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Prostaglandin Analogues for  
Ophthalmic Use: Analysis of  
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*Supporting Informed Decisions*

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CADTH  
600-865 Carling Avenue  
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**Canadian Agency for Drugs and Technology in Health**

**Prostaglandin Analogues for Ophthalmic Use:  
Analysis of Clinical and Cost-Effectiveness**

William G. Hodge, MD PhD FRCSC<sup>1</sup>

Jean Lachaine, PhD<sup>2</sup>

Isabella Steffensen, PhD<sup>2</sup>

Christine Murray, PhD<sup>2</sup>

David Barnes, MD<sup>2</sup>

Vicki Foerster, MD MSc<sup>2</sup>

Thierry Ducruet, MSc<sup>2</sup>

Andra Morrison, BSc<sup>3</sup>

June 2007

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<sup>1</sup> University of Ottawa Eye Institute, Ottawa ON

<sup>2</sup> Meta-Business Advantage Ltd., Kanata ON

<sup>3</sup> Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa ON

## Reviewers

*These individuals kindly provided comments on this report:*

### **External Reviewers**

Yvonne M. Buys, MD FRCSC  
Associate Professor, Department of  
Ophthalmology  
University of Toronto  
Toronto ON

Frederick S. Mikelberg, MD FRCSC  
Professor and Head, Department of  
Ophthalmology and Visual Sciences  
University of British Columbia  
Vancouver BC

Robert Borden Hopkins, BA BSc MA  
Research Biostatistician  
Program for the Assessment of Technology in  
Health (PATH)  
Hamilton ON

Marcelo T. Nicolela, MD FRCSC  
Associate Professor, Department of  
Ophthalmology and Visual Sciences  
Dalhousie University  
Halifax NS

### **CADTH Peer Review Group Reviewers**

Gina Bravo, PhD  
Professor, Department of Community Health  
Sciences  
University of Sherbrooke  
Sherbrooke QC

Doug Coyle, PhD MA MSc  
Associate Professor  
University of Ottawa  
Ottawa ON

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## Authorship

William Hodge led the clinical review, and participated in the design of the project and interpretation of the data.

Jean Lachaine led the economic evaluation, and was responsible for design of the study, data analysis and interpretation, and writing of the economic section of the report.

Isabella Steffensen, overall research lead, co-ordinated the project, and was involved in the design of the study, trial selection, data analysis and interpretation, and writing of the report.

Christine Murray participated in trial selection, data analysis and interpretation, and writing of the report.

Vicki Foerster and David Barnes were responsible for extracting and tabulating data from the selected trials.

Thierry Ducruet was responsible for the biostatistics and assisted in the economic analysis.

Andra Morrison participated in the screening of the literature, citation management, and final preparation of the report.

## **Conflict of Interest**

Dr. Yvonne M. Buys is an Advisory Board member, and has received research grants and honorariums from Alcon Canada Inc., Allergan Canada Inc., Merck Frosst Canada, and Pfizer Canada Inc.

Dr. Marcelo T. Nicolela has been a speaker, and has received research grants and honorariums from Pfizer Canada Inc, Alcon Canada Inc., and Allergan Inc.

## Prostaglandin Analogues for Ophthalmic Use: Analysis of Clinical and Cost-Effectiveness

### Technology and Condition

Prostaglandin analogues (PGAs) in the treatment of elevated intraocular pressure (IOP): bimatoprost, latanoprost, and travoprost

### Issue

PGAs are more costly than alternative agents for the lowering of IOP. One policy decision to be made is whether reimbursement of these agents as first-line therapy with no restrictions represents an optimal use of limited resources.

### Methods and Results

A systematic review of the clinical literature was conducted. Twenty-two RCTs comparing PGAs to alternative therapy in individuals >18 years old with elevated IOP who were treatment-naïve or who experienced appropriate washout before treatment were included. A cost-effectiveness analysis was conducted from the perspective of Canadian ministries of health. A decision-analytic model using a three-month time horizon calculated the associated costs and consequences of using latanoprost versus timolol, dorzolamide, and brimonidine; and travoprost versus timolol.

### Implications for Decision Making

- **Not all PGAs are the same.** There is evidence that latanoprost and travoprost reduce IOP more effectively than timolol. The same evidence does not exist for bimatoprost.
- **Timolol that is used as a first-line option could represent an optimal use of scarce resources.** For appropriate patients, it would be preferable, from a cost-effectiveness standpoint, to start treatment with timolol and reserve the PGAs as an alternative treatment or as add-on therapy for patients not achieving a clinical response with timolol.
- **PGAs may be cost-saving, depending on the alternative.** Compared to dorzolamide, latanoprost is more effective and less costly. Compared to brimonidine, latanoprost is associated with additional costs, at a lower cost per mm Hg reduced.
- **The long-term benefit from PGAs is unclear.** There is no evidence that greater reductions in IOP translate into reductions in visits to a physician or surgical procedures, or an increase in health-related quality of life.

This summary is based on a comprehensive health technology assessment available from CADTH's web site ([www.cadth.ca](http://www.cadth.ca)): Hodge WG, Lachaine J, Steffensen I, Murray C, Barnes D, Foerster V, Ducruet T, Morrison A. *Prostaglandin analogues for ophthalmic use: analysis of clinical and cost-effectiveness.*

# EXECUTIVE SUMMARY

## The Issue

Prostaglandin analogues (PGAs) for ophthalmic use are open listed (i.e., they have unrestricted coverage) by jurisdictional drug plans, but are more costly than alternative agents for the lowering of intraocular pressure (IOP). One policy decision to be made is whether reimbursement of these agents as first-line therapy with no restrictions represents an optimal use of limited resources.

## Objective

The objective of this analysis is to perform a systematic review and economic evaluation of PGAs for the treatment of increased IOP, using evidence from published and unpublished randomized controlled trials (RCTs).

## Systematic Review of Efficacy and Harm

**Methods:** A systematic review of available literature was performed to identify relevant RCTs of PGAs for ophthalmic use. Two authors independently applied the selection criteria for screening, and data from the included studies were extracted into evidence tables and analyzed. The study quality of RCTs was assessed using the Jadad scale. Outcomes assessed included reduction in IOP among patients, adverse events (AEs), and withdrawals due to AEs.

**Results:** This systematic review included 22 unique RCTs evaluating a total of 5,304 individuals. Meta-analysed three-month data from six studies with 984 patients showed a significant reduction in the mean IOP from baseline in the latanoprost group compared with the timolol group [weighted mean difference (WMD)  $-1.26$  (95% confidence interval (CI):  $-1.63, -0.89$ );  $p < 0.00001$ ]. A significant reduction in IOP for latanoprost versus timolol was maintained when six- and 12-month data were analyzed [WMD  $-1.06$  (95% CI:  $-1.64, -0.48$ ),  $p = 0.0004$ , and WMD  $-1.04$  (95% CI:  $-1.63, -0.46$ ),  $p = 0.0004$  respectively]. A meta-analysis of three-month data from three studies with 471 patients did not show a significant reduction in the mean IOP from baseline in patients receiving latanoprost compared with those receiving brimonidine [WMD  $-1.04$  (95% CI:  $-3.01, 0.93$ );  $p = 0.30$ ]. A meta-analysis of three-month data from three studies with 328 patients showed a significant reduction in the mean IOP from baseline in the latanoprost group compared with the dorzolamide group [WMD  $-2.64$  (95% CI:  $-3.25, -2.04$ );  $p < 0.00001$ ]. Meta-analysed three-month data from three studies with 951 patients showed a significant reduction in the mean IOP from baseline in the 0.004% travoprost group compared with the timolol group [WMD  $-1.21$  (95% CI:  $-1.58, -0.85$ );  $p < 0.00001$ ]. A significant reduction in IOP for travoprost versus timolol was maintained when six-month data were analyzed [WMD  $-0.92$  (95% CI:  $-1.25, -0.60$ );  $p < 0.00001$ ].

The incidence of ocular hyperemia and the incidence of ocular AEs (excluding hyperemia) were significantly higher in patients treated with latanoprost compared with patients treated with timolol [risk difference (RD) 0.09 (95% CI: 0.06, 0.12), and RD 0.06 (95% CI: 0.00, 0.12)]. The number of respiratory and cardiac AEs potentially related to timolol (i.e., bradycardia, hypotension, dyspnea, asthma or bronchospasm, arrhythmia, cardiac block, and congestive heart failure) was significantly higher in the timolol group compared with the latanoprost group [RD 0.02 (95% CI: 0.00, 0.03)]. The incidence of ocular hyperemia and the incidence of ocular AEs (excluding hyperemia) were significantly higher in the 0.004% travoprost group compared with the timolol group [RD 0.29 (95%

CI: 0.25, 0.33)], and RD 0.15 (95% CI: 0.07, 0.23)]. The number of withdrawals due to AEs was significantly higher in patients receiving 0.004% travoprost compared with those receiving timolol [RD 0.02 (95% CI: 0.01, 0.04)]. The number of ocular AEs (excluding hyperemia) was significantly higher in the brimonidine group compared with the latanoprost group [RD 0.11 (95% CI: 0.05, 0.16)].

## Economic Analysis

**Methods:** The cost-effectiveness of PGAs was assessed using a decision-analytic model. Latanoprost was compared with timolol, dorzolamide, and brimonidine; and travoprost was compared to timolol. Effectiveness data used for this economic analysis were the number of millimetres of mercury (mm Hg) of IOP reduction compared with the baseline and the incidence of AEs resulting in a patient's withdrawal from the study. In accordance with the adopted ministry of health perspective, the costs considered in the evaluation are those of medications used to reduce IOP, and of physician visits for the initial prescribing of treatment and for the handling of AEs. Sensitivity analyses were conducted to assess the robustness of the study results, and the impact of patients' non-persistence on the cost-effectiveness was estimated.

**Results:** Compared with latanoprost, dorzolamide is not a cost-effective strategy. Compared with brimonidine, latanoprost provides a higher IOP reduction with an incremental cost-effectiveness ratio (ICER) of C\$16.17 (base case). The additional mm Hg reduction with latanoprost is obtained at a cost inferior to the average cost per mm Hg reduction obtained with brimonidine. Therefore, latanoprost can be considered to be a cost-effective alternative to brimonidine if the relationship between reductions in IOP and improvements in health is shown to be linear. Compared with timolol, latanoprost and travoprost are more effective, but more costly. The better treatment persistence that is associated with PGAs improves their cost-effectiveness.

## Health Services Impact

It is estimated that the number of Canadians afflicted with vision loss will increase from 67,900 blind and 319,000 visually impaired persons in 2001 to 120,000 and 600,000 respectively in 2026 – an increase of 86% in the number of Canadians with significant vision loss. Because glaucoma is the second-largest cause of visual disability in Canada, after age-related macular degeneration, cost-effective therapeutic options and optimal policy decisions for therapeutic eye care in Canada are challenges over the next 20 years.

## Conclusions

As first-line therapy, latanoprost, travoprost, and bimatoprost all showed statistically significant improvement in IOP reduction relative to timolol; although for bimatoprost, the evidence was limited to one small, low-quality study. Compared with timolol, PGAs reduced the average IOP by 0.92 mm Hg to 1.48 mm Hg. Latanoprost was found to reduce IOP further than dorzolamide, betaxolol, or combined therapy with carteolol plus pilocarpine. One large, high-quality RCT indicated that latanoprost was similarly effective as combined therapy with dorzolamide plus timolol. Latanoprost was not found to significantly reduce IOP compared with brimonidine. Neither travoprost nor bimatoprost were compared with other IOP-reducing agents. One study, which compared latanoprost versus brimonidine, examined a PGA as second-line therapy. Although long-term studies are lacking, current studies suggest that PGAs are well tolerated.

For the treatment of glaucoma and elevated IOP, latanoprost is a dominant strategy compared with dorzolamide, and is cost-effective compared with brimonidine if we assume that reductions in IOP directly correspond to health benefit and that no threshold value for IOP reduction exists. Latanoprost and travoprost are more effective than timolol, but more expensive. For those for whom timolol is not contraindicated, it would be preferable, from a cost-effectiveness standpoint, to start treatment with timolol and reserve the PGAs as an alternative treatment or as add-on therapy for patients not achieving a clinical response with timolol.

Except for trials comparing latanoprost or travoprost with timolol, there was a significant lack of trials comparing the other IOP-lowering agents. This, combined with the short-term nature of the clinical data, is a limitation.

## ABBREVIATIONS

AE(s)	adverse event(s)
AGIS	Advanced Glaucoma Intervention Study
CADTH	Canadian Agency for Drugs and Technologies in Health
CAG	closed-angle glaucoma
CER	cost-effectiveness ratio
CI	confidence interval
HALS	Health and Activity Limitation Survey
HEED	Health Economic Evaluations Database
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IOP	intraocular pressure
ITT	intention to treat
mm Hg	millimetres of mercury
N	number of participants
NNH	number needed to harm
NR	not reported
OAG	open-angle glaucoma
PGA	prostaglandin analogue
POAG	primary open-angle glaucoma
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RD	risk difference
RR	relative risk
SD	standard deviation
UK	United Kingdom
US	United States
WMD	weighted mean difference

# TABLE OF CONTENTS

<b>EXECUTIVE SUMMARY .....</b>	<b>IV</b>
<b>ABBREVIATIONS .....</b>	<b>VII</b>
<b>1 INTRODUCTION.....</b>	<b>1</b>
1.1 Background .....	1
1.1.1 Management of OAG.....	2
1.1.2 Goals of IOP management .....	2
1.2 Overview of Technology.....	3
1.2.1 Description of technology .....	3
1.2.2 Regulatory status in Canada .....	4
1.3 Drug-Utilization Trends.....	4
<b>2 THE ISSUE .....</b>	<b>4</b>
<b>3 OBJECTIVES .....</b>	<b>4</b>
<b>4 CLINICAL REVIEW .....</b>	<b>6</b>
4.1 Methods .....	6
4.1.1 Literature search strategy.....	6
4.1.2 Selection criteria .....	6
4.1.3 Selection method.....	7
4.1.4 Data-extraction strategy .....	7
4.1.5 Assessment of quality.....	7
4.1.6 Data-analysis methods .....	7
<b>5 RESULTS .....</b>	<b>8</b>
5.1 Quantity and quality of available trials.....	8
5.2 Trial characteristics .....	8
5.3 Data analyses and synthesis.....	10
<b>6 DISCUSSION.....</b>	<b>18</b>
6.1 Assessment of Clinical Effectiveness.....	18
6.2 Study Limitations.....	19
6.2.1 Outcomes .....	19
6.2.2 Patient population.....	20
6.2.3 Interventions .....	20
<b>7 ECONOMIC EVALUATION .....</b>	<b>20</b>
7.1 Objective .....	20
7.2 Review of Economic Studies.....	21
7.2.1 Literature-search strategy.....	21
7.2.2 Results.....	21
7.3 Methods for Economic Evaluation.....	22
7.3.1 Type of economic evaluation.....	22
7.3.2 Target population.....	22
7.3.3 Treatment comparators .....	22
7.3.4 Perspective.....	23

7.3.5	Effectiveness .....	23
7.4	Results of Economic Evaluation.....	25
7.4.1	Data parameters.....	25
7.4.2	Sensitivity analyses .....	26
7.4.3	Probabilistic and univariate sensitivity analyses.....	28
7.5	Discussion.....	29
7.5.1	Limitations .....	29
<b>8</b>	<b>CONCLUSIONS.....</b>	<b>31</b>
<b>9</b>	<b>HEALTH-SERVICES IMPACT .....</b>	<b>31</b>
<b>10</b>	<b>REFERENCES.....</b>	<b>32</b>

**APPENDICES – available from CADTH's website [www.cadth.ca](http://www.cadth.ca)**

- APPENDIX 1: Literature Search Strategy (Clinical)
- APPENDIX 1B: Literature Search Strategy (Economic)
- APPENDIX 2: Relevance Assessment Forms
- APPENDIX 3: Characteristics of included studies
- APPENDIX 4: Evidence Tables
- APPENDIX 5: Summary
- APPENDIX 6: List of Excluded Studies

# 1 INTRODUCTION

## 1.1 Background

Glaucoma is a chronic ocular disorder characterized by the slow, progressive degeneration of the optic nerve, which can lead to total and irreversible blindness over time. Typically, central vision loss is unnoticeable until there has been a significant level of nerve damage. As a result, many people presenting with glaucoma are unaware of their disease. In Canada and other industrialized countries, glaucoma is one of the most common causes of blindness. At least 300,000 Canadians are affected with glaucoma, with 50% of patients unaware of their disease.<sup>1</sup> Quigley and Broman estimate that 60.5 million people will have glaucoma by 2010, increasing to 79.6 million by 2020.<sup>2</sup> Once diagnosed, patients must be monitored and treated for the remainder of their lives.

Although not always associated with glaucoma, high intraocular pressure (IOP) is recognized as the most important risk factor contributing to the development and progression of glaucoma.<sup>3</sup> Elevated IOP is neither necessary nor sufficient to cause glaucoma because an estimated 90% of patients with elevated IOP [ $>21$  millimetres of mercury (mm Hg)] never develop glaucoma.<sup>4</sup> Conversely, normal- or low-tension glaucoma occurs in individuals without high IOP. These patients still benefit from IOP reduction.<sup>5</sup> Other risk factors include increasing age, being of African descent, family history of glaucoma, myopia, central corneal thickness, steroid use, and to a lesser extent, hypertension, type 2 diabetes, and a history of migraines or sleep apnea.<sup>3,6</sup>

There are two types of glaucoma in adults: open-angle glaucoma (OAG) and closed-angle glaucoma (CAG). OAG and CAG can be primary or secondary conditions. Glaucoma is primary when the cause is unknown. Secondary glaucoma can be traced to a known cause, such as an injury (traumatic glaucoma) or a tumour. Pseudoexfoliation glaucoma and pigmentary glaucoma are forms of secondary OAG. Pseudoexfoliation glaucoma is the most common identifiable cause of secondary OAG, and is associated with the production and deposition of fibrillar extracellular material in the ocular tissue. Pigmentary glaucoma is a sequela of pigmentary dispersion syndrome, a disorder characterized by the deposition of pigment granules in the eye.

Primary open-angle glaucoma (POAG) is the most common form of glaucoma in Canada and other industrialized countries, accounting for 60% of glaucoma cases.<sup>7</sup> This chronic condition is characterized by slow and progressive damage to the optic nerve, usually causing gradual loss of vision. Both eyes can be affected, although one may be affected more than the other. POAG usually progresses with few or no symptoms until the condition reaches an advanced stage. Nerve-fibre losses of up to 50% can occur before patients may start to notice a loss of peripheral vision, which, if left untreated, will progress to tunnel vision and then blindness.<sup>8</sup>

The elevated IOP observed in the classic presentation of POAG is thought to result from the decreased drainage of the aqueous humour, the fluid that fills the anterior and posterior chambers of the eye. Aqueous humour is produced in the ciliary body of the posterior chamber, circulates around the lens, passes through the pupil, and flows into the anterior chamber.<sup>3</sup> OAG is thought to be caused by impaired outflow of aqueous humour, increasing the IOP, although the mechanism underlying this increased resistance to flow is incompletely understood.<sup>9</sup> Pseudoexfoliation glaucoma and pigmentary glaucoma are caused by obstruction of the trabecular meshwork by fibrillar material and pigment respectively, resulting in elevation of IOP.

Clinically, OAG is characterized by cupping of the optic nerve head (viewed by ophthalmoscopy or slit-lamp stereo-biomicroscopy) and a distinctive pattern of visual field loss. Cupping results from the loss of retinal ganglion cells and axons, combined with the collapse of the lamina cribrosa, a section of connective tissue at the back of the eye through which the optic nerve passes.<sup>10</sup> Deformation of the lamina cribrosa can pinch the optic nerve, causing axon death.

### 1.1.1 Management of OAG

The goal of current glaucoma treatment is to lower IOP, the only modifiable risk factor for glaucoma progression. Although no surrogate marker has been validated for glaucoma, IOP is the most widely used surrogate measure of visual function outcome. Studies have shown that the lowering of IOP is associated with a reduction in optic-nerve damage and glaucoma-related blindness. A 1 mm Hg change in IOP has been associated with clinically significant differences.<sup>11-14</sup> These studies include the Early Manifest Glaucoma Trial,<sup>13,15</sup> the Collaborative Normal-Tension Glaucoma Study,<sup>5</sup> the Advanced Glaucoma Intervention Study (AGIS),<sup>16</sup> and the Ocular Hypertension Treatment Study.<sup>4,17</sup> These are gold-standard studies supporting the lowering of IOP in patients with glaucoma.<sup>18</sup> Maier *et al.* reported the results of a meta-analysis confirming that lowering IOP in patients with ocular hypertension or manifest glaucoma was associated with a reduction in the risk of visual field loss in the long term.<sup>19</sup>

The approaches to reducing IOP include pharmacotherapy or surgery. Pharmacotherapy is usually the first line of treatment for elevated IOP and chronic OAG. Five classes of drugs are used to manage glaucoma and elevated IOP.<sup>3,20</sup>

- beta-adrenergic antagonists
- adrenergic agonists
- carbonic anhydrase inhibitors
- cholinergics (acetylcholine receptor agonists)
- prostaglandin analogues (PGAs).

Beta-adrenergic antagonists and carbonic anhydrase inhibitors reduce IOP by decreasing the production of aqueous humour. The cholinergics increase trabecular outflow.<sup>9</sup> Alpha2-adrenergic agents decrease IOP by decreasing aqueous production and increasing uveoscleral outflow, another drainage pathway.<sup>9</sup> The PGAs increase uveoscleral outflow.<sup>9</sup>

Surgical approaches to lowering IOP include laser trabeculoplasty (argon laser or selective laser), which is used to improve the fluid outflow from the trabecular meshwork; and trabeculectomy (filtration surgery), the surgical creation of a fistula from the anterior chamber to the subconjunctival space. In advanced cases, intraocular valves are placed in the eye to lower IOP. Treatment approaches vary among patients and depend on many factors including disease severity, response to medications, and patients' adherence.

### 1.1.2 Goals of IOP management

Treatment is aimed at lowering IOP to preserve visual field and vision. Several approaches have been advocated for setting appropriate IOP treatment goals. The American Academy of Ophthalmology, for example, recommends a lowering of at least 20% from baseline IOP,<sup>6</sup> whereas the European Glaucoma Society recommends a lowering of at least 30% from baseline IOP.<sup>21</sup> An IOP of 18 mm Hg has been recommended as an upper limit, based on results of the AGIS, which showed that patients with always

<18 mmHg of IOP had minimal visual-field progression.<sup>16</sup> It is controversial whether the target IOP should be calculated as an absolute level or as a percentage decrease from the baseline value.<sup>22</sup>

Consensus guidelines on setting targets for IOP were established in a series of cross-Canada workshops, based on discussions of randomized controlled trial (RCT) results and case studies.<sup>18</sup> The consensus was that IOP is a dynamic concept varying between patients and between eyes, and that target pressure must take into account the severity of the optic-nerve damage, patients' baseline IOP, the rapidity and progression of damage, and other risk factors for progression. Damji *et al.* identified several limitations to setting target IOP values, including diurnal fluctuations in IOP and non-IOP risk factors (e.g., type of instrument, operator variability, and corneal variations).<sup>18</sup> Damji *et al.* recommend that, when assessing treatment efficacy, the IOP should be obtained at the same time of day to avoid confounding diurnal fluctuations. They also recommend that the IOP and optic nerve be re-evaluated every three to 12 months.<sup>18</sup>

## 1.2 Overview of Technology

PGAs are the newest class of glaucoma medications to be introduced onto the Canadian market (Table 1). Appropriate comparators identified for this review appear in Table 2.

<b>Table 1: Single-agent PGAs for glaucoma treatment available in Canada</b>				
<b>Generic Name</b>	<b>Trade Name (Manufacturer)</b>	<b>Strength and Dosage Form</b>	<b>Cost Per Unit* (\$)</b>	<b>Approved Dosage</b>
latanoprost	Xalatan <sup>®</sup> (Pfizer Canada Inc.)	0.005% ophthalmic solution, 2.5 mL package	26.00	once daily
travoprost	Travatan <sup>®</sup> (Alcon Canada Inc.)	0.004% ophthalmic solution, 2.5 mL package	26.50	once daily
bimatoprost	Lumigan <sup>®</sup> (Allergan Inc.)	0.03% ophthalmic solution, 2.5 mL package	26.00	once daily

\*Cost and dosing information obtained from online Ontario Drug Benefit Formulary effective from April 4, 2006.<sup>23</sup>

<b>Table 2: Comparator glaucoma drugs available in Canada*</b>	
<b>Drug Class</b>	<b>Generic Names</b>
beta-blockers	betaxolol, levobunolol, timolol
adrenergic agents	apraclonidine, brimonidine, dipivefrin
carbonic anhydrase inhibitors	brinzolamide, dorzolamide
cholinergics	pilocarpine, carbachol, acetylcholine, echothiophate

\*From Ontario Drug Benefit Formulary.

### 1.2.1 Description of technology

PGAs are lipophilic agents derived from arachidonic acid. PGAs lower IOP by increasing the outflow of aqueous humour, primarily through the uveoscleral pathway. Although the mechanism of action is unclear, they are thought to exert their effect by binding to the prostanoid FP receptors of the ciliary body, up-regulating the production of metalloproteinases.<sup>20</sup> Metalloproteinases are zinc-dependent endoproteinases that are involved in normal and pathogenic remodelling of the extracellular matrix. PGAs are thought to induce metalloproteinase remodelling, rendering the extracellular matrix more

permeable to aqueous humour, which leads to the enhanced outflow of aqueous humour and reduction of IOP.<sup>24</sup> PGAs also relax the ciliary muscle, further facilitating uveoscleral outflow.<sup>25</sup>

## 1.2.2 Regulatory status in Canada

Three PGAs are approved in Canada for the treatment of patients with elevated IOP or glaucoma (Table 1): latanoprost (Xalatan<sup>®</sup>), travoprost (Travatan<sup>®</sup>), and bimatoprost (Lumigan<sup>®</sup>). They are indicated for the reduction of IOP in patients who have OAG or ocular hypertension. Most provincial government-sponsored drug programs provide unrestricted coverage or open listing for these drugs. In Ontario and New Brunswick, coverage is restricted and specific clinical criteria must be fulfilled before approval is obtained for reimbursement.

Latanoprost, a selective partial agonist of the prostaglandin F2 receptor, was approved for use in Canada on January 17, 2000. Travoprost, which is a full agonist of the prostaglandin F2 receptor, was approved on July 7, 2002. Bimatoprost is a synthetic prostamide analogue that differs from other prostaglandins in that it contains an amide rather than an ester group at the carboxy-terminal end. Bimatoprost was approved for use in Canada on April 6, 2004.

## 1.3 Drug-Utilization Trends

Members of the Advisory Committee on Pharmaceuticals were contacted by the Canadian Agency for Drugs and Technologies in Health (CADTH) to obtain information on the number of prescriptions and claims reimbursed by their respective drug plans for PGAs and comparator agents available in Canada (Table 3). From 2001 to 2005, there has been a steady decrease in the use of beta-blockers and a steady increase in the use of PGAs in Canada. The use of beta-blockers may not be declining as rapidly as Table 3 suggests, given the increased use of combined medications that include beta-blockers such as Xalacom<sup>™</sup> (latanoprost plus timolol). The use of miotics and parasympathomimetics has not varied greatly over the past five years. Trends in the use of adrenergic agents or carbonic anhydrase inhibitors vary depending on the agent or dosage.

## 2 THE ISSUE

PGAs for ophthalmic use are open listed by jurisdictional drug plans, but are more costly than alternative agents for the lowering of IOP. One policy decision to be made is whether reimbursement of these agents as first-line therapy with no restrictions represents an optimal use of limited resources.

## 3 OBJECTIVES

The objective of this project was to perform a systematic review and economic evaluation of the PGAs for the treatment of increased IOP, using evidence from published and unpublished RCTs. This objective was accomplished by addressing the following questions:

- What is the effectiveness of using PGAs (bimatoprost, latanoprost, travoprost) for ophthalmic use as first-line agents for the lowering of ophthalmic IOP in patients with ocular hypertension and OAG, or isolated ocular hypertension?

- What is the effectiveness of using PGAs for the lowering of IOP in patients with ocular hypertension and OAG, or isolated ocular hypertension, who cannot use or have failed therapy with other IOP-lowering agents?
- What is the cost-effectiveness of using PGAs for ophthalmic use:
  - as first-line agents
  - in patients with ocular hypertension and glaucoma, or isolated ocular hypertension, who cannot use or have failed other IOP-lowering agents?

**Table 3: Utilization of glaucoma medications over five years, based on Canadian jurisdictional claims data\***

Glaucoma Medication <sup>†</sup>	Number of Prescriptions Reimbursed				
	2005	2004	2003	2002	2001
<b>PGAs</b>					
bimatoprost 0.03%	98,486	62,731	11,869	NA	NA
latanoprost 0.005%	472,712	477,317	453,520	435,020	337,475
travoprost 0.004%	99,690	88,944	64,723	20,097	NA
total	670,880	628,992	530,112	455,117	337,475
<b>Adrenergic agents</b>					
brimonidine tartrate 0.15%	23,875	4,136	NA	NA	NA
brimonidine tartrate 0.2%	122,821	149,183	158,489	172,670	168,008
total	146,696	153,319	158,489	172,670	168,008
<b>Beta-blockers</b>					
betaxolol HCL 0.25%	61,420	75,074	85,960	100,555	112,088
levobunolol HCL 0.5%	66,351	78,390	88,991	106,449	120,113
timolol maleate 0.25%	12,565	12,531	15,512	18,781	21,148
timolol maleate 0.5%	125,667	133,347	144,587	177,437	186,032
total	266,003	299,342	335,050	403,222	439,381
<b>Carbonic anhydrase inhibitors</b>					
brinzolamide 1%	33,393	29,254	25,759	23,905	18,301
dorzolamide HCL%	68,026	75,428	85,969	101,296	115,163
total	101,420	104,682	111,728	125,201	133,464
<b>Miotics or parasympathomimetics</b>					
carbachol 1.5%	1,749	1,642	1,464	1,883	1,874
carbachol 3%	3,526	3,229	3,088	3,529	3,542
pilocarpine HCL%	4,789	5,551	6,416	7,300	8,128
pilocarpine HCL%	15,573	12,749	11,351	12,394	16,571
pilocarpine HCL%	18,720	15,301	15,244	17,479	19,560
total	44,357	38,472	37,569	41,585	49,675

\*Jurisdictions included British Columbia, Department of National Defence, First Nations and Inuit Health Branch, Manitoba, New Brunswick, Ontario, and Saskatchewan; <sup>†</sup>ophthalmic solutions, any size; NA=not applicable.

## 4 CLINICAL REVIEW

### 4.1 Methods

#### 4.1.1 Literature search strategy

Published literature was obtained by cross-searching MEDLINE<sup>®</sup> (1951 to present), BIOSIS Previews<sup>®</sup> (1969 to present), ToxFile (1964 to present), and EMBASE<sup>®</sup> (1974 to present) databases, with no language restrictions, through the Dialog<sup>®</sup> system. A broad search strategy with appropriate descriptors and keywords was used with a filter to restrict results to controlled trials, meta-analyses, and systematic reviews. A parallel search on PubMed and the Cochrane database was conducted, and several trial registries were searched. Searches were not restricted by publication date, but were restricted by language (i.e., reports written in languages other than English were excluded).<sup>26,27</sup> The literature-search strategy appears in Appendix 1.

The original search was performed in November 2005. We established regular alerts on MEDLINE<sup>®</sup>, BIOSIS Previews<sup>®</sup>, ToxFile, and EMBASE<sup>®</sup> databases to capture new studies until October 3, 2006, and updated searches on the Cochrane databases regularly. The last Cochrane updates for this report were performed on Issue 3, 2006.

Grey literature was obtained by searching the web sites of regulatory, health technology assessment, and near-technology assessment agencies. Specialized databases such as the University of York NHS Centre for Reviews and Dissemination and the Latin American and Caribbean Center on Health Sciences Information were searched. The Internet was searched using the Google<sup>™</sup> and Yahoo!<sup>®</sup> search engines. The web sites of professional associations such as the Association of Research in Vision and Ophthalmology, American Optometric Association, the International Glaucoma Association, the Canadian Glaucoma Society, and the Association of International Glaucoma Societies and their associated conference sites were searched. Trial registries were searched for completed and ongoing trials. The manufacturers of relevant pharmaceutical agents were contacted for additional materials.

#### 4.1.2 Selection criteria

Selected studies included published and unpublished RCTs, and RCTs published in abstract form. Reports of RCTs that were deemed to be confidential and that were not publicly available were excluded. Reports written in languages other than English were excluded.<sup>26,27</sup> RCTs using a parallel group and cross-over design were included. For cross-over studies, only data from the first treatment period were extracted to avoid confounding from possible carry-over effects. Two reviewers (IS and CM) independently screened the clinical-search results according to established selection criteria (Appendix 2). Evidence was screened using inclusion and exclusion criteria.

##### **a) Inclusion criteria**

- Reports on a RCT that meet all the following criteria:
  - involving human adult subjects (>18 years old) with raised IOP
  - where at least one intervention is a PGA
  - includes treatment-naïve patients, or patients who have received an appropriate washout period before treatment.

##### **b) Exclusion criteria**

- reports on a RCT in which the comparators were not another IOP-lowering agent or a placebo

- reports on a RCT evaluating patients with CAG.

#### **4.1.3 Selection method**

Potentially relevant bibliographic records were imported into a reference database, with duplicates removed manually. The relevant references were exported to SRS 3.0 (Trialstat Corporation, Ottawa ON), a web-based data-management software system for systematic reviews. The software was used to present each bibliographic record, along with selection criteria; to record and compare each reviewer's ratings; and to determine the record's eligibility in accordance with selection criteria. Two reviewers (IS and CM) independently screened the title and abstract for relevance by applying broad eligibility criteria (level 1 screening form, Appendix 2). If both reviewers agreed that the citation title or abstract met all the criteria, or if there was uncertainty or disagreement between reviewers, the publication was obtained in full text. The reviewers then applied the selection criteria to the full text articles (level 2 screening form, Appendix 2) to select the relevant articles to be included in the review. Disagreements were resolved through consensus.

#### **4.1.4 Data-extraction strategy**

One reviewer (VF) independently extracted data from the studies. Completed evidence tables were independently checked for accuracy by a second reviewer (DB). Data regarding study design, patient population, interventions, comparators, results, harm and adverse events (AEs), and limitations were entered into the evidence tables.

##### **a) Outcomes of interest**

###### **Primary outcome**

- absolute change in IOP from baseline in individual patients, at minimum three-month follow-up.

###### **Secondary outcomes (at minimum three-month follow-up)**

- slow or stop progression of visual field defects
- slow or stop increase in cupping of the optic nerve
- lack of response or loss of therapeutic effect
- all adverse events (AEs)
- withdrawals and dropouts for any reason
- withdrawals due to AEs.

#### **4.1.5 Assessment of quality**

The quality of each included trial was independently assessed by two reviewers (VF and DB), using the Jadad scale.<sup>28</sup> The Jadad scale assesses the reporting of randomization, double blinding, and the inclusion of data for withdrawals and dropouts. Total scores ranged from zero to five, with a score <3 indicating low quality. Concealment of allocation to treatment was also categorized by the reviewer as adequate, inadequate, or unclear.<sup>29</sup>

#### **4.1.6 Data-analysis methods**

Analyses were performed using the RevMan software (release 4.2.7) provided by the Cochrane collaboration group and SAS statistical software (release 9.1.3, SAS Institute, Cary NC). The software was used to compute statistics and generate forest plots to compare outcomes in the different treatment arms.

For continuous data, the weighted mean difference (WMD) and 95% confidence interval (CI) were calculated. A chi-square test (using  $n-1$  degrees of freedom and a  $p$  value  $<0.05$ ) and an  $I^2$  test were used to test for statistical heterogeneity between studies. If significant heterogeneity was detected, it was investigated using a sensitivity analysis based on trial characteristics. If significant heterogeneity remained, or if the  $I^2$  value indicated moderate to high heterogeneity (i.e.,  $>25\%$ ),<sup>30</sup> the data were summarized using a random-effects analysis. The test for overall effect, studies' sample sizes, and percent weights were also presented. Studies were grouped according to the length of follow-up. Sensitivity analyses were undertaken to evaluate the effect of study quality and intention to treat (ITT) analysis on the primary-outcome measure. The ITT population was defined as patients who received at least one treatment and had at least one evaluation after treatment. A descriptive summary was provided for data that were unsuitable for pooling.

## 5 RESULTS

### 5.1 Quantity and quality of available trials

Of the 195 potentially relevant reports identified for retrieval, 26 reports of 22 unique RCTs, reporting on 5,304 individuals, were included in this systematic review (Figure 1 and Appendix 3). Of the 22 included RCTs, all were reported in peer-reviewed journals. Alm and Stjernschantz<sup>31</sup> was published in two other journals with different first authors.<sup>32,33</sup> Camras and Sheu<sup>34</sup> was previously reported as a conference abstract<sup>35</sup>, and Fechtner *et al.*<sup>36</sup> was previously reported as a conference abstract.<sup>37</sup> The kappa score was 0.90, indicating a good level of agreement between reviewers.

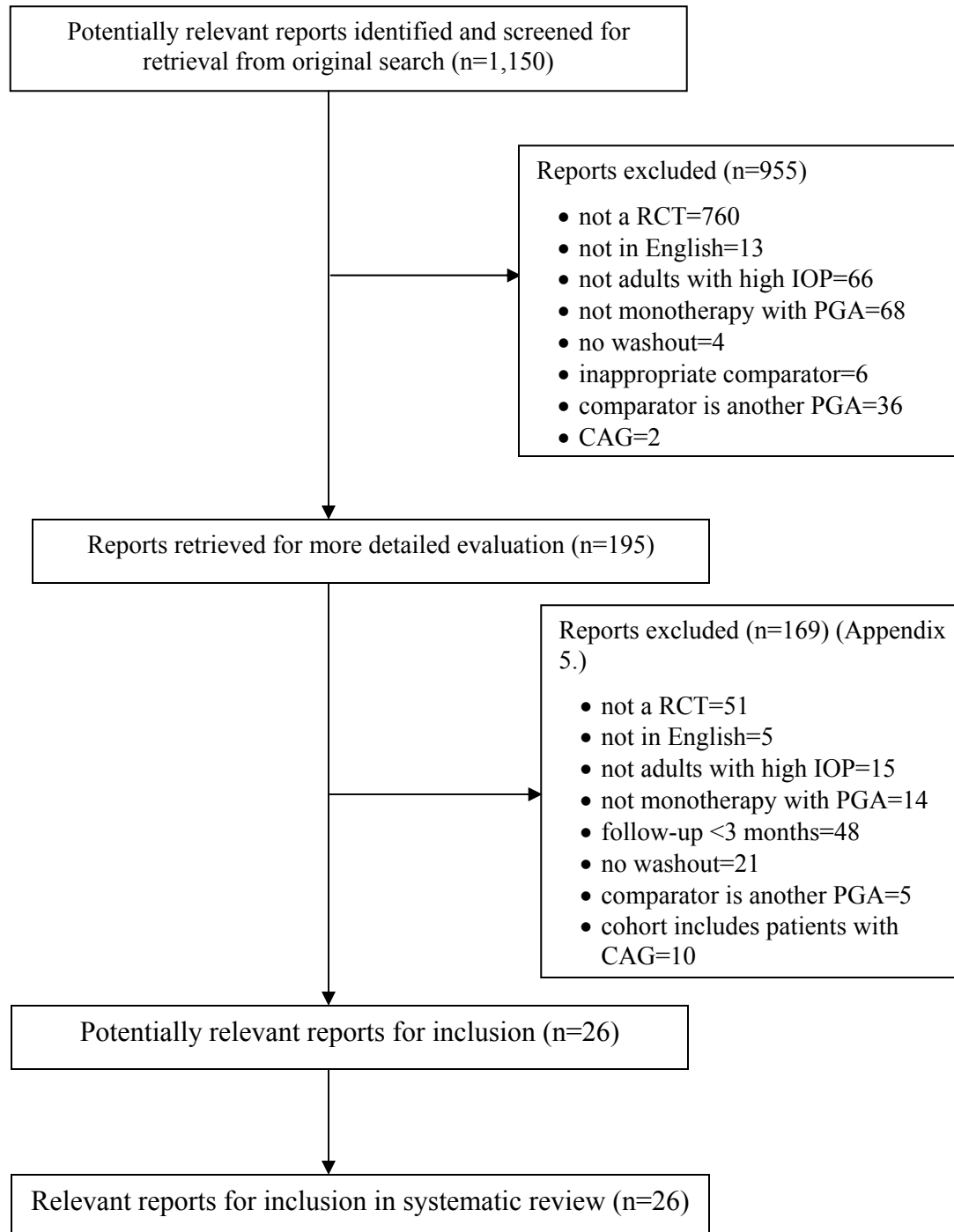
Fourteen of the 22 studies (64%) were of higher quality (Jadad score  $\geq 3$ ),<sup>31,34,36,38-48</sup> with 10 studies (45%) receiving the highest score (Jadad score=5).<sup>31,34,36,39-42,46,48,49</sup> Eight studies (36%) were of lower quality (Jadad score  $\leq 2$ ) (Appendix 3). Allocation concealment was rated as adequate in all the higher quality studies and unclear in those of lower quality (Appendix 3). Four trials were open-label studies<sup>43,50-52</sup> and hence, the rating of allocation concealment was inapplicable.

### 5.2 Trial characteristics

Details of each study, including study design, participant characteristics, interventions, outcomes, and funding source(s) appear in Appendices 3, 4, and 5.

Except for one study,<sup>47</sup> which was a cross-over design, all the studies were of parallel design. One study<sup>49</sup> did not report on the age of included participants ( $n=60$ ). Of the remaining 5,244 participants, the range of mean ages was from 46 to 70 years. Of the data available, 3,471 (78%) were white and 547 (12%) were black; 2,678 (52%) were female and 2,490 (48%) were male. Of the studies reporting on diagnosis, 2,845 (57%) had POAG; 1,730 (35%) had isolated ocular hypertension; 63 (1.3%) had pigmentary glaucoma, and 139 (2.8%) had exfoliation glaucoma. Of the available data, baseline IOP levels of patients in the included studies ranged from 21 mm Hg to 36 mm Hg in at least one eye, with or without ocular hypotensive drugs.

**Figure 1:** Report-screening and selection procedure



Eighteen studies examined the PGA latanoprost,<sup>31,34,36,39,40,43-48,50-56</sup> four examined travoprost,<sup>38,41,42,46</sup> and one examined bimatoprost.<sup>49</sup> Eight studies compared latanoprost with timolol,<sup>31,39,43-48</sup> one study compared latanoprost with betaxolol,<sup>55</sup> four compared latanoprost with brimonidine,<sup>34,40,50,51</sup> three compared latanoprost with dorzolamide,<sup>52-54</sup> and two compared latanoprost with combination therapy (dorzolamide+timolol<sup>36</sup> and carteolol+pilocarpine).<sup>56</sup> One study compared bimatoprost with timolol.<sup>49</sup> For all treatments and comparators, the dosage was the same across the included trials (Appendix 5).

In 17 included studies, a PGA was evaluated in a mixed cohort of patients who were treatment-naïve (first-line therapy) or who had received therapy with an IOP-reducing agent (Appendix 5).<sup>34,36,38-46,48-50,52-54</sup> Four of the included studies examined a PGA as first-line therapy.<sup>31,47,55,56</sup> One study examined a PGA in patients who could not use, or had failed therapy with, an IOP-lowering agent (second-line therapy).<sup>51</sup>

For most studies, the washout of previous ocular hypotensive agents ranged from three to four weeks for  $\beta$ -adrenergic antagonists and PGAs, two weeks for adrenergic agonists, and three to five days for cholinergic agonists and carbonic anhydrase inhibitors (Appendix 4).

All 22 trials assessed change in IOP from baseline. Four trials reported on the number of patients reaching a target IOP or achieving a  $\geq 20\%$  reduction in IOP from baseline (Appendix 4).<sup>34,40,47,51</sup> Diurnal IOP (at least two measurements, one in the morning and one in the evening) was the main outcome measures in 17 trials. Four of the remaining five trials indicated that one IOP measurement was obtained per visit (usually in the morning).<sup>40,45,50,55</sup> The fifth trial did not provide details regarding when IOP measurements were obtained.<sup>49</sup> All studies reported that IOP was measured using Goldmann applanation tonometry.

Seven studies reported assessing visual-field defects during the study.<sup>36,41,42,44,46,48,55</sup> Three studies reported assessing changes in optic-nerve cupping (i.e., optic cup-to-disc ratio).<sup>41,42,46</sup>

Twenty studies reported on withdrawals due to AEs.<sup>31,34,36,39-52,54-56</sup> Serious AEs were reported in 15 studies<sup>31,34,36,39-42,44,46-48,51,52,54,56</sup> and 20 studies reported ocular AEs.<sup>31,34,36,38-49,51-54,56</sup>

Four studies reported on respiratory and cardiac AEs.<sup>43,45,46,48</sup> Five studies reported mean heart rate and blood pressure for each treatment group.<sup>38,39,41,46,50</sup> One study reported only on mean heart rate.<sup>42</sup>

### 5.3 Data analyses and synthesis

Meta-analyses of studies were performed for the following outcome measures:

- IOP change from baseline
- withdrawals due to AEs
- ocular hyperemia
- all other ocular AEs
- respiratory and cardiac AEs (potentially related to timolol)
- serious AEs.

The results of these meta-analyses appear in Tables 4 and 5. Several trials did not report the standard deviations (SDs) of the mean.<sup>34,41,42,45-48,50</sup> In these cases, the most frequently reported SD (mode) was used, and the 95% CIs around these estimates should be interpreted with caution.

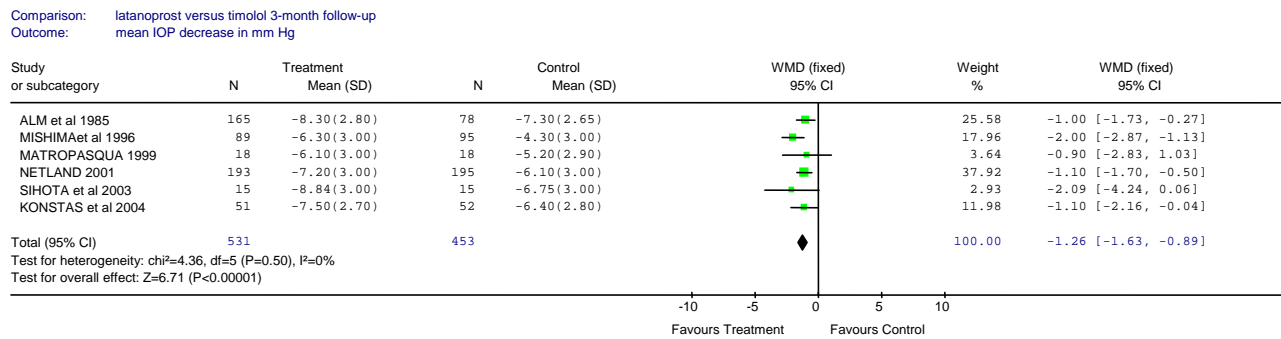
**a) Reduction in IOP**

Meta-analyses comparing data on PGAs and comparators on the reduction of IOP appear in Table 4 and corresponding forest plots.

**Latanoprost versus timolol**

**Three-month follow-up:** A meta-analysis of data from six studies with 984 patients showed a significant reduction in the mean IOP from baseline in the latanoprost group compared with the timolol group [WMD -1.26 (95% CI: -1.63, -0.89);  $p < 0.00001$ ] (Figure 2).<sup>31,43-47</sup>

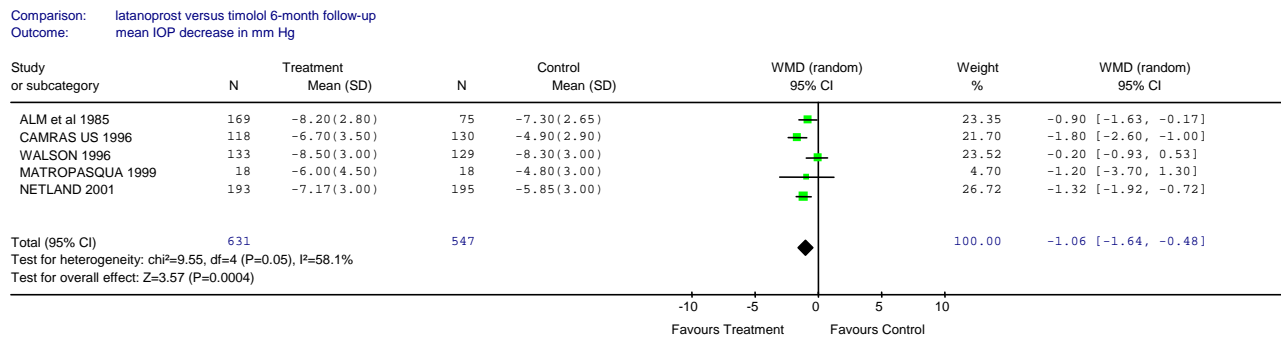
**Figure 2: Pooled three-month data for latanoprost versus timolol: reduction in IOP (random-effects model)**



CI=confidence interval; N=number of participants; IOP=intra-ocular pressure; SD=standard deviation; WMD=weighted mean difference.

**Six-month follow-up:** A meta-analysis of data from five studies with 1,178 patients showed a significant reduction in the mean IOP from baseline in the latanoprost group compared with the timolol group [WMD -1.06 (95% CI: -1.64, -0.48);  $p=0.0004$ ] (Figure 3).<sup>31,39,44,46,48</sup>

**Figure 3: Pooled six-month data for latanoprost versus timolol: reduction in IOP (random-effects model)**

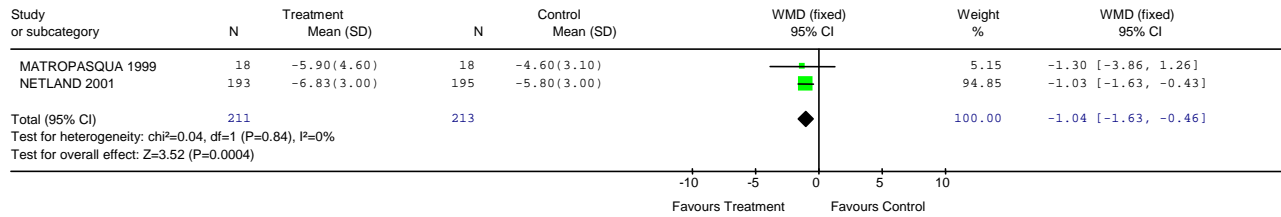


CI=confidence interval; IOP=intra-ocular pressure; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

**Twelve-month follow-up:** A meta-analysis of data from two studies with 424 patients showed a significant reduction in the mean IOP from baseline in the latanoprost group compared with the timolol group [WMD -1.04 (95% CI: -1.63, -0.46);  $p=0.0004$ ] (Figure 4).<sup>44,46</sup>

**Figure 4: Pooled 12-month data for latanoprost versus timolol: reduction in IOP**

Comparison: latanoprost versus timolol 12-month follow-up  
Outcome: mean IOP decrease in mm Hg

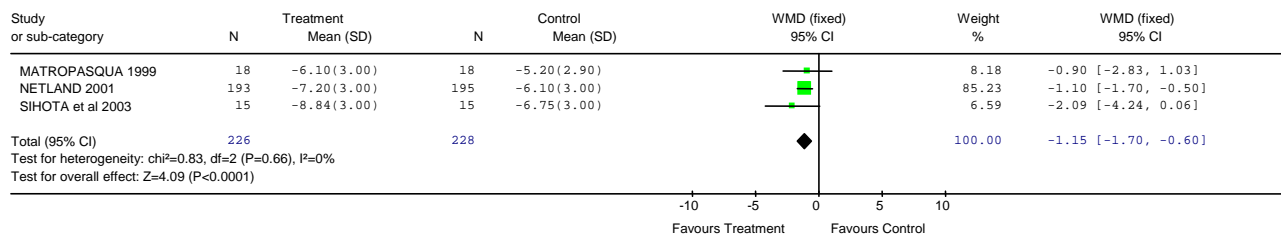


CI=confidence interval; IOP=intra-ocular pressure; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

**Sensitivity analyses:** When only studies using an ITT analysis were pooled for the meta-analysis, the reduction in IOP remained significant at the three- and six-month time-points (Figures 5 and 6). A sensitivity analysis for quality was not performed, because all studies were of higher quality (Jadad score  $\geq 3$ ).

**Figure 5: Pooled three-month data for latanoprost versus timolol: reduction in IOP, studies with ITT analysis**

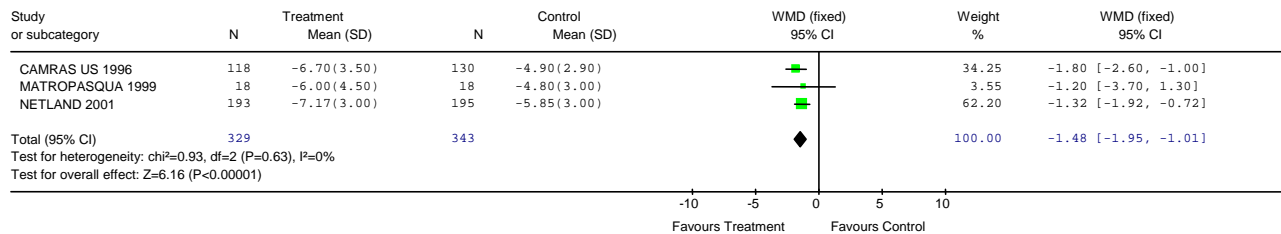
Comparison: latanoprost versus timolol 3-month follow-up ITT  
Outcome: mean IOP decrease in mm Hg



CI=confidence interval; IOP=intra-ocular pressure; ITT=intention to treat; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

**Figure 6: Pooled six-month data for latanoprost versus timolol: reduction in IOP, studies with ITT analysis**

Comparison: latanoprost versus timolol 6-month follow-up ITT  
Outcome: mean IOP decrease in mm Hg



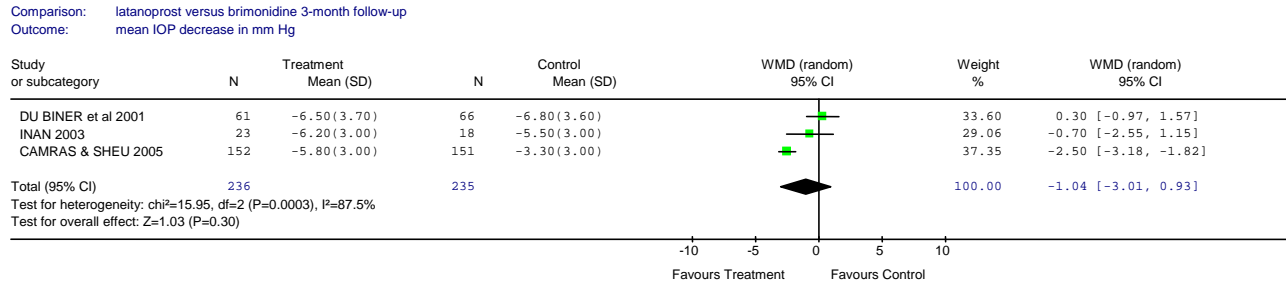
CI=confidence interval; IOP=intra-ocular pressure; ITT=intention to treat; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

## Latanoprost versus brimonidine

**Three-month follow-up:** A meta-analysis of data from three studies with 471 patients did not show a significant reduction in the mean IOP from baseline in the latanoprost group compared with the brimonidine group [WMD -1.04 (95% CI: -3.01, 0.93);  $p=0.30$ ] (Figure 7).<sup>34,40,50</sup> This result did not

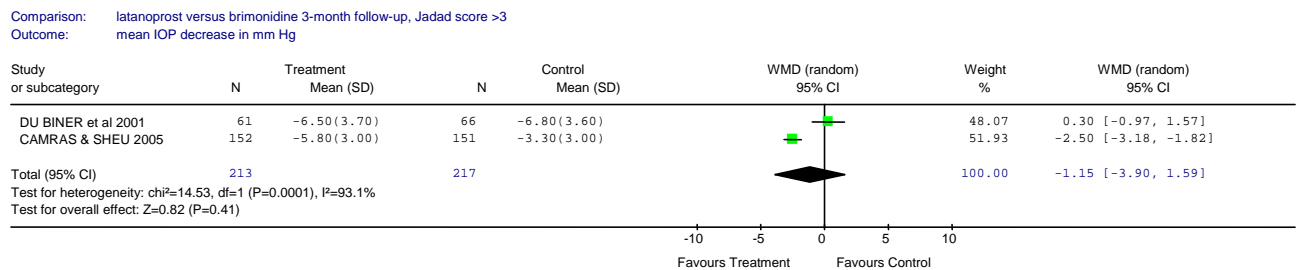
change when only higher quality studies were pooled for the meta-analysis (Figure 8).<sup>34,40</sup> A sensitivity analysis for ITT was not performed, because only one study used an ITT analysis.<sup>50</sup>

**Figure 7:** Pooled three-month data for latanoprost versus brimonidine: reduction in IOP



CI=confidence interval; IOP=intra-ocular pressure; ITT=intention to treat; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

**Figure 8:** Pooled three-month data for latanoprost versus brimonidine: reduction in IOP, studies of higher quality (random-effects model)

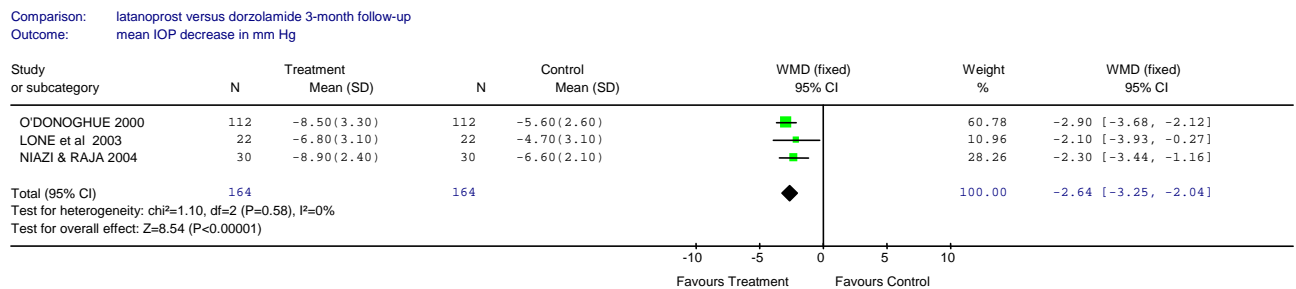


CI=confidence interval; IOP=intra-ocular pressure; ITT=intention to treat; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

## Latanoprost versus dorzolamide

**Three-month follow-up:** A meta-analysis of data from three studies with 328 patients showed a significant reduction in the mean IOP from baseline in the latanoprost group compared with the dorzolamide group [WMD -2.64 (95% CI: -3.25, -2.04);  $p<0.00001$ ] (Figure 9).<sup>52-54</sup>

**Figure 9:** Pooled three-month data for latanoprost versus dorzolamide: reduction in IOP



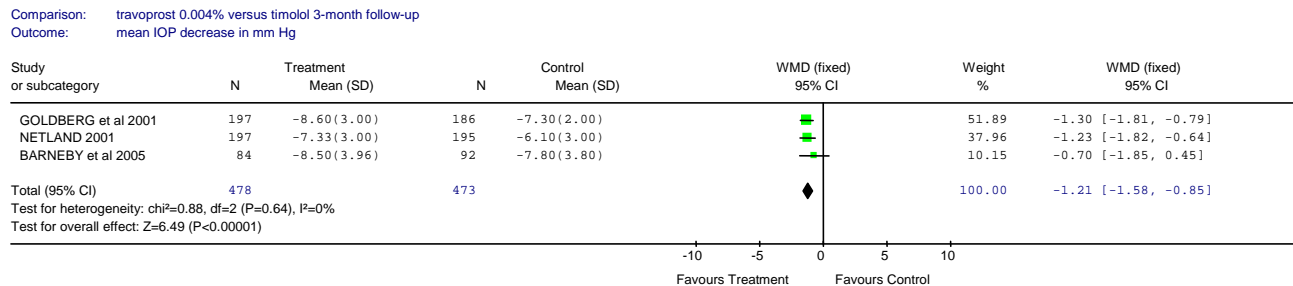
CI=confidence interval; IOP=intra-ocular pressure; ITT=intention to treat; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

A sensitivity analysis for quality was not performed, because all studies were of lower quality (Jadad score=2). A sensitivity analysis for ITT was not performed, because only one study used an ITT analysis.<sup>53</sup>

### Travoprost versus timolol

**Three-month follow-up:** A meta-analysis of data from three studies with 951 patients showed a significant reduction in the mean IOP from baseline in the travoprost group compared with the timolol group [WMD -1.21 (95% CI: -1.58, -0.85); p<0.00001] (Figure 10).<sup>38,42,46</sup>

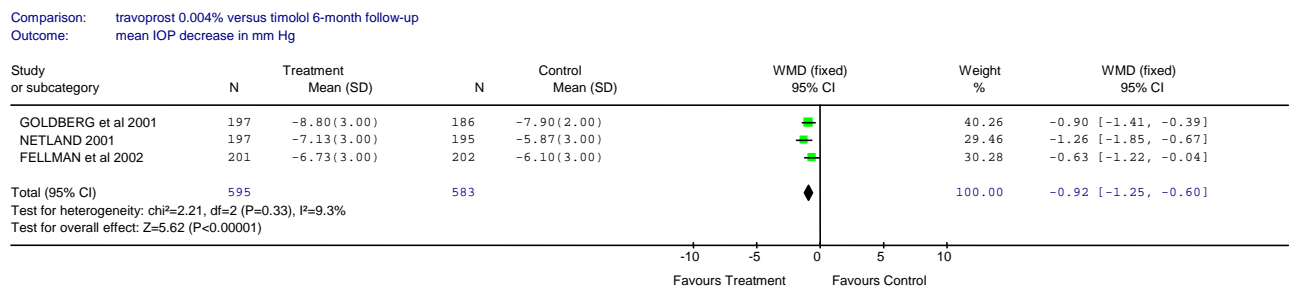
**Figure 10:** Pooled three-month data for 0.004% travoprost versus timolol: reduction in IOP



CI=confidence interval; IOP=intra-ocular pressure; ITT=intention to treat; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

**Six-month follow-up:** A meta-analysis of data from three studies with 1,178 patients showed a significant reduction in the mean IOP from baseline in the travoprost group compared with the timolol group [WMD -0.92 (95% CI: -1.25, -0.60); p<0.00001] (Figure 11).<sup>41,42,46</sup>

**Figure 11:** Pooled six-month data for 0.004% travoprost versus timolol: reduction in IOP



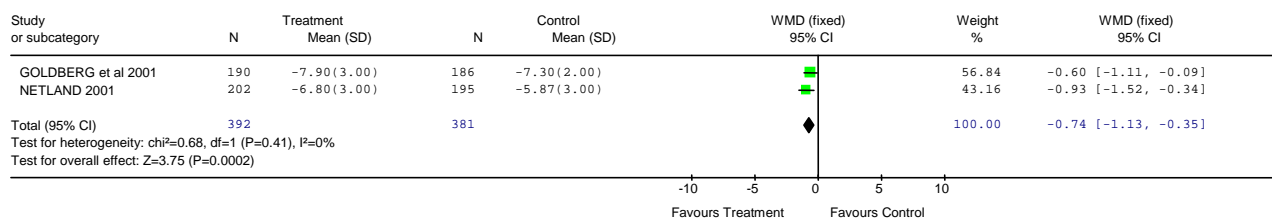
CI=confidence interval; IOP=intra-ocular pressure; ITT=intention to treat; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

**Sensitivity analysis:** A sensitivity analysis for quality was not performed, because all studies were of higher quality (Jadad score=4 or 5). A sensitivity analysis for ITT was not performed, because all studies used an ITT analysis.

**Low-dose travoprost:** Although travoprost 0.0015% is not approved for use in Canada, data from studies evaluating this low dose were included for comparative purposes (Figures 12 and 13).

**Figure 12: Pooled three-month data for 0.0015% travoprost versus timolol**

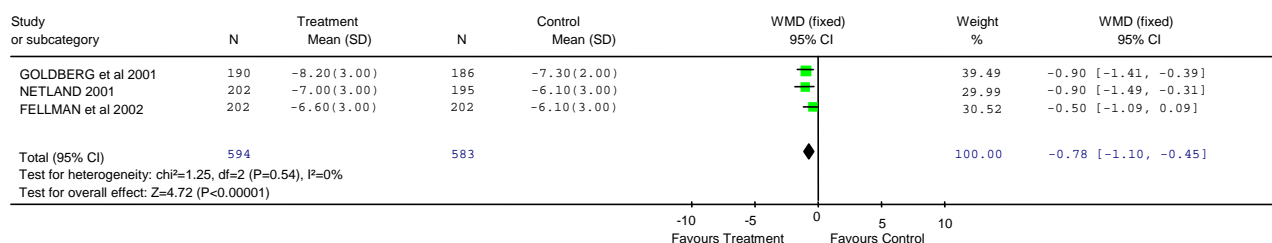
Comparison: travoprost 0.0015% versus timolol 3-month follow-up  
 Outcome: mean IOP decrease in mm Hg



CI=confidence interval; IOP=intra-ocular pressure; ITT=intention to treat; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

**Figure 13: Pooled six-month data for 0.0015% travoprost versus timolol: reduction in IOP**

Comparison: travoprost 0.0015% versus timolol 6-month follow-up  
 Outcome: mean IOP decrease in mm Hg



CI=confidence interval; IOP=intra-ocular pressure; ITT=intention to treat; N=number of participants; SD=standard deviation; WMD=weighted mean difference.

**Table 4: IOP data from meta-analysis of PGAs versus comparators**

Comparison	Trials Reporting Outcome	Number of Participants	WMD (95% CI)	P
<b>latanoprost versus timolol: 8 trials</b> <sup>31,39,43-48</sup>				
3-month follow-up	31,43-47	984	-1.26 (-1.63, -0.89)	<0.00001
6-month follow-up	31,39,44,46,48	1,178	-1.06 (-1.64, -0.48)	0.0004
12-month follow-up*	44,46	424	-1.04 (-1.63, -0.46)	0.0004
<b>latanoprost versus timolol (ITT): 4 trials</b> <sup>39,44,46,47</sup>				
3-month follow-up	44,46,47	454	-1.15 (-1.70, -0.60)	<0.0001
6-month follow-up	39,44,46	672	-1.48 (-1.95, -1.01)	<0.00001
<b>latanoprost versus brimonidine: 3 trials</b> <sup>34,40,50</sup>				
3-month follow-up	34,40,50	471	-1.04 (-3.01, 0.93)	0.30
Jadad score $\geq 3$	34,40	430	-1.15 (-3.90, 1.59)	0.41
<b>latanoprost versus dorzolamide: 3 trials</b> <sup>52-54</sup>				
3-month follow-up	52-54	328	-2.64 (-3.25, -2.04)	<0.00001
<b>travoprost (0.0015%) versus timolol: 3 trials</b> <sup>41,42,46</sup>				
3-month follow-up	42,46	773	-0.74 (-1.13, -0.35)	0.0002
6-month follow-up	41,42,46	1,177	-0.78 (-1.10, -0.45)	<0.00001
<b>travoprost (0.004%) versus timolol: 4 trials</b> <sup>38,41,42,46</sup>				
3-month follow-up	38,42,46	951	-1.21 (-1.58, -0.85)	<0.00001
6-month follow-up	41,42,46	1,178	-0.92 (-1.25, -0.60)	<0.00001

\*Mastropasqua et al.<sup>44</sup> ITT analysis used for 6-month, not 12-month, data.

**Withdrawals due to AEs:** For the 0.004% travoprost versus timolol comparison, there was a statistically significant risk difference for this outcome of 2% (1% to 4%) favouring timolol (Table 5). The number needed to harm (NNH) was 50 (25, 100) relative to timolol. There were no other significant differences between PGAs and comparators for withdrawals due to AEs (Table 5). Netland *et al.*, evaluating 801 patients, <sup>46</sup> reported no patient withdrawals due to AEs.

**Ocular hyperemia and other ocular AEs:** A meta-analysis of six studies (1,274 patients) comparing latanoprost versus timolol showed that for ocular hyperemia, there was a significant risk difference of 9% (6% to 12%) favouring timolol (Table 5).<sup>31,43-46,48</sup> The NNH was 11 (8, 17) relative to timolol.

Pooled results from six studies of 1,526 patients comparing latanoprost and timolol found that for ocular AEs (excluding hyperemia), there was a significant risk difference of 6% (0% to 12%) favouring timolol (Table 5).<sup>31,39,43,45,46,48</sup> The NNH was 17 (8, ∞) relative to timolol.

A meta-analysis of three studies (1,185 patients) of 0.0015% travoprost versus timolol showed that for ocular hyperemia, there was a significant risk difference of 21% (17% to 26%) in favour of timolol (Table 5).<sup>41,42,46</sup> A meta-analysis of four studies (1,364 patients) comparing 0.004% travoprost and timolol found that there was a significant risk difference of 29% (25% to 33%) favouring timolol (Table 5).<sup>38,41,42,46</sup> The NNH was 3 (3, 4) relative to timolol.

Pooled results from four studies of 1,364 patients of high-dose travoprost versus timolol showed that for ocular AEs (excluding hyperemia), there was a significant risk difference of 15% (7% to 23%) in favour of timolol (Table 5).<sup>38,41,42,46</sup> The NNH was 7 (4, 14) relative to timolol.

Table 5: Meta-analyses of harms data				
Outcome Measure	Event Rate		RD (95% CI)	NNH
	PGA (Number of Trials)	Comparator (Number of Trials)		
<b>Latanoprost versus timolol</b>				
withdrawals due to AEs	19/755 (7)	21/669 (7) <sup>31,39,43,44,46,48,52</sup>	0.00 (-0.02, 0.02)	NA
ocular hyperemia	100/684 (6)	43/590 (6) <sup>31,43-46,48</sup>	0.09 (0.06, 0.12)	11 (8, 17)*
all other ocular AEs	215/794 (6)	161/732 (6) <sup>31,39,43,45,46,48</sup>	0.06 (0.00, 0.12)	17 (8, ∞)*
cardiac and respiratory AEs <sup>‡</sup>	2/483 (4)	11/488 (4) <sup>43,45,46,48</sup>	-0.02 (-0.03, 0.00)	50 (33, ∞)†
serious AEs	23/674 (5)	17/587 (5) <sup>31,39,44,46,48</sup>	0.00 (-0.02, 0.02)	NA
<b>0.004% travoprost versus timolol</b>				
withdrawals due to AEs	18/598 (3)	5/588 (3) <sup>41,42,46</sup>	0.02 (0.01, 0.04)	50 (25, 100)*
ocular hyperemia	260/684 (4)	60/680 (4) <sup>38,41,42,46</sup>	0.29 (0.25, 0.33)	3 (3, 4)*
all other ocular AEs	237/684 (4)	126/680 (4) <sup>38,41,42,46</sup>	0.15 (0.07, 0.23)	7 (4, 14)*
serious AEs	0/598 (3)	0/588 (3) <sup>41,42,46</sup>	—	—
<b>0.0015% travoprost versus timolol</b>				
withdrawals due to AEs	7/597 (3)	5/588 (3) <sup>41,42,46</sup>	0.00 (-0.01, 0.02)	NA
ocular hyperemia	187/597 (3)	59/588 (3) <sup>31,41,42</sup>	0.21 (0.17, 0.26)	5 (4, 6)*

**Table 5: Meta-analyses of harms data**

Outcome Measure	Event Rate		RD (95% CI)	NNH
	PGA (Number of Trials)	Comparator (Number of Trials)		
all other ocular AEs	136/597 (3)	114/588 (3) <sup>41,42,46</sup>	0.03 (-0.01, 0.08)	NA
serious AEs	0/597 (3)	0/588 (3) <sup>41,42,46</sup>	—	—
<b>Latanoprost versus brimonidine</b>				
withdrawals due to AEs	12/423 (4)	46/423 (4) <sup>34,40,50,51</sup>	-0.03 (-0.13, 0.06)	NA
ocular hyperemia	18/248 (2)	15/252 (2) <sup>40,51</sup>	0.01 (-0.03, 0.06)	NA
all other ocular AEs	82/400 (3)	125/403 (3) <sup>34,40,51</sup>	-0.11 (-0.16, -0.05)	9 (6, 20) <sup>†</sup>
serious AEs	8/400 (3)	13/403 (3) <sup>34,40,51</sup>	-0.01 (-0.03, 0.01)	NA
<b>Latanoprost versus dorzolamide</b>				
withdrawals due to AEs	1/127 (2)	1/127 (2) <sup>47,54</sup>	0.00 (-0.03, 0.03)	NA
ocular hyperemia	13/179 (4)	11/179 (4) <sup>47,52-54</sup>	0.01 (-0.04, 0.03)	NA
all other ocular AEs	73/179 (4)	80/179 (4) <sup>47,52-54</sup>	-0.04 (-0.13, 0.05)	NA
serious AEs	3/157 (3)	3/157 (3) <sup>47,52,54</sup>	0.00 (-0.03, 0.03)	NA

\*for PGA relative to timolol; <sup>†</sup>for comparator relative to PGA; <sup>‡</sup>bradycardia, hypotension, dyspnea, asthma and bronchospasm, asthma or bronchospasm, arrhythmia, cardiac block, and congestive heart failure; for trials with event rate of zero, 0.5 added to each cell of 2 × 2 table for calculations; AE(s)=adverse event(s); NA=not applicable; NNH=number needed to harm; PGA=prostaglandin analogue; RD=risk difference.

Pooled results from three studies (803 patients) comparing brimonidine and latanoprost found that for ocular AEs (excluding hyperemia), there was a significant risk difference of 11% (5% to 16%) favouring latanoprost (Table 5).<sup>34,40,51</sup> The NNH was 9 (6, 20) relative to latanoprost.

There were no other statistically significant differences between PGAs and comparators for this outcome (Table 5).

**Respiratory and cardiac AEs:** Respiratory and cardiac AEs potentially related to timolol (i.e., bradycardia, hypotension, dyspnea, asthma or bronchospasm, arrhythmia, cardiac block, and congestive heart failure)<sup>57</sup> were pooled for the latanoprost versus timolol comparison. A meta-analysis of four studies of 971 patients showed that there was a significant risk difference of 2% (0% to 3%) in favour of latanoprost (Table 5).<sup>43,45,46,48</sup> The NNH was 50 (33, ∞) relative to latanoprost.

**Serious AEs:** There were no significant differences between treatment groups for this outcome (Table 5). Two serious AEs occurring in patients treated with timolol were thought to be potentially related to treatment: one case of shortness of breath<sup>39</sup> and one case of sick sinus syndrome with syncope.<sup>39</sup>

### **b) Qualitative synthesis**

The one study comparing bimatoprost with timolol (n=60) showed a statistically significant decrease in mean IOP from baseline at six months for patients treated with bimatoprost compared with those receiving timolol (10.6 mmHg versus 7.5 mmHg, p=0.003).<sup>49</sup> The study was of poor quality (Jadad score=2).

There were insufficient data to perform meta-analyses for the outcomes of visual field, optic-disc cupping, and non-responders. Of the studies that reported assessing visual-field defects<sup>36,41,42,44,46,48,55</sup> and optic cup-to-disc ratio,<sup>41,42,46</sup> three reported no clinically significant treatment differences in change from baseline for either outcome.<sup>41,42,46</sup> The other studies did not provide results for these outcomes.

Five trials reported on the number of patients who did not respond to treatment.<sup>31,36,51,53,54</sup> The frequency of non-responders was low in the treatment and control groups (Appendix 4).

The frequency of iris pigmentation in patients treated with latanoprost was 1.8% (event rate 20/1,110, pooled data from 11 trials).<sup>31,36,39,43,44,46-48,51,52,56</sup> The frequency of iris pigmentation in patients treated with high-dose travoprost was 2.5% (event rate 15/598, pooled data from three trials<sup>41,42,46</sup>). There were no incidences of iris pigmentation recorded for the comparator agents.

Four studies reported no clinically significant, treatment-related differences in heart rate after treatment with IOP-lowering agents.<sup>38,42,46,50</sup> Two studies reported significant decreases in heart rate in patients treated with timolol, but not with latanoprost<sup>39</sup> or travoprost.<sup>41</sup> Camras *et al.* reported that heart rate was significantly reduced from 75±10 beats per minute to 71±10 beats per minute after six months of treatment with timolol ( $p<0.001$ ).<sup>39</sup> In the Fellman *et al.* study, timolol-treated patients had a statistically significant decrease in heart rate compared with patients treated with travoprost ( $p=0.0001$ ).<sup>41</sup>

Three studies reported no significant treatment differences in blood pressure from baseline for patients treated with IOP lowering agents.<sup>38,46,50</sup> Fellman *et al.* reported a significant decrease in systolic blood pressure in timolol-treated patients compared with patients treated with travoprost ( $p=0.0022$ ).<sup>41</sup>

### **c) Second-line therapy**

One study examined a PGA in patients who could not use, or had failed therapy with, an IOP-lowering agent.<sup>51</sup> This study compared latanoprost with brimonidine in patients with glaucoma or ocular hypertension inadequately controlled with monotherapy or dual therapy. Of the 375 patients included in the ITT analysis, 76% of the latanoprost-treated patients and 53% of the brimonidine-treated patients obtained a mean IOP reduction of at least 20% from baseline to month 6 of treatment ( $p=0.013$ ). The mean IOP reduction difference at six months was 1.9 mm Hg in favour of latanoprost ( $p<0.001$ ).

## **6 DISCUSSION**

### **6.1 Assessment of Clinical Effectiveness**

All PGAs that were evaluated – latanoprost, travoprost, and bimatoprost – showed statistically significant improvement in IOP reduction relative to timolol, although for bimatoprost, the evidence was limited to one small, low-quality study.<sup>49</sup> Neither travoprost nor bimatoprost were compared with other IOP-reducing agents.

Latanoprost was found to be significantly superior to dorzolamide, although the pooled data was from low quality studies (Jadad score=2).<sup>52-54</sup> Latanoprost was not found to significantly reduce IOP compared with brimonidine; chi-square and  $I^2$  analyses demonstrated significant heterogeneity among the pooled studies.<sup>34,40,50</sup> Underlying this heterogeneity could be the fact that only one of the three studies used diurnal IOP.<sup>34</sup> Although one of the three studies was of low quality,<sup>50</sup> removing this study

from the pooled analysis did not alter the results. Latanoprost was found to be superior to betaxolol, although the evidence was limited to one small, low-quality study.<sup>55</sup> One large, good-quality RCT indicated that latanoprost was equally effective to combined therapy with dorzolamide+timolol,<sup>36</sup> and one small, low-quality study indicated that latanoprost was equally effective to combined therapy with carteolol+pilocarpine.<sup>56</sup>

The additional IOP reduction observed with the PGAs ranged from a mean of 0.92 mm Hg to 1.48 mm Hg more than timolol, and 2.64 mm Hg more than dorzolamide. Although this is a small change in IOP, previous studies have shown that even a 1 mm Hg change in IOP has been associated with differences in glaucomatous damage.<sup>11-14</sup> The Early Manifest Glaucoma Trial, for example, demonstrated a 10% decrease in the risk of progression with each mm Hg reduction in IOP from baseline.<sup>13</sup>

Ocular hyperemia and all other ocular AEs occurred more often among patients treated with PGAs compared with those treated with timolol, except brimonidine. Brimonidine was associated with a higher incidence of all other ocular AEs compared with latanoprost. Although ocular hyperemia associated with ocular hypotensive agents has been shown to have a significant impact on patients' satisfaction,<sup>58</sup> few patients discontinue therapy because of intolerance to ocular hyperemia.<sup>59</sup> While evidence suggests that PGA-induced iris pigmentation is a cosmetic, although probably irreversible, side effect, ongoing surveillance is required to understand the long-term consequences.

There were no significant differences in the occurrence of serious AEs and withdrawals due to AEs between the PGAs and all other comparators.

Significantly more cardiac and respiratory AEs were reported in patients receiving timolol than those receiving latanoprost. This finding may be clinically relevant given that patients at high risk for these events would have been excluded from these trials. No studies evaluating travoprost reported on cardiac and respiratory AEs.

## 6.2 Study Limitations

### 6.2.1 Outcomes

IOP fluctuates during a 24-hour period, and one measurement may not reflect the IOP at other times of the day or night.<sup>60</sup> Four trials indicated that only one IOP measurement was obtained per visit (usually in the morning),<sup>40,45,50,55</sup> whereas a fifth trial did not provide details regarding when IOP measurements were obtained.<sup>49</sup>

Although all studies compared the absolute change in IOP from baseline, a clinically significant response, defined as reaching a target IOP or achieving a  $\geq 20\%$  reduction in IOP from baseline, was only evaluated in four studies.<sup>34,40,47,51</sup>

The short-term nature of the clinical data, combined with the use of a surrogate marker, makes it difficult to extrapolate results from these studies to long-term clinical outcomes. Although IOP is a widely used surrogate marker of glaucomatous damage,<sup>19</sup> the overall goal of glaucoma therapy is to preserve vision, and none of the studies were of enough duration to detect changes in the optic nerve or the visual field. As a result, more long-term studies evaluating the impact of these agents on clinical outcomes are warranted.

### 6.2.2 Patient population

The patient population evaluated in this study was mainly Caucasian, and is not representative of the glaucoma cohort, given that the prevalence of POAG is estimated to be six times more common in blacks than whites in the same age group.<sup>61</sup> Different racial groups may have differing responses to IOP-lowering agents, so the findings of this study may be inapplicable to these subgroups.<sup>62-64</sup>

The population in this study included patients with OAG and those with isolated ocular hypertension. There were insufficient data to perform subgroup analysis on these disease cohorts, which may differ in disease progression and patients' adherence.<sup>65</sup>

Most studies evaluated a mixed population of patients who were treatment naïve, who had received previous treatment with an IOP-lowering agent, and those who had failed prior therapy. There were insufficient data to pool results from these patient subgroups. Few studies evaluated only patients who were receiving IOP-lowering agents as first-line therapy. It was inappropriate to pool data from these studies. Only one study evaluated patients who had failed prior therapy.

### 6.2.3 Interventions

Timolol was the only comparator IOP-lowering agent consistently used in the included studies. Data on the other comparators were limited. The only other agents examined were dorzolamide and brimonidine, and both of these were only evaluated in comparative studies with latanoprost. For bimatoprost, only one study was identified. Therefore, the lack of head-to-head studies comparing the IOP-reducing agents is a weakness of the literature.

## 7 ECONOMIC EVALUATION

In the systematic clinical review, latanoprost and travoprost showed significant improvement in IOP reduction compared with timolol. Latanoprost was also found to be significantly better than dorzolamide, but was not significantly superior to brimonidine. There were no significant differences in the occurrence of serious AEs, or withdrawals due to AEs, between the PGAs and other comparators. The relative efficacy and safety of these agents represent key determinants when deciding which product to select, but in the context of limited resources, it is essential to consider the economic impact of these agents. Is the improvement in efficacy associated with the PGAs worth the increased cost associated with these agents?

### 7.1 Objective

The objective of this economic evaluation was to estimate the cost-effectiveness of PGAs for ophthalmic use compared with other medications used for the treatment of glaucoma in Canada.

## 7.2 Review of Economic Studies

### 7.2.1 Literature-search strategy

Published literature was obtained by cross searching MEDLINE<sup>®</sup> (1951 to present), BIOSIS Previews<sup>®</sup> (1969 to present), ToxFile (1964 to present), and EMBASE<sup>®</sup> (1974 to present) databases, with no language restrictions, through the Dialog interface. A broad search strategy with appropriate descriptors and keywords was used with an economic filter to restrict results to relevant economic records. A parallel search on PubMed and the Cochrane database was also conducted. The literature-search strategy appears in Appendix 1B.

The original search was performed in November 2005. We established regular alerts on the MEDLINE<sup>®</sup>, BIOSIS Previews<sup>®</sup>, ToxFile, and EMBASE<sup>®</sup> databases to capture new studies until December 2006 and updated searches on the Cochrane databases regularly. A search was run on the Health Economic Evaluations Database (HEED), using a parallel-search strategy.

### 7.2.2 Results

A total of 65 articles were retrieved. Of these, five were economic evaluations comparing PGAs with other IOP-lowering medications as first-line treatment.<sup>66-70</sup>

Other studies compared PGAs with other IOP-lowering medications, but as second-line therapy<sup>71,72</sup> or in terms of cost comparison.<sup>72-80</sup>

The study by Goldberg *et al.*<sup>66</sup> was a cost-effectiveness analysis based on the results of published studies reporting the percentage of patients with elevated IOP achieving individualized target IOPs. They found that the incremental cost of achieving additional success with bimatoprost compared with timolol ranged from US\$800 to US\$1,700 (C\$960 to C\$2,040). Latanoprost was less effective and more costly than bimatoprost.

The cost-effectiveness study by Holmstrom *et al.*<sup>67</sup> was based on data from published clinical trials reporting the proportion of patients achieving specific IOP targets. In this study comparing timolol, bimatoprost, and latanoprost as initial treatment, but allowing add-on treatment, they found that the most cost-effective strategy was to use timolol as first-line therapy and to add bimatoprost if the target was not met.

Bernard *et al.*<sup>68</sup> performed a cost-effectiveness analysis based on a decision model populated with data from a retrospective chart review comparing latanoprost with beta-blockers, and allowing for non-adherence and switching to other treatments. The incremental cost per day of IOP control when latanoprost was used as a first-line treatment compared with a beta-blocker as first-line treatment was €0.82 (C\$1.23) and €0.36 (C\$0.54) over two and three years respectively.

The study by Day *et al.*<sup>69</sup> was based on data from a retrospective chart review and compared latanoprost, bimatoprost, and beta-blockers. They estimated IOP reduction, persistence to treatment, and cost associated with each treatment, but did not calculate a cost-effectiveness ratio. Their study indicated that patients on latanoprost had better persistence and lower IOP compared with bimatoprost or beta-blockers, but beta-blockers provided lower overall costs.

LePen *et al.*<sup>70</sup> performed a cost-effectiveness and a cost-utility analysis comparing travoprost, latanoprost, and timolol in advanced glaucoma, in Austria, France, Germany, the Netherlands, and the UK. They constructed a Markov model considering the probability of stable versus unstable visual acuity and two health states (stable glaucoma and visual-field defect). The time horizon of the model was five years, with 60 cycles of one month. Probabilities were taken from a study by Stewart *et al.*,<sup>81</sup> and utility values were estimated using the formula developed by Sharma *et al.*<sup>82</sup> or using utilities measured in Brown *et al.*<sup>83</sup> For the cost-effectiveness analysis, the effectiveness was defined as the time spent without disease progression. The results of the cost-effectiveness analysis indicate that travoprost dominated latanoprost in all countries except France, where they found an incremental cost-effectiveness ratio (ICER) of €825 (C\$1,237). ICERs for travoprost compared with timolol varied from €823 (C\$1,234) to €1,495 (C\$2,242), depending on the country. In the cost-utility analysis, travoprost also dominated latanoprost in all countries except France, where they found an incremental cost-utility ratio (ICUR) of €23,948 (C\$35,922). ICURs for travoprost compared with timolol varied from €23,828 (C\$35,742) to €43,296 (C\$64,944), depending on the country.

## 7.3 Methods for Economic Evaluation

### 7.3.1 Type of economic evaluation

The clinical outcomes of glaucoma treatment are usually measured in terms of reduction of IOP. In most studies comparing PGAs with other glaucoma medications, the results were estimated in terms of changes in IOP from the baseline. In only a few studies, the results were reported in terms of proportion of patients achieving a given percentage of reduction from baseline or in terms of proportion of patients achieving a given IOP threshold.

For this economic evaluation, cost-effectiveness analyses were performed using the change in IOP from baseline as the main outcome measure, because it was the only efficacy parameter available from the studies retained in the systematic clinical review.

### 7.3.2 Target population

The target population included adult patients (>18 years) with raised IOP and treated with a PGA or other glaucoma medication available in Canada.

### 7.3.3 Treatment comparators

Treatment comparators for the economic analysis were those retained in the clinical review. Low-dose travoprost (0.0015%) was not considered because this dose is not approved for use in Canada. The included treatment comparators were latanoprost, travoprost, timolol, brimonidine, and dorzolamide. In accordance with the clinical data available, cost-effectiveness analyses were performed for the following sets of comparators:

- latanoprost versus brimonidine
- latanoprost versus dorzolamide
- latanoprost versus timolol
- travoprost versus timolol.

### 7.3.4 Perspective

This economic analysis was performed from the perspective of a public third-party payer (ministry of health). Consequently, only costs assumed by a ministry of health were considered in this evaluation, and the specific perspective of the Ministry of Health of Ontario was adopted.

### 7.3.5 Effectiveness

The effectiveness of compared treatments was taken from the literature as presented in the clinical review. For each treatment comparison, effectiveness data used for the cost-effectiveness analyses were restricted to the results of studies comparing the two treatments and retained in the clinical review. Efficacy data that were excluded in the clinical review were not used for the economic evaluation.

Effectiveness data used for this economic analysis were the number of mm Hg of IOP reduction compared with the baseline and the incidence of AEs resulting in a withdrawal of the patient from the study. For patients who withdraw for AEs, it was assumed that they would not benefit from the treatment.

Ocular hyperemia and all other ocular AEs were not considered in the cost-effectiveness equation because these events typically resolve without treatment. If the events were severe enough to cause a treatment discontinuation, the probabilities of these events were factored into the analyses as withdrawals due to AEs.

Outside of ocular hyperemia and all other ocular AEs, only cardiac and respiratory AEs had a statistically higher incidence rate in the timolol group. Of these AEs, only those leading to withdrawal were taken into account in the analyses. Other possibilities regarding the inclusion of these AEs in the model could have been conceivable, but would have been hypothetical given the nature of the data available from the clinical trials.

#### **a) Time horizon**

For the base-case analysis, the time horizon was restricted to three months, in accordance with the most frequent endpoint found in the included RCTs. Sensitivity analyses were performed with six- and 12-month endpoints, when available.

#### **b) Modelling**

This economic analysis was conducted in the framework of a decision-analytic model. For each treatment, the decision tree included three endpoints:

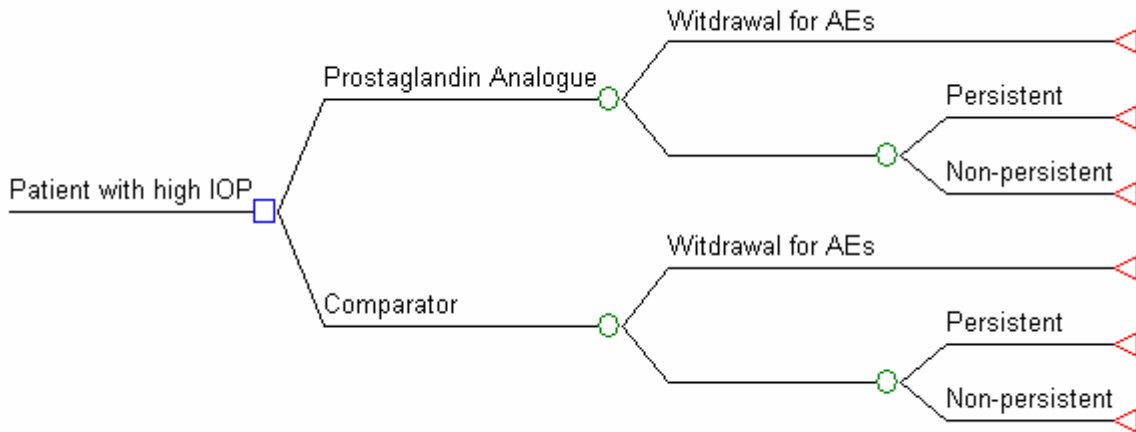
- withdrawn for AEs
- persistent to treatment
- non-persistent to treatment.
- 

For the base-case analyses, all patients were considered persistent to their treatment. The impact of non-persistence was estimated in sensitivity analyses.

#### **c) Resource use and costs**

In accordance with the adopted ministry of health's perspective, the costs considered in the evaluation are those of medications used to reduce IOP, those of visits to a physician for the initial prescribing of treatment, and those for the handling of AEs.

**Figure 14:** Decision-analysis tree



AE=adverse event; IOP=intraocular pressure.

The costs of medications were estimated using amounts reimbursed by the Ontario Drug Benefit Formulary,<sup>84</sup> to which the pharmacist's dispensing fee was added. The cost per day was calculated by estimating the number of millilitres (mL) per bottle, and adjusting for each product with the specific number of drops per mL and the usual daily frequency of administration. The number of drops per mL was taken from the study by Fiscilla *et al.*<sup>75</sup> As is usually the case in current practice, it was assumed that all patients were treated for both eyes.

For each treatment, the fee for an initial visit with an ophthalmologist was added. In practice, a consultation fee is charged when the patient is referred from another physician (general practitioners or specialists). When the patient is referred from an optometrist, an assessment fee is charged. For the base-case analysis, it was assumed that these two fees were paid using a 50-to-50 ratio. For patients experiencing AEs requiring treatment withdrawal, a repeat consultation fee was added. The amounts of ophthalmologists' fees were taken from the Ontario Schedule of Benefits for Physicians Services.<sup>85</sup> For patients who withdrew because of AEs, it was assumed that they would not benefit from the discontinued treatment but that they had to incur the cost of one bottle of medication.

#### **d) Discounting**

As the base-case analyses were limited to a three-month period and the sensitivity analyses did not exceed a 12-month time horizon, there was no need for discounting costs or outcomes.

#### **e) Sensitivity analyses**

Data comparing latanoprost with timolol at six and 12 months were available, as were data for the comparison of travoprost to timolol at six months. The cost-effectiveness analyses were performed using these longer-term data.

Contrary to what is observed in a clinical trial, in current practice, the patients' adherence to their treatment represents a significant issue. This was considered in sensitivity analyses where the impact of patients' persistence on the cost-effectiveness was estimated. Persistence refers to the long-term continuation of treatment, which is one dimension of treatment adherence. Levels of persistence associated with each glaucoma medication were obtained from the literature and used for these

analyses. For patients who were not persistent, it was assumed that they would not benefit from the treatment and that, on average, they would have consumed the medication for half of the time horizon.

A series of sensitivity analyses were performed for each cost-effectiveness analysis to ascertain the robustness of their results. The difference in IOP reduction between comparators was varied with the value of the 95% CI. The cost of medication was varied by  $\pm 25\%$ , to take potential wastage into account. This percentage was arbitrarily chosen to estimate the potential impact of wastage.

**f) Data analysis**

The decision tree was built, and the cost-effectiveness analyses and some sensitivity analyses were performed with the TreeAge Pro 2006 Suite software (release 1.2, TreeAge Software Inc, Williamson MA). The probabilistic sensitivity analyses were performed with the Crystal Ball software (release 7.2.2, Decisioneering Inc, Denver CO).

## 7.4 Results of Economic Evaluation

### 7.4.1 Data parameters

**a) Clinical outcomes**

The probability of withdrawal due to AEs and the reduction in IOP for each comparison analyzed appear in Table 6. For the primary analysis, the difference in IOP reduction was based on those assessed at three months, while the probability of withdrawal due to AEs was based on those reported in the clinical studies and are unassociated with a specific time frame. The CIs for the average reduction in IOP were estimated using the same weights associated with each study used for the estimation of the mean difference in IOP in the clinical review.

<b>Table 6: Clinical outcomes for primary analysis</b>		
<b>Comparison</b>	<b>Probability of Withdrawal due to AEs</b>	<b>Average Reduction in IOP (95% CI)</b>
latanoprost versus timolol	19/755 (2.52%)	7.36 (7.12 to 7.61)
	21/669 (3.14%)	6.11 (5.84 to 6.37)
latanoprost versus brimonidine	12/423 (2.84%)	6.15 (5.74 to 6.57)
	46/423 (10.87%)	5.12 (4.70 to 5.33)
latanoprost versus dorzolamide	1/127 (0.79%)	8.43 (7.96 to 8.89)
	1/127 (0.79%)	5.78 (5.40 to 6.17)
travoprost versus timolol	18/598 (3.01%)	8.11 (7.83 to 8.39)
	5/588 (0.85%)	6.90 (6.67 to 7.12)

AE=adverse event;IOP=intraocular pressure

**b) Costs**

The pharmacist’s dispensing fee and the ophthalmologist’s fees appear in Table 7. The cost per day was estimated for each medication. The data used for these estimations appear in Table 8.

**c) Incremental cost-effectiveness analyses – base case**

For each treatment comparison, an ICER was calculated. Details of these cost-effectiveness analyses appear in Table 9. Compared with timolol, latanoprost and travoprost had a positive ICER of C\$34.48 and C\$39.06 respectively. Compared with brimonidine, latanoprost had an ICER of C\$16.17. Latanoprost was more effective and less costly than dorzolamide.

**Table 7: Pharmacist's and ophthalmologist's fees**

Item	Cost (C\$)	Source
Pharmacist's dispensing fee	\$6.54	Ontario Drug Benefit Dispensing Fees, Ontario Ministry of Health and Long-Term Care web site (consulted January 11, 2007)
Ophthalmologist's fees: <ul style="list-style-type: none"> <li>• consultation</li> <li>• specific assessment</li> <li>• repeat consultation</li> </ul>	\$66.30 \$42.15 \$45.85	Ontario Ministry of Health and Long-Term Care Schedule of Benefits <i>Physician Services Under the Health Insurance Act, January 1, 2007</i>

**Table 8: Cost of ophthalmic preparations**

IOP-lowering Agent	Format	Cost* (C\$)	Dispensing Fee	Drops per mL <sup>†</sup>	Drops per Day × 2 Eyes	Cost per Day (C\$)
latanoprost	2.5 mL	\$26.00	\$6.54	32.0	2	0.8135
travoprost	2.5 mL	\$26.50	\$6.54	34.5	2	0.7661
timolol	10 mL	\$18.60	\$6.54	31.5	4	0.3192
dorzolamide	5 mL	\$16.50	\$6.54	25.8	6	1.0716
brimonidine	10 mL	\$23.10	\$6.54	22.2	4	0.5341

IOP=intraocular pressure; \*Ontario Drug Benefit Formulary and Comparative Drug Index 39, Sept 2005; <sup>†</sup>Fiscella *et al.*<sup>75</sup>

**Table 9: Incremental cost-effectiveness analyses**

IOP-lowering Agent	Cost (\$C)	Change in Cost (\$C)	mm Hg Reduction	Change in mm Hg Reduction	Average CER (\$C)	ICER (\$C)
timolol	84.08		5.92		14.21	
latanoprost	127.41	43.33	7.17	1.26	17.76	34.48
brimonidine	104.57		4.56		22.92	
latanoprost	127.41	22.84	5.98	1.41	21.32	16.17
dorzolamide	150.41		5.73		26.23	
latanoprost	127.43	-22.97	8.36	2.63	15.24	latanoprost dominant
timolol	83.26		6.84		12.17	
travoprost	123.28	40.02	7.87	1.02	15.67	39.06

CER=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio; IOP=intraocular pressure.

## 7.4.2 Sensitivity analyses

### a) Clinical outcomes at six and 12 months

For some treatment comparisons, reductions in IOP at six and 12 months were available (Table 10). Using these data, ICERs were also calculated (Table 11).

**Table 10: Average reduction in IOP at six and 12 month**

Comparison	Average Reduction in IOP at 6 Months (95% CI)	Average Reduction in IOP at 12 Months (95% CI)
latanoprost versus timolol	7.55 (7.32 to 7.81) 6.11 (5.84 to 6.37)	6.78 (6.36 to 7.20) 5.74 (5.33 to 6.14)
travoprost versus timolol	7.68 (7.47 to 7.89) 6.79 (6.58 to 7.01)	NA

CI=confidence level; IOP=intraocular pressure; NA=not applicable.

<b>Table 11: Incremental cost-effectiveness analyses at six and 12 months</b>						
<b>Comparison</b>	<b>Cost (\$C)</b>	<b>Change in Cost (\$C)</b>	<b>mm Hg Reduction</b>	<b>Change in mm Hg Reduction</b>	<b>Average CER (\$C)</b>	<b>ICER (\$C)</b>
timolol latanoprost (6 months)	112.52 200.37	87.85	6.31 7.38	1.07	17.84 27.15	81.80
timolol latanoprost (12 months)	169.10 345.49	176.39	5.56 6.61	1.05	30.42 52.27	168.06
timolol travoprost (6 months)	112.38 191.64	79.26	6.73 7.45	0.72	16.69 25.73	110.61

CER=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio.

**b) Persistence to treatment**

Adherence to glaucoma medications has been estimated in many studies. In 11 of these studies, treatment adherence to a PGA was compared to other glaucoma medications.<sup>65,68,69,71,86-93</sup> All these studies focused on the persistence dimension of adherence and were based on chart-review data or on data from administrative-claims databases. In all these studies, persistence to the PGA was always better than to the other comparators. In some studies, patients were considered non-persistent if they had stopped taking any glaucoma medication, whereas in other studies, patients who had switched to another medication were also considered as non-persistent. In most studies, results were estimated in terms of hazard-rate ratios, which are unsuitable for inclusion in the decision tree. The study by Dasgupta *et al.*<sup>86</sup> reported results regarding proportion of patients who were still persistent to their treatment after two years. The persistence rate, excluding those patients who switched to another medication, was 77% for latanoprost, 63% for beta-blockers, 64% for carbonic anhydrase inhibitors, and 67% for brimonidine. Cost-effectiveness analyses incorporating persistence data were performed. A persistence rate of 77% was used for latanoprost and travoprost. For timolol, the persistence rate of 63% for beta-blockers was used; for dorzolamide, the 64% rate associated with carbonic anhydrase inhibitors was used; and the 67% rate was used for brimonidine. All other parameters were the same as in the base-case analyses. The results of these cost-effectiveness analyses appear in Table 12. As was observed with the base-case analyses, latanoprost was a dominant strategy compared with dorzolamide, and all other ICERs remained positive, although inferior to those estimated in the base case.

<b>Table 12: Incremental cost-effectiveness analyses with persistence data</b>						
<b>Comparison</b>	<b>Cost (\$C)</b>	<b>Change in Cost (\$C)</b>	<b>mmHg Reduction</b>	<b>Change in mmHg Reduction</b>	<b>Average CER (\$C)</b>	<b>ICER (\$C)</b>
timolol latanoprost	78.93 119.20	40.27	3.73 5.52	1.80	21.17 21.58	22.42
brimonidine latanoprost	97.50 119.23	21.72	3.06 4.60	1.54	31.89 25.91	14.07
dorzolamide latanoprost	133.18 119.08	-14.10	3.67 6.44	2.77	36.29 18.49	latanoprost dominant
timolol travoprost	77.99 115.59	37.60	4.31 6.06	1.75	18.10 19.08	21.53
timolol latanoprost (6 months)	102.11 183.77	81.66	3.97 5.68	1.71	25.70 32.34	47.46

<b>Table 12: Incremental cost-effectiveness analyses with persistence data</b>						
<b>Comparison</b>	<b>Cost (\$C)</b>	<b>Change in Cost (\$C)</b>	<b>mmHg Reduction</b>	<b>Change in mmHg Reduction</b>	<b>Average CER (\$C)</b>	<b>ICER (\$C)</b>
timolol latanoprost (12 months)	148.23 312.21	163.98	3.50 5.09	1.59	42.32 61.35	103.36
timolol travoprost (6 months)	101.72 176.09	74.37	4.24 5.74	1.49	23.98 30.70	49.77

CER=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio.

<b>Table 13: Results of probabilistic sensitivity analyses on reduction of IOP</b>						
<b>Comparison</b>	<b>Base-case ICER (C\$)</b>	<b>Results of Probabilistic Sensitivity Analyses</b>				
		<b>Mean (±SD) (C\$)</b>	<b>Median (C\$)</b>	<b>Minimum (C\$)</b>	<b>Maximum (C\$)</b>	
timolol versus latanoprost (3 months)	34.48	35.13 (6.46)	34.00	22.33	90.05	
brimonidine versus latanoprost (3 months)	16.17	17.17 (5.91)	15.87	9.08	99.33	
dorzolamide versus latanoprost (3 months)	-8.74	-9.00 (1.34)	-8.83	-18.16	-5.86	
timolol versus travoprost (3 months)	39.06	41.02 (10.41)	39.26	22.39	116.67	
timolol versus latanoprost (6 months)	81.80	85.20 (18.40)	81.79	47.81	208.98	
timolol versus travoprost (6 months)	110.61	119.04 (35.05)	111.11	59.50	321.46	
timolol versus latanoprost (3 months) with persistence	22.42	22.52 (1.91)	22.33	18.17	31.58	
brimonidine versus latanoprost (3 months) with persistence	14.07	14.28 (2.45)	13.85	8.86	27.11	
dorzolamide versus latanoprost (3 months) with persistence	-5.09	-5.19 (0.51)	-5.15	-7.80	-3.94	
timolol versus travoprost (3 months) with persistence	21.53	21.62 (1.87)	21.44	17.24	31.19	
timolol versus latanoprost (6 months) with persistence	47.76	48.35 (4.20)	47.85	38.63	68.04	
timolol versus latanoprost (12 months) with persistence	103.36	105.75 (17.08)	103.37	179.99	108.95	
timolol versus travoprost (6 months) with persistence	49.77	50.07 (4.43)	49.76	39.08	71.66	

ICER=incremental cost-effectiveness ratio; SD=standard deviation.

### 7.4.3 Probabilistic and univariate sensitivity analyses

Probabilistic sensitivity analyses were done with the IOP reduction using the 95% CI of the mean estimate. For each analysis, 1,000 first-order Monte Carlo simulations were run, using a normal distribution (Table 13). Univariate sensitivity analyses were performed to factor in a 25% wastage rate for when patients inappropriately used their medication. Base-case results were robust to all these

sensitivity analyses. Relative to dorzolamide, latanoprost remained in all cases a dominant strategy, and a positive ICER was found for all other comparisons.

## 7.5 Discussion

This economic evaluation comprised many cost-effectiveness analyses with different comparators, different time-frames, and different settings. Some key findings emerged from these analyses.

Compared with latanoprost, dorzolamide is not a cost-effective strategy. It was dominated by latanoprost in the base-case analysis and all the sensitivity analyses.

Compared with brimonidine, latanoprost provides a higher IOP reduction with an ICER of \$16.17 (base case). Latanoprost is a more effective and more costly strategy than brimonidine, but in this case, additional IOP reduction with latanoprost is obtained at a cost lower than the average cost of IOP reduction with brimonidine (ICER of \$16.17 and average CER for brimonidine of \$22.92). Selecting brimonidine, the less costly alternative, implies a willingness to pay \$22.92 per IOP reduction. An additional reduction in IOP obtained with latanoprost costs \$16.17, which is below the willingness to pay amount for brimonidine. Therefore, based on its ICER, latanoprost could be considered as a cost-effective strategy compared to brimonidine if the relationship between reductions in IOP and improved health is shown to be linear.

Compared with timolol, latanoprost and travoprost are more effective, but also more costly. As for most cost-effectiveness analyses, it is difficult to form a judgment on such ICERs. There are no implicit values for the mm Hg reduction in IOP. In some of the cost-effectiveness analyses, the ICER is close to the average cost per mm Hg of IOP reduction associated with timolol, but in some cases, it is significantly higher. The implication of these findings for clinical practice could be to use timolol as a first-line strategy, reserving latanoprost or travoprost for those patients who do not achieve a clinical response with timolol or for whom timolol would be contraindicated. As indicated by Holmstrom *et al.*,<sup>67</sup> add-on treatments, which were not considered in the scope of this evaluation, could be potential alternative strategies for patients not achieving a clinical response with timolol.

A better treatment persistence associated with PGAs improves their cost-effectiveness, as was shown in the sensitivity analyses.

### 7.5.1 Limitations

Although many treatment comparisons were analyzed, available clinical data have limited the scope of the economic evaluation to some of the IOP-lowering agents available in Canada. The evaluation was limited to these agents being used as single-therapy, first-line agents, whereas in clinical practice, IOP-lowering agents are often used in combination or as second- or third-line agents. In limiting the economic evaluation to the studies retained in the systematic clinical review, other clinical evidences were not considered.

The clinical outcome selected for this economic evaluation was the reduction in IOP. The results of the cost-effectiveness analyses were therefore expressed in terms of cost per mm Hg reduction. It would have been more meaningful to estimate the cost-effectiveness ratios in terms of cost per patient achieving a specific IOP target. This approach was taken by Goldberg *et al.*, but was based on five studies<sup>94-98</sup> that did not meet the selection criteria of our systematic review. The same approach was

taken by Holmstrom *et al.*<sup>67</sup> using data from 20 published studies,<sup>99</sup> but only two of these 20 studies were retained in the clinical review.

One limitation of the analysis is the use of IOP reduction as the measure of effectiveness. The value of an additional mm Hg of IOP reduction is not readily recognized. With cost-utility analysis, where the result is expressed in terms of cost per quality-adjusted life-year (QALY), the interpretation is easier because the result of a given analysis can be compared with the cost per QALY ratios of other interventions. To be able to estimate the number of QALYs obtained with each IOP-lowering agent, a specific health state arising from these treatments would have to have been identified to allow for estimation of a utility value. Given that the clinical outcomes obtained from the retained studies were limited to reduction of IOP, it was impossible to derive usable utility values for performing a cost-utility analysis. Also, the relationship between IOP reduction and changes in health states utility is unclear. For IOP to be a suitable measure for economic analysis and to allow adequate interpretation of the results of the analysis, any relationship between IOP reduction and QALY gains must be linear. For example, a 30% reduction in IOP must be associated with twice as much a gain in QALYs as that associated with a 15% reduction. Because the characteristics of the relationship between changes in IOP and QALYs are unknown, there is difficulty in interpreting the results of this economic analysis.

Because glaucoma is a chronic disease, patients are expected to take IOP-lowering agents for extended periods, i.e., the duration of the patient's life. It would have been preferable to evaluate the cost-effectiveness of the IOP-lowering agent over a longer time-horizon. The results from clinical trials, however, were based on limited periods – three months in most cases and up to six to 12 months in a few studies.

Another limitation of relying on results from clinical trials is that they may reflect inadequately what is happening in real life. One concern is with patients' adherence to treatment, which would be expected to differ between a clinical trial setting and a real-life setting. Dasgupta *et al.*<sup>86</sup> and others have observed that when patients' persistence was estimated using administrative claims databases, which better reflect the real-life setting, treatment persistence was far from optimal. In the sensitivity analyses, we incorporated the impact of potential non-persistence to estimate its impact on the relative cost-effectiveness of the studied medications, and we used an estimate of persistence after two years. Although the analyses were for a shorter time-horizon, it would have been inappropriate to use persistence rates at three or six months, if they had been available (which was not the case), because glaucoma has to be treated for a long time.

Another concern with the clinical trial setting is the reported incidence of AEs. Because of the patient-selection criteria imposed by the study protocols, the incidence of AEs could be lower than their incidence in a real clinical practice. For example, patients with cardiac problems were excluded from most studies, reducing the risk of potential cardiac AEs. On the other hand, given the requirements of clinical trials, more AEs are typically reported than would normally be reported in clinical practice. The incidence of AEs could affect the relative cost-effectiveness of treatments. Because it would usually be the case in clinical practice, we considered AEs requiring withdrawals to be those for which an intervention would be necessary. In the cost-effectiveness analyses, it was assumed that these patients would require an additional visit to the ophthalmologist. Other assumptions could have been conceivable, but they would have been hypothetical given the nature of the data available from the clinical trials.

The clinical review identified one study evaluating a PGA as second-line therapy. Thus, there were insufficient data to include this treatment modality in the cost-effectiveness evaluation.

## 8 CONCLUSIONS

As first-line therapy, latanoprost, travoprost, and bimatoprost all showed statistically significant improvement in IOP reduction relative to timolol. For bimatoprost, the evidence was limited to one small, low-quality study. Compared with timolol, PGAs reduced the average IOP by 0.92 mm Hg to 1.48 mm Hg. Latanoprost was found to reduce IOP further than dorzolamide, betaxolol, or combined therapy with carteolol plus pilocarpine. One large, high-quality RCT indicated that latanoprost was similarly effective as combined therapy with dorzolamide plus timolol. Latanoprost was not found to significantly reduce IOP compared with brimonidine. Neither travoprost nor bimatoprost were compared with other IOP-reducing agents. One study, which compared latanoprost versus brimonidine, examined a PGA as second-line therapy. Although long-term studies are lacking, current studies suggest that PGAs are well tolerated.

For the treatment of glaucoma and elevated IOP, latanoprost is a dominant strategy compared with dorzolamide and is cost-effective compared with brimonidine if we assume that reductions in IOP directly correspond to health benefit and that no threshold value for IOP reduction exists. Latanoprost and travoprost are more effective than timolol, but more expensive. For those for whom timolol is not contraindicated, it would be preferable, from a cost-effectiveness standpoint, to start treatment with timolol and reserve the PGAs as an alternative treatment or as add-on therapy for patients not achieving a clinical response with timolol.

Except for trials comparing latanoprost or travoprost with timolol, there was a significant lack of trials comparing the other IOP-lowering agents. This, combined with the short-term nature of the clinical data, is a limitation.

## 9 HEALTH-SERVICES IMPACT

Vision loss is a common manifestation of aging. In 2000, senior citizens accounted for 13% of the Canadian population, but this number is expected to increase to 21% by 2026.<sup>100</sup> While most specialties are expecting to provide an increase in volume and services over the next two decades to accommodate the aging population, only cardiac surgery is expected to increase more than eye care.<sup>74</sup>

It is estimated that the number of Canadians afflicted with vision loss will increase from 67,900 blind and 319,000 visually impaired persons in 2001 to 120,000 and 600,000 respectively in 2026 – an increase of 86% in the number of Canadians with significant vision loss.<sup>101</sup> The 1994 post-census Health and Activity Limitation Survey (HALS)<sup>73</sup> predicted that by 65 years of age, one in nine Canadians will experience severe vision loss, and by 85 years of age, this figure will increase to one in four. Adding to an aging population is the push for earlier detection, which will increase the demand for IOP-lowering therapies. Because glaucoma is the second most common cause of visual disability in Canada, after age-related macular degeneration, cost-effective therapeutic options and correct policy decisions for therapeutic eye care in Canada are challenges over the next 20 years.

Maximum effectiveness in glaucoma control requires balancing safety and efficacy with tolerability and quality of life. The maximal use of drug therapy for the greatest reduction in IOP for patients with glaucoma is being used as the primary approach for disease management. The introduction of newer drug therapies may serve to reduce or delay the requirement for more invasive treatments such as surgery. A retrospective analysis of treatments for glaucoma patients in Ontario between 1992 and

2005 demonstrated a reduction in the number of trabeculectomies performed.<sup>102</sup> The long-term benefits of avoiding or delaying surgery are unclear at this time.

A potential increase in drug costs associated with newer therapies may be offset by incremental benefits, such as reductions in visits to a physician and surgical procedures. These have implications for the patient, and health care providers and payers. A value must be established to gain acceptance and utilization from providers, and unrestricted reimbursement from payers. The results of this study can be used to help outline a course of care that is clinically and fiscally prudent, leading to the intelligent use of resources.

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## **APPENDICES**

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