

iStent for Adults With Glaucoma: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

Glaucoma is a condition in which the eye's drainage system does not work properly. Pressure in the eye builds, causing progressive damage to the optic nerve. This can lead to vision loss or irreversible blindness. Medication (eye drops) and laser therapy can reduce pressure in the eye for people with mild glaucoma. But those with advanced glaucoma may need an invasive treatment called filtration surgery.

Minimally invasive glaucoma surgery (MIGS) is the newest group of surgical procedures for glaucoma. Most MIGS procedures are done at the same time as cataract surgery (an eye surgery to remove a cloudy lens) and may be safer than more invasive surgeries for glaucoma. iStent is a form of MIGS in which a tiny device is implanted in the eye to drain fluid and reduce pressure.

This health technology assessment examines how safe, effective, and cost-effective iStent is for adults with glaucoma. It also evaluates the potential budget impact of publicly funding iStent and on the preferences and values of people with glaucoma.

What Did This Health Technology Assessment Find?

From the evidence available, it is not clear whether iStent alone (not combined with cataract surgery) is more effective than filtration surgery and whether iStent plus cataract surgery is more effective compared with other MIGS procedures plus cataract surgery. There may be no difference in the effectiveness of iStent alone compared with medication. Compared with cataract surgery alone, iStent combined with cataract surgery may reduce pressure in the eye and the number of medications needed for people with mild to moderate glaucoma.

Compared with medication, iStent may be cost-effective, but it may not be cost-effective when compared with filtration surgery or when used in combination with cataract surgery compared with cataract surgery alone. If iStent becomes publicly funded in Ontario, it may reduce spending on medication, but overall it will likely lead to additional costs to the health system.

People with glaucoma said avoiding blindness was their main priority in deciding on treatment. Among people who had a MIGS procedure, they generally felt the treatment was successful, with few side effects and a short recovery time. But no one we spoke with knew whether they had received an iStent so they could not comment on this specific MIGS procedure.

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Abstract

Background

Glaucoma is a condition that causes progressive damage to the optic nerve, which can lead to visual impairment and potentially to irreversible blindness. The iStent and iStent inject are devices implanted in the eye during a type of minimally invasive glaucoma surgery (MIGS) to reduce intraocular pressure by increasing trabecular outflow by bypassing the trabecular meshwork. We summarized two health technology assessments and additional recent publications that evaluated iStent for people with glaucoma, including effectiveness, safety, cost-effectiveness, the budget impact of publicly funding iStent, and patient preferences and values.

Methods

We summarized two health technology assessments recently completed in Canada. In addition, we summarized new evidence we identified through expert consultation and scoping of the literature. We reported the quality of the body of clinical evidence as reported by the included health technology assessments, according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.

Results

Comparing iStent with pharmacotherapy, there may be no difference in comparative clinical effectiveness (GRADE: Very low to Low). There was uncertainty around the comparative clinical effectiveness of iStent compared with filtration surgery and of iStent plus cataract surgery compared with a different MIGS procedure plus cataract surgery (GRADE: Very low). iStent with cataract surgery may improve comparative clinical effectiveness (reduced intraocular pressure and number of medications) compared with cataract surgery alone (GRADE: Low).

iStent may be cost-effective compared with pharmacotherapy (incremental cost-effectiveness ratios [ICER]: \$14,120–\$25,596/quality-adjusted life-year [QALY]; 60%–76% and 65%–100% of iterations cost-effective at willingness-to-pay values of \$50,000/QALY and \$100,000/QALY, respectively). iStent with cataract surgery may not be cost-effective compared with cataract surgery alone (ICERs: \$108,934–\$112,380/QALY; 17%–46% and 46%–68% of iterations cost-effective at willingness-to-pay values of \$50,000/QALY and \$100,000/QALY, respectively). iStent may not be cost-effective compared with filtration surgery (iStent was less effective and more expensive than filtration surgery). These estimates are influenced by the long-term effectiveness of iStent.

The iStent device costs approximately \$1,250 (for two iStent or iStent inject devices). Based on a recent analysis by Quebec's Institut national d'excellence en santé et en services sociaux (INESSS) and our previous analysis on MIGS, publicly funding iStent may reduce some spending on glaucoma medication but, overall, iStent is likely to lead to additional costs for the public health care system. In Ontario, publicly funding MIGS over 5 years is estimated to cost a total of \$40 million if uptake is slow (25,000 people) and \$199 million, if uptake is fast (100,000 people). In Quebec, publicly funding iStent over 3 years is estimated to cost a total of \$29 million (15,000 people).

People with glaucoma with whom we spoke reported that pharmacotherapy can be challenging and that they relied on trust in their physician to determine if surgery was necessary to avoid potential consequences of glaucoma, such as blindness. Those who received MIGS procedures found it beneficial,

with minimal side effects and recovery time. However, they were often unaware what type of MIGS procedure they received, so they could not specifically comment on iStent.

Conclusions

We are uncertain about the comparative clinical effectiveness of iStent compared with filtration surgery, as well as iStent combined with cataract surgery versus other MIGS procedures combined with cataract surgery. There may be no difference in the comparative clinical effectiveness of iStent compared with pharmacotherapy. iStent combined with cataract surgery may improve clinical effectiveness (mainly intraocular pressure and number of medications) when compared with cataract surgery alone.

In some instances, iStent may be cost-effective (i.e., when compared with pharmacotherapy) but in other instances it may not be cost-effective (i.e., when iStent combined with cataract surgery is compared with cataract surgery alone or when iStent is compared with filtration surgery). Publicly funding iStent may reduce some spending on pharmacotherapy but, overall, is likely to lead to additional costs for the public health system. People with glaucoma reported that pharmacotherapy adherence could be challenging, and that avoiding blindness was their main priority for treatment. Experiences with MIGS procedures were positive, although patients were unable to comment on iStent specifically.

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Objective

This health technology assessment examines the evidence for the effectiveness, safety, cost-effectiveness, budget impact, and patient preferences of iStent for adults with glaucoma.

Background

Health Condition

Glaucoma is a condition that causes progressive damage to the optic nerve that can lead to visual impairment and potentially to irreversible blindness.¹⁻³ Risk factors include elevated intraocular pressure (IOP), increasing age, family history of glaucoma, race, and comorbidities, such as diabetes, hypertension, and hypothyroidism.^{2,4,5} An IOP higher than normal can damage the optic nerve.^{3,6} Intraocular pressure is the most important and the only modifiable risk factor for glaucoma.^{2,7} With every 1 mm Hg (millimetres of mercury) increase in IOP, there is a 10% higher risk for both the development and progression of the condition.⁸

Clinical Need and Target Population

It was estimated in 2002/03 that glaucoma affected approximately 400,000 Canadians.⁹ In Ontario, an estimated 290,000 (2019) to 323,000 (2023) people have glaucoma, based on a previous budget impact analysis conducted by Ontario Health.¹⁰ Among these people in Ontario, approximately 23,000 undergo cataract surgery annually.¹⁰ Open-angle glaucoma is the most common form of the condition.^{5,11} It occurs when the part of the eye known as the Schlemm's canal, including the trabecular meshwork (responsible for draining fluid from the eye), is anatomically open but not working optimally. Another type of glaucoma, called angle-closure glaucoma, occurs when the Schlemm's canal is anatomically blocked.⁷

Current Treatment Options

Treatment for glaucoma aims to lower intraocular pressure. There is a spectrum of current treatments for glaucoma that includes pharmacotherapy (eye drops), laser therapy, and the more invasive option of filtration surgery.^{12,13} All current treatments have their challenges. Pharmacotherapy challenges include ineffective use,^{14,15} local and systemic side effects,¹⁶ and lifetime costs.¹⁷ Laser therapy can be associated with ocular discomfort, IOP spikes, and the need for repeat procedures.^{18,19} Lastly, filtration surgery, while generally effective, is an invasive procedure that can have intra- and postoperative complications.^{5,12,20,21}

Health Technology Under Review

Minimally invasive glaucoma surgery (MIGS) is the newer surgical option to treat glaucoma. The iStent (first generation) and iStent inject (second generation) are devices used in a type of MIGS designed to reduce intraocular pressure by bypassing the trabecular meshwork, allowing for improved drainage. The iStent inject is a micro-bypass stent system, where tiny devices (0.3 mm × 0.4 mm) are inserted into the trabecular mesh, to act as a shunt for fluid in the eye.²² This can be done as a stand-alone procedure or at the same time as cataract surgery (also known as phacoemulsification, a common type of cataract surgery). In Ontario and Quebec, the majority of MIGS procedures are assumed to take place at the same time as cataract surgery.^{10,23} The safety profile of iStent may be better than that of more invasive procedures.²⁴

In this report, we use “iStent” to refer to either generation of this device, unless specified, and to the iStent procedure.

Regulatory Information

Health Canada approved the first generation iStent in 2009 and the second generation, iStent inject, in 2015.

Table 1: iStent Devices Licensed by Health Canada

Manufacturer	Device First Issue Date	Device Class	Device Name	Licence Number
Glaukos Corporation	2009-07-15	III	iStent Trabecular Micro-Bypass Stent System (Left and Right)	80214
	2009-09-21	II	iStent Trabecular Micro-Bypass Inserter	80717
	2015-08-04	III	iStent inject Trabecular Micro-Bypass System	95520

Ontario, Canadian, and International Context

Currently in Ontario, MIGS devices and procedures (including iStent) are not publicly funded, and a small number of facilities provide MIGS. To our knowledge, device costs are primarily covered by each centre, although some patients may pay for some or all device costs. In Ontario, there are no physician fee codes that are specific for MIGS procedures, but physicians can use more generic fee codes to receive payment for MIGS from the Ontario Health Insurance Plan (OHIP).²⁵ Currently, people with glaucoma have access to publicly funded annual eye exams.²⁵ Other current treatments for glaucoma are publicly funded through OHIP (e.g., medication for those patients covered by the Ontario Drug Benefit program and surgery) or covered by private insurance plans (e.g., medication for those not covered by the Ontario Drug Benefit program). A recent quality standard by Ontario Health outlines high-quality care for glaucoma.²⁶

Two Canadian provinces (Alberta and Quebec) have billing codes for MIGS (which includes iStent). In the United States, public coverage for iStent and other types of MIGS exists through Medicare when combined with cataract surgery.²⁷ In Australia, the Medical Services Advisory Committee has made a draft recommendation, not yet finalized at the time of writing this report, to fund trabecular micro-bypass glaucoma surgery (iStent and Hydrus) as a stand-alone procedure.²⁸

Methods

We summarized the results specific to iStent of two recent health technology assessments on minimally invasive glaucoma surgery (MIGS). The research questions and both the clinical and economic methods of the two included health technology assessments aligned with the purpose of this review. The first was a collaborative health technology assessment completed by the Canadian Agency for Drugs and Technologies in Health (CADTH) and Ontario Health in 2019.^{10,29} The second was completed in 2020 by Quebec's health technology assessment agency, the Institut national d'excellence en santé et en services sociaux (INESSS).²³ Details of the specific methods and results of these health technology assessments are available in the original publications.^{10,23,29}

In addition, we reviewed additional clinical and economic evidence identified through public comments, scoping, and consultations with manufacturer.

Clinical Evidence

Included Health Technology Assessments

Health Technology Assessment by CADTH and Ontario Health

RESEARCH QUESTIONS

- What are the comparative clinical effectiveness and safety of MIGS (specifically, iStent) versus pharmacotherapy, laser therapy, filtration surgery, or a different type of MIGS, for the treatment of glaucoma in adults?
- What are the comparative clinical effectiveness and safety of MIGS (iStent combined with cataract surgery) versus a different type of MIGS combined with cataract surgery, filtration surgery plus cataract surgery, or cataract surgery alone for the treatment of glaucoma in adults?

METHODS

This collaborative health technology assessment conducted a systematic review of primary studies, and databases were searched from January 1, 2000, to November 2017. Regular alerts were also established to update the search strategy until the final collaborative health technology assessment was published (January 4, 2019). The overall quality of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Outcomes of interest included quality of life, reduction in intraocular pressure, number of medications, visual field and acuity, and adverse events.²⁹

RESULTS

This health technology assessment included 11 studies (five randomized controlled trials and six retrospective cohorts) that reported on iStent.²⁹ Appendix 1 (Tables A1 to A7) presents a summary of the results.

Based on evidence of very low quality, there was uncertainty around the comparative clinical effectiveness and safety of iStent versus pharmacotherapy and iStent versus filtration surgery, as well as iStent plus cataract surgery versus a different MIGS procedure plus cataract surgery (Tables A1, A2, and A4 to A7). Based on evidence of very low to low quality, the clinical effectiveness of iStent (specifically, treatment with two iStent procedures in a single eye) in combination with cataract surgery may improve intraocular pressure and reduce the number of medications patients used, compared with cataract surgery alone. Most reported adverse events were considered minor and similar rates were observed across treatment groups.²⁹

Health Technology Assessment by INESSS

RESEARCH QUESTIONS

- What are the comparative clinical effectiveness and safety of two iStents (a procedure in which two iStents are placed in a single eye) versus pharmacotherapy for the treatment of glaucoma in adults?
- What are the comparative clinical effectiveness and safety of two iStents with cataract surgery versus cataract surgery alone for the treatment of glaucoma in adults?

METHODS

This health technology assessment evaluated the clinical effectiveness and safety of iStent, with or without cataract surgery, compared with pharmacotherapy or cataract surgery alone.²³ Their methods included updating a literature search from a review completed by CADTH in November 2017 to identify randomized controlled trials published after 2017. The overall quality of evidence for each outcome was assessed by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Outcomes of interest included intraocular pressure, number of medications, visual field and acuity, and adverse events.

RESULTS

The INESSS clinical evidence review²³ included only randomized controlled trials that evaluated the use of the two-iStent procedure. In total, the review included seven randomized controlled trials. Appendix 1 (Tables A8 and A9) presents a summary of the results.

Based on evidence of very low to low quality, there was no difference around the comparative clinical effectiveness and safety of iStent versus pharmacotherapy. Also based on evidence of very low to low quality, the clinical effectiveness of iStent in combination with cataract surgery, compared with cataract surgery alone, may improve intraocular pressure (inconsistent results from two randomized controlled trials) and reduce the number of medications used (however, medication use was not eliminated). Most of the reported adverse events were considered minor and similar rates of events were observed across treatment groups.²³

Additional Clinical Evidence

An additional systematic review examining iStent was published subsequent to the two health technology assessments described above.³⁰ That review demonstrated a reduction in intraocular pressure and the number of medications used when iStent was combined with cataract surgery, compared with cataract surgery alone. However, several limitations to this review reduced its quality. We used the Risk of Bias in Systematic Reviews (ROBIS) tool to assess the risk of bias and limitations of the systematic review, which included no reporting of which studies were included in the analysis (randomized controlled trials and case series may have been analyzed together) and no forest plots were presented in the paper. Additionally, the report acknowledges that the author was a consultant to industry. Appendix 2 (Table A10) presents our ROBIS assessment.

We also found several case series published in 2019 that indicate reductions in intraocular pressure and the number of medications patients used after receiving iStent.³¹⁻³⁵ These studies were not included in the health technology assessments summarized above because none had a comparator group. Therefore, they do not report any new information comparing iStent with other treatments.

Clinical Evidence Conclusions

Based on the evidence reported in two health technology assessments about the effectiveness and safety of iStent for adults with glaucoma:

- There may be no difference in comparative clinical effectiveness of iStent when compared with pharmacotherapy
- We are uncertain about the comparative clinical effectiveness of iStent when compared with filtration surgery
- We are uncertain about the comparative clinical effectiveness of iStent with cataract surgery when compared with other MIGS procedures with cataract surgery
- However, iStent with cataract surgery may improve clinical effectiveness (i.e., decreases intraocular pressure and number of medications) when compared with cataract surgery alone

Economic Evidence: Economic Evaluation and Budget Impact Analysis

Included Economic Evaluations

Health Technology Assessment by CADTH and Ontario Health

RESEARCH QUESTIONS

- What is the cost-effectiveness of MIGS (specifically, iStent) versus a different type of MIGS, pharmacotherapy, laser therapy, or filtration surgery, for the treatment of glaucoma in adults?
- What is the cost-effectiveness of MIGS (specifically, iStent) plus cataract surgery versus a different type of MIGS plus cataract surgery, filtration surgery plus cataract surgery, or cataract surgery alone, for the treatment of glaucoma in adults?

METHODS

The primary economic evaluation by CADTH and Ontario Health²⁹ sought to understand the cost-effectiveness of MIGS as a class (with or without cataract surgery) compared with alternative treatments in adults with glaucoma. Based on the availability of clinical literature, the cost-effectiveness of iStent was examined in three comparisons: using two iStents versus pharmacotherapy, one iStent with cataract surgery versus cataract surgery alone, and two iStents versus filtration therapy.

Using a Markov model, CADTH and Ontario Health examined how iStent and alternatives affect glaucoma progression, quality of life, and costs over a lifetime horizon. The analyses used a Canadian public health care payer perspective. Clinical inputs were derived from the clinical evidence review in the health technology assessment and the published literature. Costs were derived from various published sources and informed by clinical expert opinion. Alberta costs were used to perform most of the analyses about iStent. Some sensitivity analyses were conducted using costs specific to Ontario. Results were presented as incremental cost-effectiveness ratios (ICER), using 2018 Canadian dollars and quality-adjusted life-years (QALY).²⁹

RESULTS

The results of the economic evaluation showed that the cost-effectiveness of iStent depended on the specific comparison (Appendix 3, Table A11).

The results suggested that using two iStents may be cost-effective compared with pharmacotherapy (ICER with Alberta costs: \$18,808/QALY; ICER with Ontario costs: \$14,120/QALY). However, probabilistic sensitivity and scenario analyses showed uncertainty in this result. Probabilistic analyses showed that two iStents was cost-effective in 60% and 65% of model iterations at willingness-to-pay values of \$50,000 per QALY gained and \$100,000 per QALY gained, respectively. While the clinical reviews included in this report found iStent may have similar clinical effectiveness when compared with pharmacotherapy, assumptions used in the economic modelling may have led to greater average QALYs for iStent compared with pharmacotherapy (i.e., assumptions around adherence to pharmacotherapy). Further, in some scenarios, using two iStents appeared dominant (less costly and more effective) compared with pharmacotherapy (e.g., when drug mark-up and dispensing fees were included).

However, in others, the ICER was greater than \$100,000 per QALY gained (e.g., with no maintenance of treatment effect after the end of clinical trial follow-up).²⁹

The results also suggested that using one iStent combined with cataract surgery is unlikely to be cost-effective compared with cataract surgery alone (ICER with Alberta costs: \$108,934/QALY). Probabilistic analyses showed that one iStent was cost-effective in 17% and 46% of model iterations at willingness-to-pay values of \$50,000 per QALY gained and \$100,000 per QALY gained, respectively.²⁹

Finally, the results suggested that filtration surgery is dominant (less costly and more effective) than using two iStents alone. However, this finding should be interpreted with caution as the clinical studies used to inform this analysis did not include measures that could be used to evaluate uncertainty (e.g., standard deviation).²⁹

Health Technology Assessment by INESSS

RESEARCH QUESTIONS

- What is the cost-effectiveness of two iStents versus pharmacotherapy for the treatment of glaucoma in adults?
- What is the cost-effectiveness of two iStents with cataract surgery versus cataract surgery alone for the treatment of glaucoma in adults?

METHODS

Using a Markov model, INESSS²³ examined how two iStents and alternatives affect glaucoma progression, quality of life, and costs over a 15-year time horizon. Their analyses used the perspective of the Quebec public health care and social services payer. They derived clinical inputs from their clinical evidence review, the manufacturer, and the published literature. Costs were derived from administrative data and various published sources. Results were presented as ICERs, using Canadian dollars (year not specified) and QALYs.

RESULTS

The results of the economic evaluation showed that cost-effectiveness of iStent depended on the specific comparison (Appendix 3, Table A11).

The results suggested that two iStents may be cost-effective compared with pharmacotherapy (ICER: \$25,596/QALY). Probabilistic analyses showed that two iStents was cost-effective in 76% and 100% of model iterations at willingness-to-pay values of \$50,000 per QALY gained and \$100,000 per QALY gained, respectively. The ICER was influenced by assumptions about the maintenance of treatment effect after the end of clinical trial follow-up (ICER with 0% maintenance: \$111,200/QALY; ICER with 100% maintenance: \$6,100/QALY).²³ While the clinical reviews included in this report found iStent may have similar clinical effectiveness when compared with pharmacotherapy, assumptions used in the economic modelling may have led to greater average QALYs for iStent compared with pharmacotherapy (i.e., assumptions around the impact of medication on quality of life).

The results also suggested that two iStents with cataract surgery is unlikely to be cost-effective compared with cataract surgery alone (ICER: \$112,380/QALY). Probabilistic analyses showed that two iStents was cost-effective in 46% and 68% of model iterations at willingness-to-pay values of \$50,000 per QALY gained and \$100,000 per QALY gained, respectively. The ICER was influenced by assumptions

about the maintenance of treatment effect after the end of clinical trial follow-up (ICER with 0% maintenance: \$503,000/QALY; ICER with 100% maintenance: \$63,700/QALY).²³

Additional Economic Evaluations

We identified two other published cost-effectiveness analyses conducted using a Canadian public payer perspective and Ontario costs.^{36,37} One study assessed the cost-effectiveness of two iStents compared with pharmacotherapy,³⁷ and the other assessed the cost-effectiveness of two iStents with cataract surgery compared to cataract surgery alone.³⁶ Both studies used Markov models to examine how iStent and alternatives affect glaucoma progression, quality of life, and costs over a lifetime horizon. Clinical inputs and costs were derived from the published literature. Both studies were financially supported by the manufacturer of iStent.

Both analyses found that treatment with two iStents (with or without cataract surgery) was less costly and more effective than alternatives. Probabilistic analyses showed that two iStents was cost-effective in 94% to 100% and 97% to 100% of model iterations at willingness-to-pay values of \$50,000 per QALY gained and \$100,000 per QALY gained, respectively. Compared to the analyses conducted in the health technology assessments by CADTH and Ontario Health²⁹ and by INESSS,²³ these studies used higher average medication costs and a slower decline in treatment effect after the end of clinical trial follow-up. There is uncertainty about the long-term maintenance of iStent's treatment benefit. If the benefit declines more rapidly, iStent would be less likely to be cost-effective.

Included Budget Impact Analyses

Health Technology Assessment by CADTH and Ontario Health

RESEARCH QUESTION

- From the perspective of the Ontario Ministry of Health, what is the potential 5-year budget impact in Ontario of publicly funding MIGS (specifically, iStent) in adults with glaucoma?

METHODS

This health technology assessment estimated the 5-year budget impact of publicly funding MIGS in adults with open-angle glaucoma in Ontario.¹⁰ The analysis looked at MIGS as a class of devices, including iStent, and assumed MIGS would be used in three subgroups: (1) MIGS in combination with cataract surgery as a replacement for cataract surgery alone in people with mild to moderate glaucoma; (2) MIGS alone as a replacement for other glaucoma treatments in people with mild to moderate glaucoma; and (3) MIGS (with or without cataract surgery) to replace filtration surgery (with or without cataract surgery) in people with advanced to severe glaucoma. Based on the cost and evidence inputs used, the first two subgroups are most applicable to iStent. The reference case of the budget impact analysis assumed 90% of MIGS devices would be used in the first two subgroups.¹⁰

RESULTS

Although publicly funding MIGS would lead to reductions in the amount spent on pharmacotherapy, overall it would lead to additional costs for the health care system. Assuming a slow uptake (N = 25,107 people over 5 years), the annual budget impact of publicly funding MIGS in Ontario over the next 5 years ranges from \$1 million in year 1 to \$18 million in year 5, for a total of \$40 million. Assuming a fast uptake (N = 96,259 people over 5 years), the annual budget impact of publicly funding MIGS in Ontario ranges from \$6 million in year 1 to \$70 million in year 5, for a total of \$199 million. The budget impact

was influenced by the uptake rate and proportion of people in each subgroup. When the analysis used alternate, less costly billing codes for MIGS, the budget impact was reduced.¹⁰

Health Technology Assessment by INESSS

RESEARCH QUESTIONS

- From the perspective of the Quebec health care system, what is the potential 3-year budget impact in Quebec of publicly funding iStent in adults with mild to moderate, primary, open-angle glaucoma?
- What is the real-world impact of MIGS procedures on claims for glaucoma medication?

METHODS

INESSS estimated the 3-year budget impact of publicly funding iStent in adults with mild to moderate primary open-angle glaucoma in Quebec.²³ The analysis looked at iStent (with or without cataract surgery) as a replacement for cataract surgery alone or with pharmacotherapy. They assumed two iStent devices cost approximately \$1,250 and that 90% of devices would be implanted during cataract surgery and replace cataract surgery alone.

In addition, INESSS used administrative data, to explore the impact of MIGS procedures on claims for glaucoma medication.²³ Between February 2013 and June 2019, INESSS collected data on medication claims before and after people who had MIGS procedures. MIGS procedures included iStent and other devices (Hydrus, XEN, Cypass, Kahook Dual Blade, and GATT).

RESULTS

Similar to our results for Ontario, this Quebec analysis found that publicly funding iStent would lead to reductions in the amount spent on pharmacotherapy but additional costs for the health care system overall. Assuming a constant rate of uptake (N = 15,255 people over 3 years), the annual budget impact of publicly funding iStent in Quebec over the next 3 years ranges from \$10 million in year 1 to \$9 million in year 3, for a total of \$28 million. The budget impact was influenced by uptake, and in sensitivity analyses the total budget impact ranged from \$5 million to \$96 million over 3 years.²³

INESSS obtained medication claims data for 1 year before and 1 year after MIGS for 1,140 people. People who received one and two MIGS procedures saved \$69 and \$154, respectively, on medication annually. In addition, INESSS analyzed data 3 years before and 3 years after MIGS for 333 people. People who received one and two MIGS procedures saved \$8 and \$82, respectively, on medication each year.²³ The reason for the drop in savings over the 3-year period compared with the 1 year period is unclear but could be due to several factors, such as improvements in devices or techniques, variation in pharmacotherapy used, and variation in the ability of MIGS to reduce pharmacotherapy over time.

Economic Evidence Conclusions

The cost-effectiveness and budget impact of iStent are influenced by assumptions about its long-term clinical effectiveness and uptake. Based on analyses conducted by CADTH and Ontario Health²⁹ and by INESSS,²³ in adults with glaucoma:

- iStent may be cost-effective compared with pharmacotherapy
- iStent performed with cataract surgery may not be cost-effective compared with cataract surgery alone
- iStent may not be cost-effective compared with filtration surgery
- While publicly funding iStent may reduce some spending on glaucoma medication, iStent is likely to lead to additional costs for the public health care system overall
- The budget impact is influenced by the rate of iStent uptake and may range from \$28 million (over 3 years) to \$200 million (over 5 years)

Preferences and Values Evidence

Included Qualitative Evidence

Health Technology Assessment by CADTH and Ontario Health

RESEARCH QUESTION

- What are the perspectives and experiences of people with glaucoma regarding glaucoma and their treatment, and of their clinical and non-clinical caregivers?

METHODS

As part of the 2019 health technology assessment by CADTH and Ontario Health, CADTH conducted a systematic review²⁹ of primary qualitative research which explored the perspectives and experiences of patients with glaucoma, and those of their caregivers. Additionally, as part of this health technology assessment, CADTH conducted qualitative interviews with three people, two of whom had undergone a MIGS procedure (the specific procedure was not identified).

RESULTS

For the systematic review of qualitative evidence, 15 studies met the inclusion criteria and were included in the review. These studies were assessed to be of low quality. The studies included a total of 329 participants with glaucoma and 31 family members.²⁹

Results of the systematic review were the following (p. 19)²⁹:

The results of the thematic synthesis centered around patients' experiences and perceptions of glaucoma. A diagnosis of glaucoma was unexpected, typically patients explained vision changes as part of normal aging, not as a prompt to seek vision care. This means that those without routine vision care may be more at risk for being diagnosed with more advanced glaucoma and therefore be ineligible for MIGS. Pharmacotherapy in the form of eye drops was disruptive to patients' lives. Despite a range of creative and committed responses, patients with comorbidities and busy lives with travel or lack of routine made adherence difficult. Reducing the number and frequency of medications was valued by patients. Patients expressed a range of views on glaucoma surgeries, from being a last resort to freedom from eye drops. Some may be conservative in assuming the risks of surgery where blindness is a possibility. Patients experienced glaucoma as an illness, not as a disease. This means that a patient's experience of glaucoma was shaped by, but not reducible to their clinical condition. While surgical treatments can offer patients improved clinical outcomes, patients still worried about the need to use additional medications or future surgery and the need for vigilance about the return of elevated IOP [intraocular pressure], pointing to the lingering impact of glaucoma.

Included Direct Patient Engagement

Health Technology Assessment by CADTH and Ontario Health

RESEARCH QUESTION

- What are the underlying values, needs, impact, and preferences of people with lived experience with glaucoma and its treatment options, including MIGS?

METHODS

Ontario Health conducted direct engagement through qualitative interviews with 10 people¹⁰:

- Four participants had received a MIGS procedure (unknown if procedures were iStent)
- Three participants had received filtration surgery
- Three participants had been treated with drops and laser therapy

Interview questions sought to examine the lived experience of people with glaucoma and its impact on their daily activities and quality of life. We also asked participants about their decision-making and values related to glaucoma treatment, their experiences with treatment, the impact of their treatments, and their impressions of MIGS procedures, if applicable. Because participants rarely knew the specific type of MIGS procedure they had received, we did not ask specific questions about iStent.

RESULTS

Participants described glaucoma as a fairly unfamiliar condition. Diagnosis was often surprising and unexpected, with asymptomatic patients typically diagnosed through routine eye examinations. Additionally, glaucoma diagnoses could be emotionally distressing because of the absence of symptoms but the potential for serious adverse consequences, including blindness.¹⁰

Treatment with medication such as eye drops, a common first-line treatment for glaucoma, was a challenge for some people, and interview participants reported difficulties adhering to their prescribed medication regimens. For the majority of our participants, first-line treatment had been unsuccessful, and they had either had a glaucoma surgery (a MIGS or more invasive procedure) or were waiting for surgery. This participation bias among those who agreed to be interviewed likely skewed the perceived effectiveness of certain types of treatments for glaucoma.¹⁰

The key factor in patients' decision-making about their treatment for glaucoma was the patient–physician relationship. Patients felt that a trusting relationship was essential for them to develop comfort in making a decision about surgery as a treatment option, perhaps because they were unfamiliar with the nature of glaucoma and its symptoms.¹⁰

Several participants raised concerns about barriers to glaucoma care. Some people noted the costs associated with ongoing glaucoma treatment as a barrier to care. Others noted that wait times for some surgical procedures could impact their quality of life as they waited for a procedure to treat their glaucoma.¹⁰

Participants who had received a MIGS procedure generally found it to be successful and beneficial, with minimal side effects and recovery time. As noted, we did not obtain specific information about people's

experiences with iStent because participants were generally unaware of the type of MIGS procedure they had received.¹⁰

Health Technology Assessment by INESSS

METHODS

As part of its 2020 health technology assessment on iStent, INESSS²³ consulted with patient associations. Representatives were contacted by email to inform them of the ongoing evaluation and to ensure that the interests, needs, and perspectives of people with glaucoma would be considered in this assessment.

Additionally, INESSS²³ conducted a secondary analysis of results from a survey of Canadians with glaucoma, capturing information on the physical, psychological, financial, and other burdens associated with the condition. The survey was conducted by the Foundation Fighting Blindness and results were used in the health technology assessment done by CADTH and Ontario Health.^{10,29}

RESULTS

In reporting their findings, INESSS²³ highlighted the challenges faced by people with glaucoma, including adherence to medications, the impact on activities of daily living, and the psychological dimension of dealing with glaucoma. The report also noted that some people were not inclined to seek professional help for challenges with their eyes due to the belief that this is a normal part of aging.

Preferences and Values Evidence Conclusions

Both the qualitative evidence systematic review and the evidence from direct patient engagement consistently showed that glaucoma presents patients with significant impacts and challenges. Fear of ultimate blindness and challenges with managing medication for glaucoma often led patients to explore other treatment options, such as laser or surgical procedures. Trust with their health care professionals was key to people's decision-making about treatment options. Patients generally viewed MIGS procedures positively, with shorter recovery times mentioned as a key benefit. We could not draw specific conclusions about iStent from this preferences and values evidence.

Conclusions of the Health Technology Assessment

In adults with glaucoma, we are uncertain about the comparative clinical effectiveness of iStent compared with filtration surgery, as well as iStent combined with cataract surgery versus other MIGS procedures combined with cataract surgery. There may be no difference in comparative clinical effectiveness of iStent compared with pharmacotherapy. However, iStent combined with cataract surgery may improve clinical effectiveness (mainly intraocular pressure and number of medications) when compared with cataract surgery alone.

In some instances, iStent may be cost-effective (i.e., when compared to pharmacotherapy) but in other instances iStent may not be cost-effective (i.e., when iStent with cataract surgery is compared with cataract surgery alone or when iStent is compared with filtration surgery). If publicly funded, iStent may reduce some spending on pharmacotherapy but, overall, is likely to lead to additional costs to the health system.

For people with glaucoma, fear of progressing to blindness and the challenges with pharmacotherapy often lead them to explore other treatment options, such as laser or surgical procedures. People with glaucoma generally viewed MIGS procedures positively, with shorter recovery times mentioned as a benefit. We could not draw conclusions about iStent in particular because survey and interview participants did not know which specific MIGS procedure they had received.

Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
INESSS	Institut national d'excellence en santé en services sociaux
IOP	Intraocular pressure
MIGS	Minimally invasive glaucoma surgery
OHIP	Ontario Health Insurance Plan
QALY	Quality-adjusted life-year
ROBIS	Risk of Bias in Systematic Reviews

Glossary

Adverse event	An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.
Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Cost-effective	A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Endoscopic cyclophotocoagulation	Endoscopic cyclophotocoagulation is a laser treatment to lower intraocular pressure.
Goniotomy	Goniotomy is a surgical procedure to lower intraocular pressure by making an incision through the trabecular meshwork to ease the outflow of fluid into Schlemm's canal.
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.
Kahook Dual Blade	The Kahook Dual Blade is a micro-incision tool used in minimally invasive glaucoma surgery to make parallel incisions in the trabecular meshwork and the wall of the Schlemm's canal, to increase the flow of fluid in the eye.

Markov model	A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.
Quality-adjusted life-year (QALY)	The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.
Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.
Scenario analysis	A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.
Sensitivity analysis	Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.
Trabectome	A trabectome is a heated electrode device used in minimally invasive glaucoma surgery to remove a strip of the trabecular meshwork along with the “inner wall” of the Schlemm’s canal, to increase the flow of fluid in the eye.
Trabeculectomy	Trabeculectomy is a common surgical procedure for glaucoma to relieve intraocular pressure by removing part of the eye’s trabecular meshwork and adjacent structures.
Willingness-to-pay value	A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Summary of Clinical Results and Critical Appraisal

Table A1: 2× iStent Procedure vs. Pharmacotherapy

Outcome	No. of Patients (Studies)	Summary of Results	Certainty of the Evidence (GRADE)
Intraocular pressure	N = 293 (2 RCTs) Fea et al, 2014 ³⁸ Vold et al, 2016 ³⁹	No conclusions drawn Reduction from baseline using iStent and pharmacotherapy (~ 8 mm Hg and 10 mm Hg) but within or between groups not tested statistically	Very low, due to serious risk of bias and imprecision
No. of medications	N/A, patients were randomized to either iStent or medication		
Visual field	N = 101 (1 RCT) Vold et al, 2016 ³⁹	No conclusions drawn Similar visual field in both groups at 12-mo follow-up but between-group differences not tested statistically	Very low, due to serious risk of bias and imprecision
Visual acuity	N = 293 (2 RCTs) Fea et al, 2014 ³⁸ Vold et al, 2016 ³⁹	No conclusions drawn Details of BCVA measurement not reported and therefore it is uncertain whether reliable, valid, and discriminative (vs. surrogate) measures were used	Very low, due to serious risk of bias and imprecision
Safety	N = 293 (2 RCTs) Fea et al, 2014 ³⁸ Vold et al, 2016 ³⁹	Number of adverse events are moderate with low or moderate severity and similar across groups	Very low, due to risk of bias, indirectness, and imprecision

Abbreviations: 2×, 2 iStents placed in a single eye; BCVA, best corrected visual acuity; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; mo, month; N/A, not applicable; no., number; RCT, randomized controlled trial; vs., versus.

Source: Adapted from Canadian Agency for Drugs and Technologies in Health, 2019.²⁹

Table A2: iStent Procedure vs. Trabeculectomy With Mitocyn C

Outcome	No. of Patients (Studies)	Summary of Results	Certainty of the Evidence (GRADE)
Quality of life	N = 45 (1 prospective cohort) Pahlitzsch et al, 2017 ⁴⁰	No difference None of the 12 quality of life parameters were different between groups at 6-mo follow-up	Very low, due to risk of bias and imprecision
Intraocular pressure	N = 45 (1 prospective cohort) Pahlitzsch et al, 2017 ⁴⁰	No conclusions drawn Reduction from baseline using iStent and trabeculectomy (from ~ 5 mm Hg to 15 mm Hg) to 6 mo (to ~ 16.0 mm Hg and 12.9 mm Hg); between-group differences were not tested statistically	Very low, due to serious risk of bias and imprecision
No. of medications	N = 45 (1 prospective cohort) Pahlitzsch et al, 2017 ⁴⁰	No conclusions drawn Reduction from baseline in the iStent group at 1 d and 6 wk, but not 3- or 6-mo follow-up, and significantly reduced from baseline in the trabeculectomy group at all follow-up time points (at 6 mo: 2.5 vs. 0.5 medications for iStent and trabeculectomy groups; between-group differences were not tested statistically)	Very low, due to risk of bias and imprecision
Visual acuity	N = 45 (1 prospective cohort) Pahlitzsch et al, 2017 ⁴⁰	Similar between groups at baseline or up to 6-mo follow-up, but this was not tested statistically	Very low, due to risk of bias, indirectness, and imprecision

Abbreviations: 2×, 2 iStents placed in a single eye; d, day; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; mo, month; N/A, not applicable; no, number; vs., versus; wk, week.

Source: Adapted from Canadian Agency for Drugs and Technologies in Health, 2019.²⁹

Table A3: 2× iStent Procedure With Cataract Surgery vs. Cataract Surgery Alone

Outcome	No. of Patients (Studies)	Summary of Results	Certainty of the Evidence (GRADE)
Intraocular pressure	N = 33 (1 RCT) Fernandez-Barrientos et al, 2010 ⁴¹	2× iStent + CS > CS alone Significantly lower in the 2× iStent + CS group vs. CS alone at 1- to 12-mo follow-up (~ 2 mm Hg to 4 mm Hg difference between groups)	Low, due to risk of bias and imprecision
No. of medications	N = 33 (1 RCT) Fernandez-Barrientos et al, 2010 ⁴¹	2× iStent + CS > CS alone Significantly lower in the 2×iStent + CS vs. CS alone group at 6 mo (~ 0.1 vs. 0.5 medications) and 12 mo (~ 0 vs. 1) follow-up	Low, due to risk of bias and imprecision
Safety	N = 33 (1 RCT) Fernandez-Barrientos et al, 2010 ⁴¹	No conclusions drawn All minor events, less events in iStent + CS vs. CS alone	Very low, due to risk of bias, indirectness, and imprecision

Abbreviations: 2×, 2 iStents placed in a single eye; BCVA, best corrected visual acuity; CS, cataract surgery; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; mo, months; RCT, randomized controlled trial; vs., versus.

Source: Adapted from Canadian Agency for Drugs and Technologies in Health, 2019.²⁹

Table A4: 2× iStent Procedure With Cataract Surgery vs. Goniotomy With Kahook Dual Blade + Cataract Surgery

Outcome	No. of Patients (Studies)	Summary of Results	Certainty of the Evidence (GRADE)
Intraocular pressure	N = 435 (1 retrospective cohort) Dorairaj et al, 2018 ⁴²	KDB + CS > iStent + CS Reduction of IOP significantly greater in the KDB + CS vs. iStent + CS group up to 6-mo follow-up	Very low, due to risk of bias and imprecision
No. of medications	N = 435 (1 retrospective cohort) Dorairaj et al, 2018 ⁴²	KDB + CS > iStent + CS Number of medications and reduction from baseline significantly lower in the KDB + CS vs. iStent + CS group at 1-, 3-, and 6-mo follow-up	Very low, due to risk of bias and imprecision
Visual acuity	N = 435 (1 retrospective cohort) Dorairaj et al, 2018 ⁴²	No difference BCVA no different between KDB + CS vs. iStent + CS at 6-mo follow-up	Very low, due to risk of bias, indirectness, and imprecision
Safety	N = 435 (1 retrospective cohort) Dorairaj et al, 2018 ⁴²	Mixed findings: =/> All minor events IOP spikes significantly greater in the KDB + CS vs. iStent + CS group but all other events were similar between groups	Very low, due to risk of bias, indirectness, and imprecision

Abbreviations: 2×, 2 iStents placed in a single eye; BCVA, best corrected visual acuity; CS, cataract surgery; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IOP, intraocular pressure; KDB, Kahook Dual Blade; mo, month; N/A, not applicable; no. number; vs., versus.

Source: Adapted from Canadian Agency for Drugs and Technologies in Health, 2019.²⁹

Table A5: 2× iStent Procedure With Cataract Surgery vs. Trabectome With Cataract Surgery

Outcome	No. of Patients (Studies)	Summary of Results	Certainty of the Evidence (GRADE)
Intraocular pressure	N = 171 (2 retrospective cohort) Kurji et al, 2017 ⁴³ Khan et al, 2015 ⁴⁴	Mixed findings: </? IOP numerically higher in trabectome + CS vs. iStent + CS at 12 mo but did not reach significance IOP was significantly higher in trabectome + CS vs. iStent + CS at 6 and 12 mo (~ 17 mm Hg vs. 14 mm Hg) in one study	Very low, due to serious risk of bias and imprecision
No. of medications	N = 171 (2 retrospective cohort) Kurji et al, 2017 ⁴³ Khan et al, 2015 ⁴⁴	No difference Absolute number of medications was not different between groups at 6- to 12-mo follow-up but the reduction of medications was greater in trabectome + CS vs. iStent + CS group at 6 mo but not 12 mo	Very low, due to risk of bias and inconsistency
Visual acuity	N = 171 (2 retrospective cohort) Kurji et al, 2017 ⁴³ Khan et al, 2015 ⁴⁴	No difference BCVA no different between KDB + CS vs. iStent + CS at 12 mo	Very low, due to risk of bias, indirectness, and inconsistency
Safety	N = 171 (2 retrospective cohort) Kurji et al, 2017 ⁴³ Khan et al, 2015 ⁴⁴	Mixed findings: </= All minor events Hyphema: trabectome + CS < 2× iStent + CS and all other events similar in one study, and more events in the iStent group in another study Secondary surgery was similar between groups in one study and greater in the iStent group in the other study	Very low, due to risk of bias, indirectness, and imprecision

Abbreviations: 2×, 2 iStents placed in a single eye; BCVA, best corrected visual acuity; CS, cataract surgery; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IOP, intraocular pressure; KDB, Kahook Dual Blade; mo, months; N/A, not applicable; no. number; vs., versus.

Source: Adapted from Canadian Agency for Drugs and Technologies in Health, 2019.²⁹

Table A6: 2× iStent Procedure With Micro-incision Cataract Surgery vs. Trabectome With Micro-incision Cataract Surgery

Outcome	No. of Patients (Studies)	Summary of Results	Certainty of the Evidence (GRADE)
Intraocular pressure	N = 50 (1 retrospective cohort) Gonnermann et al, 2017 ⁴⁵	No difference No difference in IOP between trabectome + MICS vs. iStent + MICS at 12 mo	Very low, due to risk of bias and imprecision
No. of medications	N = 50 (1 retrospective cohort) Gonnermann et al, 2017 ⁴⁵	No difference No difference in number of medications between trabectome + MICS vs. iStent + MICS at 12 mo	Very low, due to risk of bias and imprecision
Visual acuity	N = 50 (1 retrospective cohort) Gonnermann et al, 2017 ⁴⁵	No difference BCVA no different between KDB + CS vs. iStent + CS at 12 mo	Very low, due to risk of bias, indirectness, and inconsistency
Safety	N = 50 (1 retrospective cohort) Gonnermann et al, 2017 ⁴⁵	No difference All minor events Events and secondary surgery were similar between groups	Very low, due to risk of bias, indirectness, and imprecision

Abbreviations: 2×, 2 iStents placed in a single eye; BCVA, best corrected visual acuity; CS, cataract surgery; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IOP, intraocular pressure; KDB, Kahook Dual Blade; MICS, micro-incision cataract surgery; mo, months; N/A, not applicable; no., number; vs., versus.

Source: Adapted from Canadian Agency for Drugs and Technologies in Health, 2019.²⁹

Table A7: iStent Procedure With Cataract Surgery vs. Endoscopic Cyclophotocoagulation + iStent With Cataract Surgery

Outcome	No. of Patients (Studies)	Summary of Results	Certainty of the Evidence (GRADE)
Intraocular pressure	N = 101 (1 retrospective cohort) Ferguson et al, 2017 ⁴⁶	ECP + iStent + CS > iStent + CS Reduction of IOP significantly greater in ECP + iStent + CS vs. iStent + CS at 12 mo	Very low, due to risk of bias and imprecision
No. of medications	N = 101 (1 retrospective cohort) Ferguson et al, 2017 ⁴⁶	ECP + iStent + CS < iStent + CS Number of medications significantly greater in ECP + iStent + CS vs. iStent + CS at 12 mo	Very low, due to risk of bias and imprecision
Safety	N = 101 (1 retrospective cohort) Ferguson et al, 2017 ⁴⁶	No difference All minor events Events and secondary surgery were similar between groups	Very low, due to risk of bias, indirectness, and imprecision

Abbreviations: CS, cataract surgery; ECP, endoscopic cyclophotocoagulation; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IOP, intraocular pressure; mo, months; no., number; vs., versus.

Source: Adapted from Canadian Agency for Drugs and Technologies in Health, 2019.²⁹

Table A8: 2× iStent Procedure vs. Pharmacotherapy

Outcome	No. of Patients (Studies)	Summary of Results	Certainty of the Evidence (GRADE)
Intraocular pressure	N = 393 (2 RCTs) Fea et al, 2014 ³⁸ Vold et al, 2016 ³⁹ Fechtner et al, 2019 ⁴⁷	No difference Significant reduction in both groups from baseline to 60-mo follow-up ($P < .001$) Numerically similar IOP in two studies at 12 (~ 13 mm Hg) and 60-mo follow-up (8.1 vs. 7.3 mm Hg)	Very low, due to serious risk of bias and imprecision
No. of medications	N/A, patients were randomized to either iStent or medication		
Visual field	N = 101 (1 RCT) Fea et al, 2014 ³⁸ Vold et al, 2016 ³⁹ Fechtner et al, 2019 ⁴⁷	No difference Similar visual field in both groups at 60-mo follow-up (7.8 ± 7.9 vs. 7.5 ± 7.5)	Low, due to risk of bias and imprecision
Visual acuity	N = 393 (2 RCTs) Fea et al, 2014 ³⁸ Vold et al, 2016 ³⁹ Fechtner et al, 2019 ⁴⁷	No difference Similar visual acuity in both groups at 12- and 60-mo follow-up	Low, due to risk of bias and imprecision
Safety	N = 393 (2 RCTs) Fea et al, 2014 ³⁸ Vold et al, 2016 ³⁹ Fechtner et al, 2019 ⁴⁷	Number of adverse events are moderate with low or moderate severity and similar across groups	Very low, due to risk of bias, indirectness, and imprecision

Abbreviations: 2×, 2 iStents placed in a single eye; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IOP, intraocular pressure; N/A, not applicable; no., number; vs., versus.

Source : Adapted from Institut national d'excellence en santé et services sociaux, 2020.²³

Table A9: 2× iStent Procedure With Cataract Surgery vs. Cataract Surgery Alone

Outcome	No. of Patients (Studies)	Summary of Results	Certainty of the Evidence (GRADE)
Intraocular pressure	N = 538 (2 RCTs) Fernandez-Barrientos et al, 2010 ⁴¹ Samuelson et al, 2019 ⁴⁸	Mixed Findings: =/>> Lower IOP in iStent + CS vs. CS alone at 12 mo in one study ($P = .04$) Similar IOP at 6-mo (~ 15 mm Hg) and 24-mo (17.1 vs 17.8 mm Hg) follow-up in the treatment and control groups in the other study Significant reduction from baseline to 24-mo unmedicated DIOP of the treatment vs control group (7.0 mmHg vs. 5.4 mmHg, $P < .001$).	Low, due to risk of bias and imprecision
No. of medications	N = 538 (2 RCTs) Fernandez-Barrientos et al, 2010 ⁴¹ Samuelson et al, 2019 ⁴⁸	2× iStent + CS > CS alone Greater reduction in medications in the iStent + CS vs. CS alone group at 23-mo follow-up (1.2 vs. 1.8, $P < .001$)	Low, due to risk of bias and imprecision
Visual field	N = 505 (1 RCT) Samuelson et al, 2019 ⁴⁸	No difference Similar visual field measurements in both groups at 24-mo follow-up (70% of eyes $\leq \pm 2.5$ dB)	Low, due to risk of bias and imprecision
Visual acuity	N = 505 (1 RCT) Samuelson et al, 2019 ⁴⁸	No difference Similar visual acuity in both groups at 24-mo follow-up	Low, due to risk of bias and imprecision
Safety	N = 538 (2 RCTs) Fernandez-Barrientos et al, 2010 ⁴¹ Samuelson et al, 2019 ⁴⁸	Number of adverse events are moderate with low or moderate severity and similar across groups	Low, due to risk of bias and imprecision

Abbreviations: 2×, 2 iStents placed in a single eye; CS, cataract surgery; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IOP, intraocular pressure; no., number; RCT, randomized controlled trial; vs., versus.

Source: Adapted from Institut national d'excellence en santé et services sociaux, 2020.²³

Appendix 2: Critical Appraisal of Systematic Review

Table A10: Risk of Bias^a Among Systematic Reviews (ROBIS Tool)

Author, Year	Phase 2			Phase 3	
	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Risk of Bias in the Review
Popovic et al, 2018 ³⁰	Low	High ^b	Low	High ^c	High

Abbreviation: ROBIS, Risk of Bias in Systematic Reviews.

^aPossible risk of bias levels: low, high, unclear.

^bDid quality screening while screening so may miss studies because of pre-emptive exclusion.

^cDid not indicate how many studies were included in analysis; may have combined randomized controlled trials and case series; heterogeneity was not assessed; no funnel plots were presented.

Appendix 3: Economic Evidence

Table A11: Summary of Economic Evaluations

Author, Year, Country	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results			
				Effectiveness (QALYs)	Costs (\$)	Cost-Effectiveness (\$/QALY)	Probability Cost-Effective at \$50K/QALY and \$100K/QALY
Ahmed et al, ³⁶ 2019, Canada	Cost-utility analysis Markov model Canadian public health care payer Lifetime horizon Discount rate = 1.5%	Adults with mild to moderate open-angle glaucoma Age (mean): 65 y	2× iStent + CS vs. CS	2× iStent + CS: 9.428 CS: 9.405 Incremental: 0.023	2× iStent + CS: \$21,384 CS: \$21,773 Incremental: -\$389	2× iStent + CS dominant (more effective, less costly)	\$50K/QALY: 94.1% \$100K/QALY: 97.0%
CADTH, ²⁹ 2019, Canada	Cost-utility analysis Markov model Canadian public health care payer Lifetime horizon Discount rate = 1.5%	Adults with mild to moderate glaucoma Age (mean): 64–72 y	2× iStent vs. pharmacotherapy	2× iStent: 12.95 Pharmacotherapy: 12.85 Incremental: 0.039	AB 2× iStent: \$12,641 AB pharmacotherapy: \$11,900 AB incremental: \$741 ON incremental: \$552	AB ICER: \$18,808/QALY ON ICER: \$14,120/QALY	\$50K/QALY: 60% \$100K/QALY: 65%
			1× iStent + CS vs. CS	1× iStent + CS: NR CS: NR Incremental: 0.016	AB 1× iStent + CS: NR AB CS: NR AB incremental: \$1,754	AB ICER: \$108,934/QALY	\$50K/QALY: ~17% \$100K/QALY: ~46%
			2× iStent vs. filtration surgery	2× iStent: NR Filtration surgery: NR Incremental: -0.214	AB 2× iStent: NR AB filtration surgery: NR AB incremental: 385	2× iStent dominated (less effective, more costly)	\$50K/QALY: 0% \$100K/QALY: 0%

Author, Year, Country	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results			
				Effectiveness (QALYs)	Costs (\$)	Cost-Effectiveness (\$/QALY)	Probability Cost-Effective at \$50K/QALY and \$100K/QALY
INESSS, ²³ 2020, Canada	Cost-utility analysis Markov model Quebec public health care and social services payer 15-year time horizon Discount rate = 1.5%	Adults with mild to moderate primary open-angle glaucoma	2× iStent vs. pharmacotherapy	2× iStent: 9.54 Pharmacotherapy: 9.50 Incremental: 0.038	2× iStent: \$12,736 Pharmacotherapy: \$11,743 Incremental: \$993	ICER: \$25,596/QALY	\$50K/QALY: 76% \$100K/QALY: ~100%
			2× iStent + CS vs. CS	2× iStent + CS: 9.47 CS: 9.45 Incremental: 0.015	2× iStent + CS: \$13,734 CS: \$12,142 Incremental: \$1,592	ICER: \$112,380/QALY	\$50K/QALY: 12% \$100K/QALY: 68%
Patel et al, ³⁷ 2019, Canada	Cost-utility analysis Markov model Canadian public health care payer Lifetime horizon Discount rate = 1.5%	Adults with mild to moderate open-angle glaucoma Age (mean): 65 y	2× iStent vs. pharmacotherapy	2× iStent: 9.239 Pharmacotherapy: 9.171 Incremental: 0.068	2× iStent: \$9,394 Pharmacotherapy: \$12,302 Incremental: -\$2,908	2× iStent dominant (more effective, less costly)	\$50K/QALY: 100% \$100K/QALY: 100%

Abbreviations: 2×, 2 iStents placed in a single eye; AB, Alberta; CADTH, Canadian Agency for Drugs and Technologies in Health; CS, cataract surgery; ICER, incremental cost-effectiveness ratio; INESSS, Institut national d'excellence en santé et services sociaux; K, thousand; NR, not reported; ON, Ontario; QALY, quality-adjusted life-year; y, year.

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Ontario Health
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: oh-hqo_hqa@ontariohealth.ca
www.hqontario.ca

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