** 36 months after iStent injection with cataract surgery showing qualified (with medications) and complete (no medications) successes depending on the threshold for IOP reduction (below 15, 18 or 21 mmHg)

Table 3 Frequency of adverse events recorded at any period up until the 6, 12, 24 or 36-month visit for eyes completing 6, 12, 24 or 36 months of follow-up

Events recorded (Number of patients, % of patients)	6 Months	12 Months	24 Months	36 Months
Subsequent procedure performed	3 (3, 4.6%)	4 (4, 8.2%)	5 (5, 14.3%)	2 (2, 10.5%)
Hyphaema	4 (3, 4.6%)	4 (3, 6.1%)	3 (2, 5.7%)	1 (1, 5.3%)
IOP increase ≥ 10 mmHg	6 (2, 3.1%)	20 (4, 8.2%)	11 (2, 5.7%)	0 (0, 0%)
Macular oedema	2 (2, 3.1%)	1 (1, 2%)	1 (1, 2.9%)	0 (0, 0%)
VA loss ≥ 10 letters	10 (3, 4.6%)	8 (2, 4.1%)	8 (2, 5.7%)	16 (1, 5.3%)

of less than or equal to 15, 18, and 21 mmHg were computed for each follow-up time point (Table 2). The QS rates at 6 months for the 15, 18, and 21 mmHg thresholds were 27.6%, 29.9%, and 32.2%, while the CS rates were 10.3%, 10.3%, and 12.6%, respectively (Fig. 1).

At 12 months, adverse events were few and are outlined in Table 3. 8.2% of eyes had undergone a secondary procedure which was either an aqueous shunt, deep sclerectomy, selective laser trabeculoplasty, or iridoplasty (Table 4).

Twelve-month outcomes were analysed based on the modified success criteria i.e., any IOP and/or medication reduction after surgery (Fig. 2). Over two-thirds (69.2%) of eyes had achieved a lower IOP with same or lower medication (anyIOP group), 56.9% of eyes had achieved any lower medication with same or lower IOP (anyMed group) and 47.7% of eyes had achieved both IOP and medication reduction (IOPMed Group).

The Cox regression model (Table 5) showed that a higher baseline IOP was associated with a statistically significant increased probability of achieving a reduction in IOP from baseline with the same or fewer medications (HR 1.13, $p=0.012$), reduction in medications from baseline with the same or lower IOP (HR 1.11, $p=0.05$) and reduction in both IOP and medications from baseline (HR 1.17, $p=0.01$). Higher number of baseline medications was also associated with increased probability of reduction in medications from baseline with the same or lower IOP (HR 1.49, $p=0.021$) and reduction in both IOP and medications from baseline (HR 1.5, $p=0.038$) respectively. No significant difference was observed in these outcomes by gender and age.

Discussion

This multi-centre, multi-surgeon observational study provides real-world data on the use of combined phacoemulsification with iStent inject implantation in Asian eyes in Australia and New Zealand. At 12 months follow up, the percentage of eyes with > 20% IOP reduction was 30.8% (Table 2) and there was a mean reduction of 0.7 medications. There was an increase in the number of eyes medication free from 14.6% preoperatively to 43.6% at 12 months ($p<0.01$). This modest reduction in IOP and medication use is consistent with the limited previous studies of iStent inject combined with cataract surgery in Asian eyes [1, 2, 7, 15].

A consistent finding across several studies is that the higher the preoperative pressure, the higher the percentage reduction of IOP. A similar finding was evident in this cohort; the mean percentage IOP reduction at 12 months was 12.5% for the entire group, but 25.6% for the subset who had a pre-treatment IOP of > 21 mmHg.

Previous series that looked at combined cataract surgery with iStent inject in eyes of mostly Caucasian descent, have reported pre-treatment IOPs ranging from 17.0–22.6 [3, 6, 13, 16] with IOP reductions between 17.8 and 39%. In contrast, publications investigating Asian eyes with POAG described mean pretreatment IOPs from 15.1 to 16.2 mmHg [7, 15] with postoperative IOP reductions from 8 to 17%. Studies of Asian eyes focusing on patients with NTG unsurprisingly had even lower pretreatment IOPs of 13.8–14.3 mmHg [1, 2] with correspondingly lower postoperative IOP reductions of 7.7 to 8.7%.

These observations are particularly relevant in an Asian population where the pre-treatment IOPs may well be lower with a higher rate of NTG. In this cohort, 21.1% of eyes had a diagnosis NTG and we

Table 4 Subsequent procedures performed prior to completing 6, 12, 24 or 36 months of follow-up

	6 Months	12 Months	24 Months	36 Months	Unique no. of eyes
Deep sclerectomy	1	1	1	0	1
Iridoplasty	1	1	1	0	1
SLT 180°	1	0	0	0	1
SLT 360°	0	1	2	2	3
Aqueous shunt	0	1	1	0	1

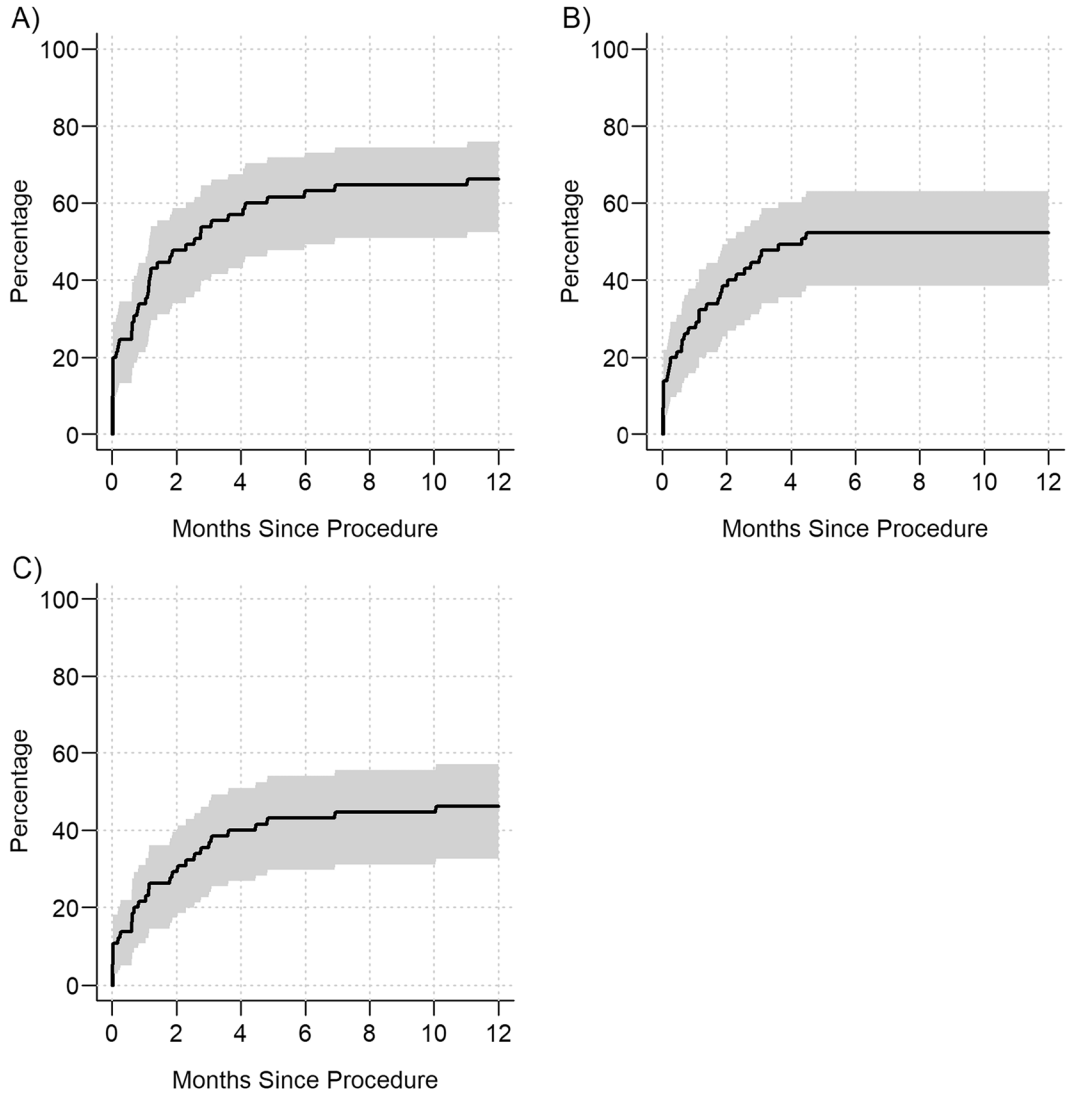

Fig. 2 Kaplan–Meier survival curves for time to **A** any reduction in IOP with the same or fewer medications, **B** any reduction in medications with the same of lower IOP, and **C** any reduction in IOP and medications

Table 5 Hazards ratios (HR) for predictors of achieving any reduction in IOP with the same or fewer medications, any reduction in medications with the same or lower IOP, or any reduction in IOP and medications

	Any IOP reduction, same or fewer medications		Any reduction in medications, same or lower IOP		Reduction in IOP and medications	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Pre-operative IOP	1.13 (1.03, 1.24)	0.012	1.11 (1, 1.23)	0.05	1.17 (1.04, 1.32)	0.01
Pre-operative Medications	1.28 (0.95, 1.71)	0.999	1.49 (1.06, 2.1)	0.021	1.5 (1.02, 2.19)	0.038
Age, per year	1 (0.96, 1.04)	0.980	1.04 (1, 1.09)	0.066	1.04 (0.99, 1.1)	0.093
Gender, male	1.01 (0.47, 2.17)	0.980	1.09 (0.46, 2.58)	0.850	1.12 (0.42, 3.01)	0.820

found an IOP reduction at 12 months of 12.5% in the context of pre-treatment IOP of 16.1 ± 4.5 mmHg. This appears to correlate well with other studies suggesting that preoperative IOP is an important driver of percentage IOP reduction.

Our cohort found medication reduction of 0.8 consistent with other studies on Asian eyes (0.7–1.5 medications)[1, 2, 7, 15]. The preoperative number of glaucoma medications in our cohort was slightly higher (2.0 ± 1.4) than other studies (1.3–1.9) [1, 2, 7, 15]. There was a significant increase in the percentage of medication free patients at 12 months from 14.6% preoperatively to 43.6% at 12 months, however this was less than reported in other studies which ranged from 70.8 to 83.3% [1, 2, 7, 15].

We report traditional measures of surgical success as recommended by the WGA [19], including a series of success definitions including IOP reduction across a range of a threshold levels (Table 2). The WGA recommendations were originally developed for reporting filtration surgery as so while they allow comparison of outcomes between studies, they are arguably less relevant as a meaningful clinical outcome in patients undergoing trabecular bypass MIGS devices. At 12 months following surgery, 35.5% of eyes had an IOP reduction with same or lower medications (anyIOP group), 25.7% had any medication reduction with the same or lower IOP (anyMed group), and 22.6% of eyes had both IOP and medication reduction (IOPMed Group). Pre-operative IOP and number of medications were significantly correlated with all three outcomes (Table 5). These findings suggest that a patient with a relatively low pre-operative IOP, where a significant further reduction of IOP is required, is less likely to achieve this goal.

Few adverse events were reported overall—the most common was subsequent procedures in 8.2% of eyes at 12 months (Table 3). The subsequent procedures performed were one aqueous shunt, one deep sclerectomy, one iridoplasty, and two SLT (Table 4). Asian eyes have been associated with generally narrower angles and shallower anterior chamber depths, possibly contributing to a higher risk of stent occlusion in Asian eyes [1]; other studies in Asian eyes reported 0 to 10% [1, 2, 7, 15] eyes with stent occlusion requiring laser iridoplasty. Salimi and colleague's study of 62 eyes with NTG did not report any cases requiring a secondary glaucoma intervention (laser or surgery) in the 12-month postoperative period. As clinicians do not routinely assess the drainage angle at reach review, we did not confirm stent occlusion, however this would cause an IOP rise as a surrogate measure which was reported in this analysis.

Some of the inherent limitations of real-world data have been addressed throughout this report. This is a retrospective analysis of prospectively collected observational data. As such there are no inclusion criteria specified, instead surgeons agree to enter consecutive patients into the registry which reflects their clinical practice and minimises selection bias. The absence of a control group (phacoemulsification alone) is because these data are not aiming to determine the "true" additional effect of the iStent inject over cataract surgery, but instead describe the outcomes of routine clinical practice. As a registry study, surgical technique was not standardized. Each surgeon performed the surgery according to their personal preference, but all involved phacoemulsification with implantation of 2 iStent inject devices. Similarly, post-operative care was not standardised with choice of post-operative IOP lowering medications being at the treating surgeon's discretion; some clinicians may routinely washout glaucoma medications immediately post-operatively, while others may wait for several visits before adjusting treatment. We have tried to compensate for this by ensuring that any IOP decrease was not the result of a medication increase. On average, we see that both mean IOP and mean number of medications are reduced at each given follow up period. In this study we did not compare outcomes between different races.

This study of an Asian cohort from multiple surgeons in the FGB registry has shown that iStent inject combined with phacoemulsification results in a clinically meaningful number of patients achieving a 20% IOP reduction and medication reduction at 12 months. There is suggestion of persistence of effect with longer follow up, but larger numbers will be required to confirm this finding.

Author contributions All authors made substantial contributions to the work, drafted and revised the work critically for intellectual content, approved the version to be published, and agree to be accountable for all aspects of the work.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval The FGB registry has research ethics approval from the Royal Australian and New Zealand College of Ophthalmology Human Research Ethics Committee, and a detailed description of the registry has been previously published [11].

Consent for publication Ethics approval through the Royal Australian and New Zealand College of Ophthalmology includes opt-out consent from all patients included in this publication.

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