• Clinical Research •

iStent *inject*® and cataract surgery for mild-to-moderate primary open angle glaucoma in Japan: a cost-utility analysis

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Abstract
● **AIM:** To evaluate the cost-utility of iStent *inject*® with cataract surgery *vs* cataract surgery alone in patients with mild-to-moderate primary open angle glaucoma (POAG) in the Japanese setting from a public payer's perspective.
● **METHODS:** A Markov model was adapted to estimate the cost-utility of iStent *inject*® plus cataract surgery *vs* cataract surgery alone in one eye in patients with mild-to-moderate POAG over lifetime horizon from the perspective of Japanese public payer. Japanese sources were used for patients' characteristics, clinical data, utility, and costs whenever available. Non-Japanese data were validated by Japanese clinical experts.
● **RESULTS:** In the probabilistic base case analysis, iStent *inject*® with cataract surgery was found to be cost-effective compared with cataract surgery alone over a lifetime horizon when using the ¥5 000 000/quality-adjusted life year (QALY) willingness-to-pay threshold. The incremental cost-utility ratio (ICUR) was estimated to be ¥1 430 647/QALY gained and the incremental cost-utility ratio (ICER) was estimated to be ¥12 845 154/blind eye avoided. iStent *inject*® with cataract surgery *vs* cataract surgery alone was found to increase costs (¥1 025 785 *vs* ¥933 759, respectively) but was more effective in increasing QALYs (12.80 *vs* 12.74) and avoiding blinded eyes (0.133 *vs* 0.141). The differences in costs were mainly driven by costs of primary surgery (¥279 903 *vs* ¥121 349). In the scenario analysis from a societal perspective, which included caregiver burden, iStent *inject*® with cataract surgery was found to dominate cataract surgery alone.
● **CONCLUSION:** The iStent *inject*® with cataract surgery is a cost-effective strategy over cataract surgery alone from the public payer's perspective and cost-saving from the societal perspective in patients with mild-to-moderate POAG in Japan.
● **KEYWORDS:** iStent *inject*®; glaucoma; cataract surgery; health-economic model; cost-utility
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INTRODUCTION
Glaucoma is a chronic, progressive disease resulting in a degeneration of the optic nerve. It is a leading cause of irreversible blindness in Japan[1]. In 2015, a nationwide survey of welfare offices in Japan ranked glaucoma as the first causative disease (29%) among newly certified visually impaired individuals ≥18y[2]. Primary open angle glaucoma (POAG) is the most common type of glaucoma[3-5]. It is characterized by a progressive vision loss due to the loss of retinal ganglion cells and optic nerve damage and by optic neuropathy combined with ocular hypertension (OHT)[6].

Population-based studies from the early 2000s estimated the prevalence of POAG in Japan to be 4% among adults aged ≥40y[1,3]. Due to the asymptomatic nature of mild-to-moderate POAG, 93% of patients with POAG in Japan remains undiagnosed and not treated[3]. The epidemiological study conducted between 2000 and 2002 found a high rate of newly diagnosed cases of glaucoma (89%)[7] despite the emphasis of the Japanese Glaucoma Society Guideline[7] on the importance of an early diagnosis and treatment for avoiding permanent vision loss.

Given the progressive nature of the disease, the main objectives of all glaucoma treatments are to safely reduce and maintain intraocular pressure (IOP) to a target level that will preserve the remaining vision[8] and to minimize the resulting negative effect on the patient's quality of life (QoL)[9-10]. Since non-adherence to therapy can have a negative impact on clinical outcomes, treatment should be selected carefully with consideration of the patient's QoL, lifestyle and comorbidities as well as medication-associated adverse events (AEs), costs and life expectancy[11-12].

According to the Japanese Glaucoma Society Guideline[7], the current treatment of POAG in Japan usually begins with topical anti-glaucoma medications followed by laser treatments in case of failure. Incisional surgeries are typically reserved as last resort therapies. To date, no specific treatment pattern has been recommended based on the severity while new therapeutic options have been developed. Their introduction to clinical practice have addressed and diminished burden associated with traditional glaucoma treatments which include non-adherence, low persistence[13-14], contraindications and intolerable AEs following anti-glaucoma medications; unsustainability of IOP reduction following laser treatment; and higher risks of life-long complications and failures following incisional surgery in patients with mild-to-moderate POAG. iStent trabecular micro-bypass stent system introduced surgeons to the first micro-invasive glaucoma surgery (MIGS) offering a safe and effective, tissue-sparing, minimally traumatic approach to treat mild-to-moderate open angle glaucoma (OAG) without compromising vision acuity. iStent *inject*® is the 2nd generation MIGS device marketed by Glaukos in 2018. It is based on the same fluidic method of action as the 1st iStent® but preloaded with 2 stents where aqueous humour outflow is improved, thereby lowering IOP and possibly decreasing the dependence on pressure-lowering topical medications[15]. The iStent *inject*® is indicated for patients undergoing treatment with IOP-lowering drugs for mild-to-moderate POAG, including those with normal-tension glaucoma, and used in conjunction with cataract surgery[16]. In the 2-year iStent *inject*® pivotal randomised controlled trial (RCT) in patients with mild-to-moderate POAG undergoing cataract surgery[17], the stents were found to be effective in lowering IOP. Furthermore, mean medication use was statistically significantly lower in the iStent *inject*® with cataract surgery cohort *vs* the cataract surgery only cohort. As the cost-utility of iStent *inject*® has not previously been evaluated in Japan, we aimed to conduct a cost-utility analysis based on Japanese data. The objective of this analysis was to evaluate the cost-utility of iStent *inject*® in combination with cataract surgery *vs* cataract surgery alone in patients with mild-to-moderate POAG in the Japanese setting, from a public payer's perspective.

SUBJECTS AND METHODS

Model Overview A Canadian health state-transition Markov model[18] was adapted to estimate the cost-utility of iStent *inject*® combined with cataract surgery compared with cataract surgery alone in one eye in patients with mild-to-moderate POAG over lifetime horizon with monthly cycle length from the perspective of Japanese public payer. Health outcomes included quality-adjusted life-year (QALY) as the primary outcome and life years and number of blind eyes as the secondary outcomes. Cost outcomes included a total cost as the primary outcomes, while secondary outcomes were surgery (cataract surgery with or without iStent *inject*®, trabeculotomy, trabeculectomy), medication, progression-related medical service (physician consultation, test), and AEs (hyphema, hyperaemia, stent obstruction, medication for AEs). The full caregiver burden was evaluated in the scenario analysis and considered productivity loss of working family caregivers and caregiver burden proxied by long-term care insurance level 1. Costs and health outcomes were discounted at a 2.0% annual rate based on the Japanese guideline[19].

Model Description The model structure has previously been published[20] and was validated by Japanese clinical experts to reflect current clinical practice in Japan (Figure 1). Patients with mild-to-moderate POAG treated with background ocular hypotensive medications entered the model initiating cataract surgery with or without iStent *inject*®. Patients could progress from baseline severity levels to next severity levels, defined according to the visual field (VF) defect (decibels, dB)[21] as mild glaucoma (0 to 6 dB), moderate glaucoma (6.01 to 12 dB), advanced glaucoma (12.01 to 20 dB), and severe glaucoma or blindness (<20 dB). Patients could discontinue background medication due to non-adherence, contraindications and intolerable AEs and receive subsequent surgeries in the case of disease progression such as trabeculotomy, followed by trabeculectomy as the last surgery. AEs of background medication, such as dryness, redness, and blurred vision and AEs of cataract surgery and iStent *inject*® combined with cataract surgery, including stent obstruction, hyperaemia, and hyphema, were considered.

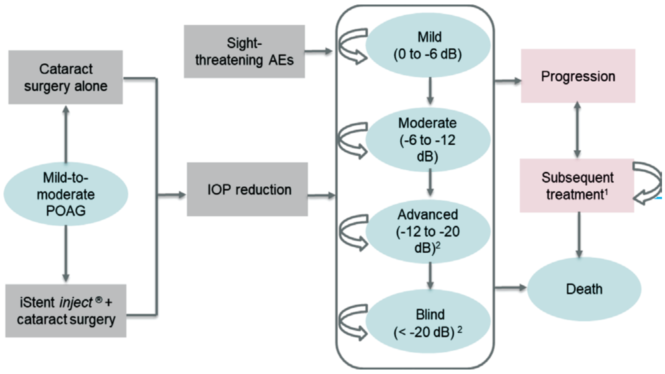

Figure 1 Model structure [1]Patients may receive subsequent treatments due to progression in VF defect; trabeculotomy, followed by trabeculectomy. Markov states are replicated for each line of subsequent treatment. [2]Merged for resource uses and quality-adjusted life-years calculation but separated for transition calculation to consider death due to blindness. AE: Adverse events; IOP: Intraocular pressure; POAG: Primary open angle glaucoma.

Model Input Inputs of the model, including patients' characteristics, clinical data, utility, and costs, were drawn from clinical trials, the literature and official Japanese sources. The Japanese data were used whenever available. Japanese clinical experts validated all assumptions and data used in the model.

Patients' Characteristics To reflect the Japanese real-world setting, the model was populated with clinical characteristics collected from the Japanese cross-sectional study[22]. Patients needing cataract surgery entered the model at a mean age of 64.5y, 60.5% in mild and 39.5% in moderate health state. In the absence of other glaucoma epidemiology in Japan, data were obtained from the Early Manifest Glaucoma Trial (EMGT) conducted in the US[23]. The relative risk of mortality was obtained from an Australian cohort[24].

Clinical Data Three types of clinical data were included in the model: treatment pattern, efficacy, and safety. As no Japanese data were identified, global data from the original model were used. In the absence of treatment pattern for glaucoma in Japan, the VF defect at entry (-3.0 dB for mild patients and -6.0 dB for moderate patients) and during progression (-0.05 dB natural decline rate per month in untreated patients), mean time to receive subsequent surgeries and hazard ratio of receiving subsequent surgeries per unit of IOP reduction compared with no IOP change (0.83) were obtained from the EMGT[23] and expert opinions. The time to background medication discontinuation (59.53mo) was based on expert opinions. The IOP reduction, utilisation of background medication, and probabilities of AEs caused by cataract surgery and subsequent surgeries were based on an RCT comparing iStent *inject*® combined with cataract surgery with cataract surgery alone[17]. Probabilities of AEs caused by background medication was obtained from a cost-utility analysis investigating the long-term health and economic outcomes of direct pressure-lowering medication for OHT[25].

Utility In the absence of Japanese data, global data from the original model were used[18,26]. Utility values of patients in different severity levels and disutility values due to subsequent surgeries and background medication for AEs were obtained from a Dutch cross-sectional survey assessing the impact of VF defect on POAG patient utility values[27]. Health preference was measured by the Health Utilities Index 3 (HUI-3) using tariffs for the Canadian population. In the absence of disutility value for trabeculotomy, the same disutility value for trabeculectomy was assumed for trabeculotomy with confirmation from the clinical experts.

Costs Five types of cost data were included in the model: surgery procedure costs, progression-related medical service costs, background medication costs, AE-related treatment costs, and societal costs. All costs were as of April 2021. Procedure fees for iStent *inject*®, cataract surgery, trabeculotomy, and trabeculectomy were obtained from the Japanese Ministry of Health, Labour and Welfare (MHLW)[28]. Progression-related medical service costs were calculated as the product of frequencies and unit costs of healthcare resource use, including physician consultation, VF defect test, optic disc imaging, examination of the ocular fundus, IOP measurement, eyesight test, slit-lamp microscopy, and gonioscopy. Frequency data were obtained from clinical experts. Unit costs were obtained from the MHLW[28].

For background medication, the cost element consisted of actual medication costs and medication service costs, including fees of prescription, basic dispensing, dispensing, and drug management instruction. According to the Japanese Glaucoma Society guidelines[7], Japanese published study[29] and clinical expert opinions, four categories of drugs are currently used as standard medications in Japan: prostaglandin (PG) as the 1st line, beta-blocker (BB) and combination of PG and BB as the 2nd line, and more than 2 combinations of carbonic anhydrase inhibitors (CAI)/BB+PG medication as the 3rd line. Market shares of medications were obtained from Inoue[29] and expert opinion. Unit costs of medications were obtained from the MHLW[30]. Unit cost of medication service per bottle were obtained from the MHLW[28]. Based on the expert input, medical wastage was not considered. To treat AEs caused by background medication, patients need to consult an ophthalmologist (1 time/mo) and have some tests run, *i.e.* slit-lamp microscopy (1 time/mo) and Goldmann applanation (2 times/mo). The healthcare resource use and frequency of treatment of AEs caused by surgeries are presented in Table 1.

Table 1 Model input

Parameters	Value, PSA distribution	DSA range, if applicable	PSA distribution, if applicable	Source
Surgery procedure costs (¥)				
Procedure for iStent *inject*®+cataract surgery	279900	(215100, 358500)	Gamma (α:62, β:4666)	April 2020, MHLW[28]
Procedure for cataract surgery	121000	(90750, 151250)	Gamma (α:62, β:1969)	April 2020, MHLW[28]
Procedure for trabeculotomy	190200	(142650, 237750)	Gamma (α:62, β:3094)	April 2020, MHLW[28]
Procedure for trabeculectomy	236000	(177000, 295000)	Gamma (α:62, β:3840)	April 2020, MHLW[28]
Progression-related medical service costs (¥)				
Physician consultation (2nd and after)	730 and 740	(730, 740)	Gamma (α:83013, β:0)	April 2020, MHLW[28]
Visual field defect test	380	(285, 475)	Gamma (α:62, β:6)	April 2020, MHLW[28]
Optic disc imaging	4000	(3000, 5000)	Gamma (α:62, β:65)	April 2020, MHLW[28]
Examination of the ocular fundus	560	(420, 700)	Gamma (α:62, β:9)	April 2020, MHLW[28]
Intraocular pressure measurement	820	(615, 1025)	Gamma (α:62, β:13)	April 2020, MHLW[28]
Eyesight test	690	(518, 863)	Gamma (α:62, β:11)	April 2020, MHLW[28]
Gonioscopy	380	(285, 475)	Gamma (α:62, β:6)	April 2020, MHLW[28]
Slit-lamp microscopy (anterior and posterior segments of the eye)	1120	(840, 1400)	Gamma (α:62, β:18)	April 2020, MHLW[28]
Background medication costs (¥)				
Average medication, (PG, BB, PG+BB, PG+BB+CAI)	2663[a]	(2052, 3264)	Gamma (α:74.1, β:35.9)	April 2021, MHLW[30]
Medication service costs (¥)				
Prescription	680	-	-	April 2020, MHLW[28]
Basic dispensing fee	420	-	-	April 2020, MHLW[28]
Dispensing fee	100	-	-	April 2020, MHLW[28]
Drug management instruction fee	430	-	-	April 2020, MHLW[28]
Adverse event-related treatment costs (¥)				
Betamethasone Sodium Phosphate	38.50	-	-	April 2021, MHLW[30]
Fluorometholone 0.1%, 0.02%	40.80; 33.40	-	-	April 2021, MHLW[30]
Levofloxacin hydrate 0.5%	91.30	-	-	April 2021, MHLW[30]
Atifloxacin	89.60	-	-	April 2021, MHLW[30]
Surgery-related adverse event costs	Healthcare resource used		Frequency/mo	-
Hyperaemia treatment[b]	Physician consultation (2nd and after); steroids; antibiotics (new quinolone)		4.0; 365/12; 365/12	Expert opinions
Stent obstruction treatment[b]	Physician consultation (2nd and after); gonioscopy; goldmann applanation		3.0; 1.0; 1.0	Expert opinions
Hyphema treatment[b]	Physician consultation (2nd and after); slit-lamp microscopy; Goldmann applanation; steroids		1.5;1.0; 1.0; 365/12	Expert opinions

[a]Average costs based on market share and expert opinions; [b]Within 1mo. PG: Prostaglandin; BB: Beta-blocker; PG+BB: Combination of PG and BB; PG+BB+CAI: More than 2 combinations of carbonic anhydrase inhibitors (CAI)/BB+PG medication.

In the scenario analysis from a societal perspective, full caregiver burden consisting of productivity loss of working family caregiver and formal caregiver burden were only applied to severely affected patients. An average wage of working family caregiver (¥307 700/mo) was collected from the MHLW[31]. It was assumed that 20% of severely affected patients would have family caregiving with a frequency of once a month. Formal caregiver burden was proxied by long-term care insurance level 1 (¥112 400/mo) as defined by the MHLW[32] under the assumption that all severely affected patients require the same level of care as patients receiving level 1 nursing care. A health economics expert verified the assumptions.

Statistical Analysis Both deterministic and probabilistic sensitivity analyses were conducted to evaluate the impact of assumptions used in the model and the variability surrounding model inputs. The deterministic one-way sensitivity analysis (OWSA) was conducted for the deterministic base case to determine the significant drivers of cost-utility. The 95% confidence interval was used as lower and upper bounds of the one-way sensitivity analysis. When not available, a ±25% variation of the deterministic base value was applied for the low and high values. Probabilistic base case analysis was conducted using 1000 iterations from random draws of the underlying parameter uncertainty. A beta distribution was used for proportion and utility values; a gamma distribution was considered for costs; a lognormal distribution was used for healthcare resource uses; and a normal distribution was considered for clinical data. The probabilistic base case analysis was expressed as ICUR scatterplot and cost-effectiveness acceptability curve (CEAC). The willingness-to-pay (WTP) threshold of ¥5 000 000/QALY in Japan, set by the Central Social Insurance Medical Council (Chuikyo), was used as a marker to judge the cost-utility[33].

Scenario Analysis Scenario analysis considering the full caregiver burden from a societal perspective was conducted to test the robustness of results.

RESULTS

Base Case The iStent *inject*® with cataract surgery strategy was found to be cost-effective compared with cataract surgery alone over a lifetime horizon in the probabilistic base case analysis. The incremental cost-utility ratio (ICUR) was estimated to be ¥1 430 647/QALY gained and the incremental cost-effectiveness ratio (ICER) was estimated to be ¥12 845 154/blind eye avoided. The iStent *inject*® with cataract strategy was found to increase cost compared to cataract surgery alone (¥1 025 785 *vs* ¥933 759, respectively) but was more effective in increasing QALYs (12.80 *vs* 12.74) and avoiding blinded eyes (0.133 *vs* 0.141) than cataract surgery alone. The differences in costs were mainly driven by the cost of primary surgery (¥279 903 *vs* ¥121 349). The iStent *inject*® with cataract surgery vs cataract surgery strategy was found to be cost-saving in two cost components: cost of secondary surgery (¥207 573 *vs* ¥211 487, respectively) and cost of medication (¥73 305 *vs* ¥136 594). Small differences were found between iStent *inject*® with cataract surgery strategy and cataract surgery strategy alone in progression-related medical cost (¥464 838 *vs* ¥464 223, respectively) and AE costs (¥165 *vs* ¥106). The base case results are depicted in Table 2.

Sensitivity Analysis The ICUR scatterplot in probabilistic base case analysis is shown in Figure 2. iStent *inject*® with cataract surgery strategy was found to produce higher QALYs in 97.8% of the iterations. All the probabilistic simulations suggest iStent *inject*® is associated with an increase in costs. Figure 3 presents the results of CEAC. At the WTP threshold of ¥5 000 000 per QALY gained, the iStent *inject*® with cataract strategy was found to have a 90% probability of being cost-effective. Figure 4 presents the results of OWSA. The top key drivers of ICUR were an IOP reduction at 2y due to cataract surgery alone, medication reduction at 2y due to cataract surgery alone and utility value of mild glaucoma.

Scenario Analysis Based on scenario analysis from the societal perspective, iStent *inject*® with cataract surgery strategy was found to dominate cataract surgery alone strategy, with a cost saving of -¥208 803, increased number of QALY gained of 0.066, and 0.008 blind eyes avoided. The results of scenario analyses are presented in Table 3.

DISCUSSION

In this cost-utility analysis, the iStent *inject*® with cataract surgery strategy was found to be cost-effective *vs* cataract surgery alone in patients with mild-to-moderate POAG needing cataract surgery. At the WTP threshold of ¥5 000 000/QALY, the iStent *inject*® with cataract surgery strategy was found to have at least a 90% probability of being cost-effective.

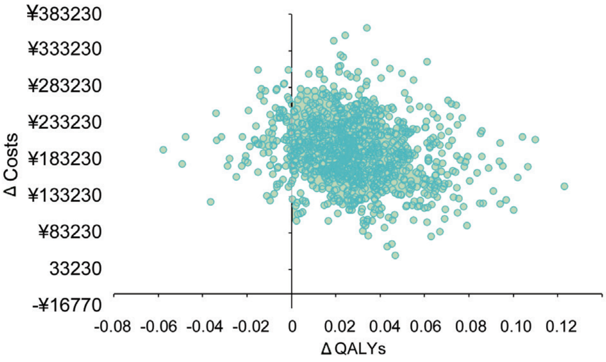

Figure 2 Incremental cost utility ratio scatterplot for the iStent *inject*® with cataract strategy *vs* cataract surgery strategy QALY: Quality-adjusted life-year.

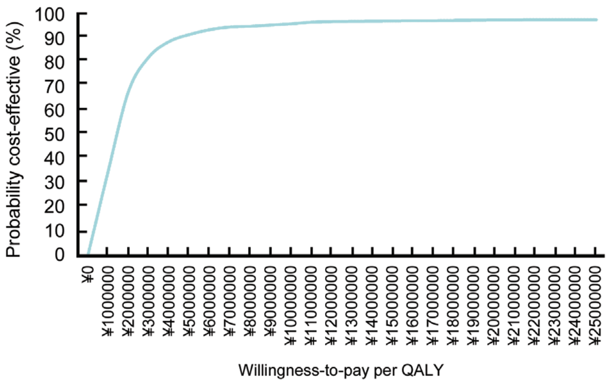

Figure 3 Incremental cost effectiveness ratio acceptability curve for the iStent *inject*® with cataract strategy *vs* cataract surgery strategy QALY: Quality-adjusted life-year.

Table 2 Base case results

Outcome	iStent *inject*®+ cataract surgery	Cataract surgery	Incremental
Total costs (¥)	1025785	933759	92026
Primary surgery	279903	121349	158554
Secondary surgeries	207573	211487	-3914
Medication costs	73305	136594	-63289
Progression-related costs	464838	464 223	615
Adverse event costs	165	106	59
QALYs	12.80	12.74	0.06
Life years	16.68	16.66	0.02
Number of blind eyes	0.14	0.14	0.01
Incremental cost / QALY gained (¥)			1430647
Incremental cost / blind eye avoided (¥)			12845154

QALY: Quality-adjusted life-year.

The results are considered robust based on one-way sensitivity analyses. Considering the loss of productivity of family caregivers and caregiver burden, the iStent *inject*® with cataract surgery strategy was found to dominate cataract surgery alone and save costs associated with loss of productivity of working family caregivers and caregiver burden in patients needing cataract surgery. When the cost of iStent *inject*® with cataract surgery increased from the original input of ¥279 900 to ¥516 300, the ICUR reached the WTP threshold ¥5 000 000/QALY gained.

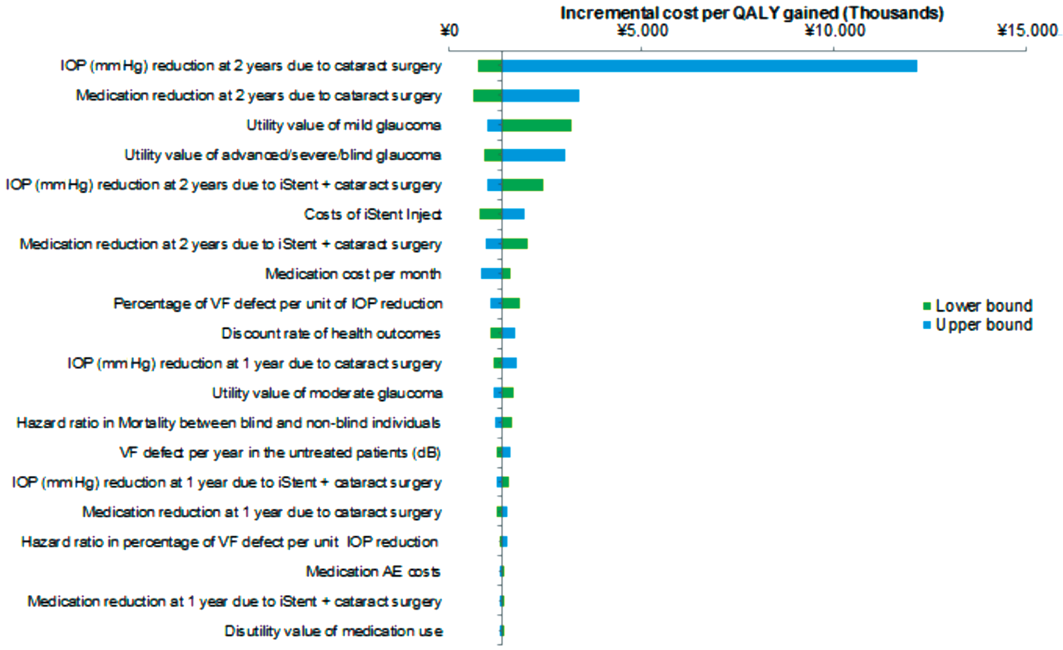

Figure 4 Tornado chart AE: Adverse event; IOP: Intraocular pressure; QALY: Quality-adjusted life-year; VF: Vision field.

Table 3 Scenario analysis results

Outcome	iStent *inject*®+cataract surgery	Cataract surgery	Incremental
Total costs (¥)	6846877	7055679	-208803
Primary surgery	280280	121380	158900
Secondary surgeries	209448	213137	-3690
Medication costs	73619	136342	-62723
Progression-related costs	462220	461590	630
Adverse event costs	165	105	60
Loss of productivity from family caregivers	173591	182596	-9005
Caregiver burden (nursing insurance)	5647554	5940529	-292974
QALYs	12.833	12.767	0.066
Life years	16.747	16.724	0.023
Number of blind eyes	0.133	0.141	0.008
Incremental cost / QALY gained (¥)			Dominant
Incremental cost / blind eye avoided (¥)			Dominant

QALY: Quality-adjusted life-year.

This is the first cost-utility analysis comparing the iStent *inject*® with cataract surgery *vs* cataract surgery alone in the Japanese patients with mild-to-moderate POAG. The model inputs were obtained from the Japanese and global data with validation by Japanese clinical experts to represent the local Japanese setting. The results from this model are consistent with previously published studies that used the same model adapted to different settings, including France[26], Canada[20] and Spain[34]. A similar cost-utility analysis to the present analysis assessed combined MIGS of one or two trabecular micro-bypass stents with cataract surgery in German patients with POAG[35]. However, the analysis was conducted separately in two subgroups of patients with moderate and advanced POAG. The study found that in the moderate stage, the implementation of two stents during cataract surgery produced the highest effectiveness and the lowest ICUR among cataract surgery combined with three alternative MIGS methods: 1) one trabecular micro-bypass stent, 2) two stents, and 3) intracanalicular scaffold, compared with cataract surgery alone. These findings reinforce the benefit of using iStent *inject*® on early stages of POAG.

The Markov model used in this analysis ensured a robust approach to evaluate the impact of iStent *inject*® compared with iStent *inject*® combined with cataract surgery in terms of effectiveness as measured by QALY, the number of blind eyes, and costs. It is particularly suited to model chronic diseases such as POAG. The Markov model allows the synthesis of data from various sources and extrapolation from primary data sources over time. Sources of the model were credible as they were based on published literature and were completed and/or validated by experts.

The interpretation of study results should consider the following limitations. First, due to limited data available for the progression of glaucoma severity and the impact of trabecular micro-bypass surgery (TBS) device, we simulated the disease progression indirectly through the IOP level and the IOP reduction by the medical device. Future models should incorporate long-term evidence on the effect of these medical devices on slowing the progression of glaucoma. Second, the relationship between IOP level and glaucoma severity progression was derived from an international study, as there are no Japanese data available. However, the data were validated by Japanese clinical experts, who confirmed that it could represent the case in Japan. Third, a constant rate of a natural decline in VF for all patients, regardless of glaucoma severity, was applied. This was a conservative assumption as an application of higher rates of the natural decline in VF for patients with moderate and advanced glaucoma would improve the cost-utility of TBS devices. And finally, assumptions were made for long-term IOP reductions by treatments because long-term IOP reduction data were not available in the literature at the time of this study. There were 2-year data available for TBS devices: a 1.2% decline in IOP reduction in the 2nd year (8.3) compared with the previous year (8.4)[17]. Yet, in the present analysis, conservative assumptions were applied: 5% decline in the efficacy on IOP reduction compared with the previous year and no efficacy after 10y.

Long-term follow-up of patients who underwent an iStent *inject*® implantation is needed to measure the change in VF loss, IOP reduction, and medication reduction. Existing modelling methods depend on assumptions for extrapolation as well as mapping of an IOP reduction to the progression of glaucoma severity. No evidence on healthcare resource utilisation by glaucoma health states is available for Japanese patients. The estimates of resource use were collected from expert opinions. Changes may have occurred in treatment practice due to the introduction of other treatment options. Updated resource use estimates related to the extent of VF loss or glaucoma severity are of need for future economic modelling purposes. The impact of medication nonadherence in patients who underwent iStent *inject*® implantation has not been examined in the literature either. A real-world observational study may provide valuable insights into the change in risk of glaucoma progression due to nonadherence in patients who underwent iStent *inject*® implantation.

In conclusion, the iStent *inject*® with cataract surgery is a cost-effective strategy over cataract surgery alone from the payer's perspective and cost-saving from the societal perspective in patients with mild-to-moderate POAG in Japan.

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Authors' contributions: Igarashi A, Ishida K, Shoji N, Chu A, and Falvey H conceived the research and designed the analyses; Han R, Ueyama M and Onishi Y acquired the data and Han R, and Ueyama M performed the analyses; all authors participated in the interpretation of the data; All authors wrote the manuscript, participated in its revisions, read and approved the final manuscript.

Conflicts of Interest: Igarashi A, Ishida K and **Shoji N** received consultant fees for their roles in study design, interpretation of results and review of the manuscript; **Igarashi A** also reports grants and other from Gilead Sciences KK., grants from Intuitive Surgical GK., grants from Boston Scientific Japan Inc., grants and personal fees from Pfizer Japan Inc., grants from Beckton Dickinson and Company, grants from Milliman Inc., personal fees and other from Terumo corporation, personal fees from Chugai Pharmaceuticals Inc., personal fees from Astellas Pharma Inc., other from Fuji film Inc., other from CSL Behring Japan Inc., personal fees from Sanofi Japan Inc., personal fees and other from Takeda Pharmaceutical Inc., personal fees from Nippon Boeringer Ingelheim Inc., personal fees from Ono pharmaceutical Inc., personal fees from Taiho pharmaceutical Co. Ltd., personal fees from Eisai Inc., personal fees from Abbvie GK, personal fees from Sumitomo Dainippon Pharma Inc., personal fees from Ayumi Pharmaceutical Inc., personal fees from Medilead Inc., personal fees from Novo Nordisk Japan Inc., personal fees from Novartis Pharma Inc., personal fees from GSK Inc., outside the submitted work. **Shoji N** also received consulting fees from Seikagaku Corporation; **Chu A** and **Falvey H** are employees of Glaukos and stockholders of Glaukos; **Han R**, **Ueyama M** and **Onishi Y** are employees of Creativ-Ceutical.

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