Ontario Health Technology Assessment Series 2011; Vol. 11, No. 2

Diurnal Tension Curves for Assessing the Development or Progression of Glaucoma

An Evidence-Based Analysis

Presented to the Ontario Health Technology Advisory Committee in November 2010

June 2011

Ontario

Medical Advisory Secretariat
Ministry of Health and Long-Term Care

Suggested Citation

This report should be cited as follows:

Medical Advisory Secretariat. Diurnal tension curves for assessing the development or progression of glaucoma: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2011 April [cited YYYY MM DD]; 11(2) 1-40. Available from: http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/diurnal_tension_curves_20110629.pdf

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to MASinfo.moh@ontario.ca.

How to Obtain Issues in the Ontario Health Technology Assessment Series

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: www.health.gov.on.ca/ohtas.

Print copies can be obtained by contacting MASinfo.moh@ontario.ca.

Conflict of Interest Statement

All analyses in the Ontario Health Technology Assessment Series are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All Medical Advisory Secretariat analyses are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

Contact Information

The Medical Advisory Secretariat
Ministry of Health and Long-Term Care
20 Dundas Street West, 10th floor
Toronto, Ontario
CANADA
M5G 2C2
Email: MASinfo.moh@ontario.ca
Telephone: 416-314-1092

ISSN 1915-7398 (Online)
ISBN 978-1-4435-6109-9 (PDF)

About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practising medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

If you are aware of any current additional evidence to inform an existing evidence-based analysis, please contact the Medical Advisory Secretariat: MASinfo.moh@ontario.ca. The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

Table of Contents

List of Abbreviations

CI	Confidence interval(s)
GAT	Goldmann applanation tonometer
IOP	Intraocular pressure
MAS	Medical Advisory Secretariat
NTG	Normal tension glaucoma
OAG	Open angle glaucoma
OHT	Ocular hypertension
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
POAG	Primary open angle glaucoma
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
VF	Visual field

Executive Summary

Clinical Need: Condition and Target Population

There are two main types of glaucoma, primary open angle (POAG) and angle closure glaucoma, of which POAG is the more common type. POAG is diagnosed by assessing degenerative changes in the optic disc and loss of visual field (VF). Risk factors for glaucoma include an increase in intraocular pressure (IOP), a family history of glaucoma, older age and being of African descent. The prevalence of POAG ranges from 1.1% to 3.0% in Western populations and from 4.2% to 8.8% in populations of African descent.

Usually the IOP associated with POAG is elevated above the normal distribution (10-20 mmHg), but when IOP is not elevated it is often referred to as normal-tension glaucoma (NTG). In population based studies, approximately one-third to half of the patients with glaucomatous VF loss have normal IOP on initial examination.

People with elevated IOP (>21 mmHg), but with no evidence of optic disc or VF damage have ocular hypertension. It has been estimated that 3 to 6 million people in the United States including 4% to 7% of those older than 40 years have elevated IOP without detectable glaucomatous damage on standard clinical tests. An Italian study found the overall prevalence of ocular hypertension, POAG, and NTG in 4,297 people over 40 years of age to be 2.1%, 1.4% and 0.6% respectively.

Diurnal Curves for Intraocular Pressure Measurement

Diurnal Curve

In normal individuals, IOP fluctuates 2 to 6 mmHg over a 24 hour period. IOP is influenced by body position with higher readings found in the supine relative to the upright position. As most individuals sleep in the supine position and are upright during the day, IOP is higher on average in people, both with and without glaucoma, in the nocturnal period. IOP is generally higher in the morning compared to the afternoon.

Multiple IOP measurements over the course of a day can be used to generate a diurnal curve and may have clinical importance in terms of diagnosis and management of patients with IOP related conditions since a solitary reading in the office may not reveal the peak IOP and fluctuation that a patient experiences. Furthermore, because of diurnal and nocturnal variation in IOP, 24-hour monitoring may reveal higher peaks and wider fluctuations than those found during office-hours and may better determine risk of glaucoma progression than single or office-hour diurnal curve measurements.

There is discrepancy in the literature regarding which parameter of IOP measurement (e.g., mean IOP or fluctuation/range of IOP) is most important as an independent risk factor for progression or development of glaucoma. The potential for increased rates or likelihood of worsening glaucoma among those with larger IOP swings within defined time periods has received increasing attention in the literature.

According to an expert consultant:

- The role of a diurnal tension curves is to assess IOP in relationship to either a risk factor for the development or progression of glaucoma or achievement of a target pressure which may direct a therapeutic change.
- Candidates for a diurnal curve are usually limited to glaucoma suspects (based on optic disc changes or less commonly visual field changes) to assess the risk for development of glaucoma or in patients

with progressive glaucoma despite normal single office IOP measurements.
- Clinically diurnal tension curves are used to determine the peak IOP and range.

Single IOP Measurements

Intraocular pressure fluctuation as a risk factor for progression of glaucoma has also been examined without the use of diurnal curves. In these cases, single IOP measurements were made every 3-6 months over several months/years. The standard deviation (SD) of the mean IOP was used as a surrogate for fluctuation since no diurnal tension curves were obtained.

Objective

1. To determine whether the use of a diurnal tension curve (multiple IOP measurements over a minimum 8 hour duration) is more effective than not using a diurnal tension curve (single IOP measurements) to assess IOP fluctuation as a risk factor for the development or progression of glaucoma.

2. To determine whether the use of a diurnal tension curve is beneficial for glaucoma suspects or patients with progressive glaucoma despite normal single office IOP measurements and leads to a more effective disease management strategy.

Research Methods

Literature Search

Search Strategy

A literature search was performed on July 22, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2006 until July 14, 2010. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with unknown eligibility were reviewed with a second clinical epidemiologist, then a group of epidemiologists until consensus was established. The quality of evidence was assessed as high, moderate, low or very low according to GRADE methodology.

Inclusion Criteria

- Open angle glaucoma (established or OHT high risk) in an adult population
- IOP measurement by Goldmann applanation tonometry (the gold standard)
- Number and timing of IOP measurements explicitly reported (e.g., 5 measurements a day for 5 visits to generate a diurnal curve or 1 measurement a day [no diurnal curve] every 3 months for 2 years)
- IOP parameters include fluctuation (range [peak minus trough] or standard deviation) and mean
- Outcome measure = progression or development of glaucoma
- Study reports results for $\geq$ 20 eyes
- Most recent publication if there are multiple publications based on the same study

Exclusion Criteria

- Angle closure glaucoma or pediatric glaucoma

- Case reports
- IOP measured by a technique other than GAT (the gold standard)
- Number and timing of IOP measurements not explicitly reported

Outcomes of Interest

- Progression or development of glaucoma

Conclusion

There is very low quality evidence (retrospective studies, patients on different treatments) for the use of a diurnal tension curve or single measurements to assess short or long-term IOP fluctuation or mean as a risk factor for the development or progression of glaucoma.

There is very low quality evidence (expert opinion) whether the use of a diurnal tension curve is beneficial for glaucoma suspects or patients with progressive glaucoma, despite normal single office IOP measurements, and leads to a more effective disease management strategy.

Background

Clinical Need and Target Population

Description of Glaucoma

Glaucoma is a progressive degenerative disease of the optic nerve which causes gradual loss of peripheral vision and in advanced states, loss of central vision. (1) There are two main types of glaucoma, primary open angle (POAG) and angle closure glaucoma, of which POAG is the more common type. POAG is diagnosed by assessing degenerative changes in the optic disc and loss of VF. (2) Risk factors for glaucoma include an increase in IOP, a family history of glaucoma, older age and being of African descent. (2)

The prevalence of POAG ranges from 1.1% to 3.0% in Western populations and from 4.2% to 8.8% in populations of African descent. (3) In Canada, glaucoma is the second leading cause of blindness in people aged 50 years and older, with POAG accounting for 90% of all cases. (4)

Usually the IOP associated with POAG is elevated above the normal distribution (10-20 mmHg), but when IOP is not elevated it is often referred to as normal-tension glaucoma (NTG). (5) An Italian study found the overall prevalence of ocular hypertension, POAG, and NTG in 4,297 people over 40 years of age to be 2.1%, 1.4% and 0.6% respectively. (6) Normal tension glaucoma is seen in older individuals, usually >55 years of age, and are typically older than patients with POAG. A relatively high prevalence of NTG is present in the Japanese population compared with other ethnic groups. (5)

People with elevated IOP (>21 mmHg), but with no evidence of optic disc or VF damage have ocular hypertension. (5) It has been estimated that 3 to 6 million people in the United States including 4% to 7% of those older than 40 years have elevated IOP without detectable glaucomatous damage on standard clinical tests (ocular hypertension). (7)

Diagnosis and Treatment of Glaucoma

Diagnosis of POAG is based on measurement of IOP (Goldmann applanation tonometer [GAT] is considered the gold standard in the literature and by experts in the field in Ontario), visualization of the optic disc (ophthalmoscopy) and evaluation of the VF (perimetry). All 3 tests are performed concurrently to make a diagnosis of glaucoma.

Lowering IOP has been shown to slow or halt disease progression in studies of those at high risk of developing glaucoma (7), those with early to moderate glaucoma (8) and those with advanced glaucoma. (9)

Intraocular Pressure Measurement

Diurnal Curve

In normal individuals, IOP fluctuates 2 to 6 mmHg over a 24 hour period. (10) IOP is influenced by body position with higher readings found in the supine relative to the upright position. (11) As most individuals sleep in the supine position and are upright during the day, IOP is higher on average in people, both with and without glaucoma, in the nocturnal period. (12) IOP is generally higher in the morning compared to the afternoon. (5)

Multiple IOP measurements over the course of a day can be used to generate a diurnal curve and may have clinical importance in terms of diagnosis and management of patients with IOP related conditions since a solitary reading in the office may not reveal the peak IOP and fluctuation that a patient experiences. (13) Furthermore, because of diurnal and nocturnal variation in IOP, 24-hour monitoring may reveal higher peaks

and wider fluctuations than those found during office-hours and may better determine risk of glaucoma progression than single or office-hour diurnal curve measurements. (14)

There is discrepancy in the literature regarding which parameter of IOP measurement (e.g., mean IOP or fluctuation of IOP) is most important as a risk factor for progression of glaucoma.(11;12) The potential for increased rates or likelihood of worsening glaucoma among those with larger IOP swings within defined time periods has received increasing attention in the literature.

Definitions of the terms used to describe fluctuation are below (10):

IOP peak	Highest IOP recorded in a stated time period
IOP trough:	Lowest IOP recorded in a stated time period
Short-term IOP fluctuation:	IOP peak minus trough measured in a stated time period, understood to be 24 hours or less (intravisit, using diurnal curve)
Long-term IOP fluctuation:	IOP peak minus IOP trough measured in a stated time period, understood to be on separate days (intervisit, using or not using diurnal curves)

The potential for increased rates or likelihood of worsening glaucoma among those with larger IOP swings within defined time periods has received increasing attention in the literature.

According to an expert consultant:

- The role of a diurnal tension curves is to assess IOP in relationship to either a risk factor for the development or progression of glaucoma or achievement of a target pressure which may direct a therapeutic change.
- Candidates for a diurnal curve are usually limited to glaucoma suspects (based on optic disc changes or less commonly visual field changes) to assess the risk for development of glaucoma or in patients with progressive glaucoma despite normal single office IOP measurements.
- Clinically diurnal tension curves are used to determine the peak IOP and range.
- A tonometry measurement takes about 15 minutes to perform per patient, and a diurnal tension curve should run for a minimum of 12 hours (personal communication, expert consultant).
- The usual course of treatment for a patient who experiences progression of their glaucoma despite normal single office IOPs (without the use of a diurnal tension curve) is:
    - If the IOP was in mid teens or higher:
        - set a lower target pressure and step up the therapy (additional medication or intervention)
    - If IOP ≤ 12 mmHg:
        - Add another medication or surgery

Single IOP Measurements

Intraocular pressure fluctuation as a risk factor for progression of glaucoma has also been examined without the use of diurnal curves. (15;16) In these cases, single IOP measurements were made every 3-6 months over several months/years. The standard deviation (SD) of the mean IOP was used as a surrogate for fluctuation since no diurnal tension curves were obtained. (15;16)

Water Drinking Test

The water drinking test (WDT) was first described in the 1960s as a diagnostic test for glaucoma. (17) After water ingestion, a 6 or 8 mm Hg rise in IOP was considered a positive test for the diagnosis of glaucoma. It was hypothesized that WDT provided a measure of the eye's aqueous humour outflow facility. However this test fell out of favour due to unacceptable false positive and false negative results. (17;18)

More recently, the WDT has been proposed as a method to predict the IOP peak of the diurnal and nocturnal

pressure curve. (19) The majority of literature describes the WDT as follows: the patient is instructed not to eat or drink for a minimum of 3 hours prior to the test and is then required to drink 1 litre of water within 5 minutes. The IOP is then measured a minimum of three times at 15 to 30 minute intervals, and IOP fluctuation is calculated as the maximum IOP minus the baseline IOP. A disadvantage to the WDT is that some patients may find it difficult to drink one litre of water in 5 minutes or less. (18)

According to an expert consultant, the WDT is not an accepted practice in North America or Europe to predict the IOP peak of the diurnal and nocturnal pressure curve.

Evidence-Based Analysis

Objective of Analysis

1. To determine whether the use of a diurnal tension curve (multiple IOP measurements over a minimum 8 hour duration) is more effective than not using a diurnal tension curve (single IOP measurements) to assess IOP fluctuation as a risk factor for the development or progression of glaucoma.

2. To determine whether the use of a diurnal tension curve is beneficial for glaucoma suspects or patients with progressive glaucoma (based on optic disc changes or less commonly visual field changes) despite normal single office IOP measurements and leads to a more effective disease management strategy.

Research Methods

Literature Search

Search Strategy

A literature search was performed on July 22, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2005 to July 14, 2010 (Appendix 1).

Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established.

Inclusion Criteria

- Open angle glaucoma (established or OHT high risk) in an adult population
- IOP measurement by Goldmann applanation tonometry (the gold standard)
- Number and timing of IOP measurements explicitly reported (e.g., 5 measurements a day for 5 visits to generate a diurnal curve or 1 measurement a day [no diurnal curve] every 3 months for 2 years)
- IOP parameters include fluctuation (range [peak minus trough] or standard deviation) and mean
- Outcome measure = progression or development of glaucoma
- Study reports results for ≥ 20 eyes
- Most recent publication if there are multiple publications based on the same study.

Exclusion Criteria

- Angle closure glaucoma or pediatric glaucoma
- Case reports
- IOP measured by a technique other than GAT (the gold standard)
- Number and timing of IOP measurements not explicitly reported

Outcomes of Interest

- Progression or development of glaucoma

Quality of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (20) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Results of Evidence-Based Analysis

The quality of the studies that were included in the evidence-based analysis is shown in Table 3. (21) The level of evidence for all studies is low (Level 4).

Table 3: Quality of Evidence of Included Studies

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	
Large RCT unpublished but reported to an international scientific meeting	1(g)	
Small RCT	2	
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3a	
Non-RCT with historical controls	3b	
Non-RCT presented at international conference	3(g)	
Surveillance (database or register)	4a	
Case series (multisite)	4b	
Case series (single site)	4c	Jonas et al. 2007 *(24 hour curve)* Bergea et al. 1999 *(diurnal curve)*
Retrospective review, modelling	4d	AGIS *(single measurement)* DIGS *(single measurement)* EMGT *(single measurement)* Choi et al. *(24 hour curve)* Bengtsson et al. *(diurnal curve)*
Case series presented at international conference	4(g)	
	Total	7

RCT refers to randomized controlled trial; g refers to grey literature.

The seven studies that met the inclusion criteria are shown in Table 4. Five of the studies were retrospective subset analyses from RCTs that were designed to compare drugs and/or surgical techniques for the treatment of ocular hypertension or established glaucoma (details of the RCTs in Appendix 2, Table 10). The other 2 studies were observational in design.

For the MAS analysis, the noncomparative studies were categorized into the following three sections:

1. Studies Using 8-Hour ("Office-Hours") Diurnal Curve for IOP Measurement
2. Studies Using >8-Hour Diurnal Curve for IOP Measurements
3. Studies Using Serial Single IOP Measurements

Table 4: Breakdown of Studies Meeting Inclusion Criteria

Studies Using 8-Hour ("Office-Hours") Diurnal Curve for IOP Measurement			
Short-Term/Intravisit (i.e., a one time diurnal curve)		**Long-Term/Intervisit (i.e., multiple diurnal curves over time)**	
Ocular Hypertension	**Established Glaucoma**	**Ocular Hypertension**	**Established Glaucoma**
None met inclusion criteria		Malmo OHS 2005 (22)	Bergea et al. 1999 (23)
Studies Using >8-Hour Diurnal Curve for IOP Measurements			
Short-Term/Intravisit (i.e., a one time 24-hour curve)		**Long-Term/Intervisit (i.e., multiple 24-hour curves over time)**	
Ocular Hypertension	**Established Glaucoma**	**Ocular Hypertension**	**Established Glaucoma**
None met inclusion criteria	Choi et al. (24)	None met inclusion criteria	Jonas et al. (25)
Studies Using Serial Single IOP Measurements (i.e., testing once a month or once a year for several months/years)			
Long-Term/Intervisit			
Ocular Hypertension	**Established Glaucoma**		
DIGS 2008 (16)	EMGT 2007 (26) AGIS 2008 (15)		

Studies Comparing a Diurnal or 24-Hour Curve to Single IOP Measurements

Since no studies were identified that met the inclusion criteria and directly compared diurnal or 24 hour IOP curves to single IOP measurements, there is no evidence to determine:

- Which measurement method (diurnal or 24-hour vs. single measurement) is more effective for assessing the risk of development or progression of glaucoma.

NonComparative Studies Examining IOP Parameters as a Risk Factor for Glaucoma Progression

The methodology used for all noncomparative studies using diurnal or 24-hour curves or serial single IOP measurements was multivariate regression or multivariate Cox hazards models in order to clarify the relationship between the measured IOP parameters and risk of glaucoma, i.e., which of the IOP parameters (range, mean IOP, peak IOP, or SD of the mean IOP) is/are an independent risk factor(s) for VF progression.

Studies Using an 8-Hour ("Office-hours) Diurnal Curve for IOP Measurement

No short-term diurnal curve (i.e., a one time diurnal curve) studies that met the inclusion criteria were identified in the literature search.

Two studies were identified that reported on the use of multiple diurnal curves to study the effect of IOP fluctuation on the development and progression of OAG. (22;23) Detailed results are shown in Table 11, Appendix 3.

Malmo Ocular Hypertension Study

Bengtsson et al. retrospectively examined 90 patients included in the Malmo Ocular Hypertension Study (OHS). The Malmo OHS was an RCT designed to compare topical timolol (an IOP lowering drug) with placebo in patients who had high untreated IOP and normal visual fields. Patients were followed every 3 months for 10 years or until they reached the outcome which was development of VF loss. All patients underwent diurnal Goldmann tonometry at 8am, 11:30am and 3:30pm.

IOP parameters that were studied were "level" and "fluctuation". "Level" was recorded 3 different ways:

- Mean of all IOP measurements
- Mean of the maximum IOP
- Mean of a randomly chosen IOP out of the 3 values that made up a diurnal curve

Similarly, "fluctuation" was recorded 3 different ways:

- Mean of the range of each diurnal tension curve
- Maximum range in all curves
- Difference between the lowest and highest IOP values measured during the study

Using univariate analyses, all parameters describing IOP level came out as highly significant risk factors but all 3 parameters describing IOP fluctuation were not significantly associated with increased risk (detailed results in Table 11, Appendix 3).

Multivariate analysis incorporating IOP levels and fluctuations found significant risk associated with mean IOP only (P=0.005) but not with fluctuation (P=0.49).

Limitations to the Malmo OHS included:

- Retrospective design
- The drug study was not powered or designed to examine IOP parameters as risk factors for development of glaucoma
- IOP was measured over 3 time points during office hours. More measurements (during and/or outside office hours) may improve estimates of fluctuation.

Bergea et al. 1999

Bergea et al. examined 76 of 82 patients with newly detected high-pressure OAG who were included in an RCT that compared primary laser trabeculoplasty with medication. (23) Bergea et al. stated "calculation of the power of the study and randomization and stratification were primarily designed for comparison of the two treatment groups, while the evaluation of the relationship between IOP regulation and the functional outcome was a secondary purpose". (23) However, an earlier paper detailing the study design did not refer to any secondary objectives of the RCT. (27)

Patients were followed up for 24 months and a daytime IOP curve, with GAT measurements taken at 8am, noon and 3pm, was obtained every second month along with an assessment of VF. Fifty-five eyes had capsular glaucoma (i.e., exfoliative glaucoma which is a secondary OAG) and 21 had POAG.

IOP parameters that were studied included:

- IOP at start defined as the mean of a daytime IOP curve recorded before any therapy was given
- Mean IOP defined as the mean value of all daytime IOP curves taken during followup
- IOP range defined as the mean of all daytime IOP ranges taken during followup
- IOP % change defined as the IOP change during followup in percent of the IOP at start
- Peak IOP defined as the highest IOP recorded during followup

Different multivariate regression models were used to examine peak IOP, IOP range and mean IOP (at start and followup). The first model involved hierarchical regression assuming linear VF progression over time. This model indicated that peak IOP and IOP range were significant risk factors (P<0.05). However, mean IOP was not selected in the same model with peak IOP or IOP range. In the second model, which involved hierarchical regression with IOP as categoric variables (assuming nonlinear VF progression over time), mean IOP showed statistically significant differences between the linear trends in the quintiles (P=0.003), however IOP range and peak were not statistically significant.

Limitations to the study by Bergea et al. included:

- The effects of followup mean IOP and followup IOP range were not simultaneously tested in the

same model. Therefore it is not possible to determine if IOP range is a risk factor for glaucoma progression independent of mean IOP.
- The study, which included a subset of patients from a RCT who were treated with primary laser trabeculoplasty or medication to lower their IOP, was not powered or designed to examine IOP parameters as risk factors for progression of glaucoma.

Studies Using a >8-Hour Diurnal Curve for IOP Measurements

Choi et al. 2007

Choi et al. performed a retrospective chart review to investigate risk factors for glaucomatous damage in 113 eyes with NTG. (24) Patients had no previous or current use of antiglaucoma medications. IOP was evaluated in-hospital over 24 hours with GAT measurements taken every 2 hours between 12pm and 10am the following day, except for the period between 12am and 6am when measurements were taken every 3 hours.

IOP parameters that were examined included:
- Fluctuation defined as the difference between the highest and lowest IOPs recorded during the 24 hour period.
- Mean IOP
- Peak IOP

Multivariable regression analysis found that mean IOP, peak IOP and fluctuation were not significantly associated with VF or optic disc deterioration (detailed results in Table 12, Appendix 3).

Limitations to the study by Choi et al. included:
- Restrospective chart review design

Jonas et al. 2007

Jonas et al. (25) measured IOP using GAT over 24 hours in 855 eyes of patients with chronic POAG or NTG. IOP was measured at 7am, noon, 5pm, 9pm and midnight. Mean(SD) followup time was 55.6± 35.1 months (median 51.5 months; range 5.4 to 124.9 months). The patients included in the study by Jonas et al. were part of a German glaucoma registry (Erlangen Glaucoma Register).

IOP parameters that were examined included:
- Fluctuation
- Mean
- Peak
- Trough

Multiple Cox proportional hazard regression was performed separately for the POAG and NTG groups (detailed results in Table 12, Appendix 3)

For POAG (681 eyes), VF progression was significantly associated with age ($P<0.001$), but not mean IOP or fluctuation. For NTG (174 eyes), VF progression was significantly associated with higher mean IOP ($P=0.04$) but not fluctuation ($P=0.05$).

Limitations to the study by Jonas et al. included:
- Study design (patients were part of a registry study).
- The patients were being treated by one or a various combination of different topical IOP lowering drugs.

Studies Using Serial Single IOP Measurements

N.B. In the following studies, standard deviation (SD) of the mean IOP was used as a surrogate for fluctuation since diurnal curves were not conducted for IOP measurement.

Advanced Glaucoma Intervention Study (AGIS)

Caprioli et al. (15) retrospectively analyzed a subset of patients (301 eyes) who were enrolled in the AGIS RCT which was designed to compare argon laser trabeculoplasty to trabeculectomy in patients on maximum therapy with advanced uncontrolled glaucoma. The purpose of the study by Caprioli et al. was to investigate the relationship of IOP fluctuation (as SD) and mean IOP to VF progression. IOP was measured 3 months after patients received the intervention and every 6 months thereafter.

IOP parameters that were studied include:

- Mean
- Fluctuation (reported as SD)

Mean(SD) followup was 7.2(2.2) years. Multivariate regression showed that IOP fluctuation was significantly associated with a higher probability of VF progression (P=0.009), but not mean IOP (P=0.09) (detailed results in Table 13, Appendix 3).

Because there was a weak but statistically significant association between fluctuation and mean IOP (r^2=0.03, P=0.01) and the treatment of IOP as a continuous variable in the multivariate regression model required the assumption of a linear trend, mean IOP was divided into terciles to evaluate the presence of interaction between mean IOP and SD (terciles do not require the assumption of a linear trend). Fluctuation was significantly associated with VF progression in the low mean IOP group (P=0.002) but not the high mean IOP group (P=0.2).

Limitations to the AGIS study included:

- Retrospective subset analysis of a RCT
- All patients received either laser trabeculoplasty or trabeculectomy (interventions used to lower IOP)
- Limited generalizability due to the patient population being restricted to moderate/advanced glaucoma that was uncontrolled despite maximal drug therapy.

Diagnostic Innovations in Glaucoma Study (DIGS)

Medeiros et al. (16) retrospectively assessed whether long-term IOP fluctuation is a risk factor for conversion from OHT to glaucoma. The study included 252 eyes of 126 patients with OHT who were untreated as part of the DIGS longitudinal study. Glaucoma conversion was defined as the development of VF loss or optic disc damage. Analyses included annual IOP measurements from baseline to time of progression or last followup visit.

IOP parameters that were studied included;

- Mean
- Fluctuation (reported as SD)

An average of 23.6 IOP measurements were available per eye included in the study. Mean followup time until conversion to glaucoma was 82.8 months. Mean followup time for nonconverters was 86.3 months.

In a multivariable Cox proportional hazards model, mean IOP was significantly predictive of conversion (P=0.005), whereas IOP fluctuation was not significantly associated with the outcome (P=0.620) (detailed results in Table 13, Appendix 3).

Limitations to the DIGS study include:

- IOP was measured annually. Optimal frequency of risk factor measurements is unknown.
- Retrospective study design.

Early Manifest Glaucoma Trial (EMGT)

Bengtsson et al. (26) retrospectively examined the role of IOP mean and fluctuation as independent risk factors for glaucoma progression. Patients with newly detected glaucoma had participated in the EMGT RCT which compared trabeculoplasty to no treatment. The retrospective study assessed the patients 3 months after their assignment to treatment (or no treatment) to the time of progression or last followup visit. Ophthalmologic exams were conducted every 3 months.

IOP parameters that were studied were:

- Mean
- Fluctuation (reported as SD)

Median followup was 8 years (range 0.1 to 11.1 years). When examining mean IOP and fluctuation in the same Cox regression time dependent model, mean IOP was a significant risk factor for progression, $P<0.0001$ (detailed results in Table 13, Appendix 3). Fluctuation was not a significant risk factor for progression ($P=0.999$). When the treatment and control groups were analyzed separately, similar results were found (Treatment group: mean IOP $P=0.041$, fluctuation $P=0.515$; Control group: mean IOP $P=0.025$, fluctuation $P=0.638$).

Limitations to the study by Bengtsson et al. include:

- Retrospective study design
- The results are applicable to patients who are newly diagnosed and have mostly mild to moderate VF loss

Studies on Diurnal Tension Curves for Glaucoma Suspects or Patients with Progressive Glaucoma Despite Normal Single Office IOP Measurements

One retrospective case series (N=93 patients) was identified that examined the usefulness of a diurnal curve to monitor IOP fluctuation in patients with progressive glaucomatous damage despite "normal" IOP. (28) IOP measurements were taken every hour from 7am to 5pm on a single day. There were 53 patients with NTG, 12 glaucoma suspects and 28 patients with POAG. One eye per patient was included in the study.

An IOP >21 mmHg was found in 3 eyes (1 in each of the 3 patient groups) and a range of IOPs >5mmHg was found in 33 eyes (19 in NTG, 6 in glaucoma suspects, 8 in POAG). The authors concluded that the IOP range may be more important than the peak because 35% of the progressing patients had a IOP range >5 mmHg compared to 3% of the patients having a peak IOP >21 mmHg. (The normal range of IOP in patients without glaucoma is approximately 5 mmHg.) The authors referred to an article by Asrani et al. (29) which reported that in glaucoma patients with office IOP in the normal range, large fluctuation in diurnal IOP is a significant risk factor for progression. The study by Asrani et al. (29) was excluded from the MAS analysis since it involved the use of a home self-tonometer designed by Asrani et al. (not GAT). Patients in the study by Asrani et al. were recruited form the private practice of 2 of the study co-authors. (29)

Results or discussion pertaining to a change in therapeutic management of the patients were not reported.

Limitations to the study by Collaer et al. (28) include:

- Retrospective case series design
- No information was reported about a change in therapeutic management.

Summary of Results

No studies were identified that met the inclusion criteria and directly compared diurnal or 24 hour IOP curves to single IOP measurements.

A summary of results for noncomparative studies is shown in Table 5. Within each section, there was heterogeneity in terms of:

- The populations studied, i.e., OHT but no VF or optic disc defects, or patients with newly diagnosed or advanced glaucoma
- Type of OAG, i.e., POAG, NTG, or exfoliative glaucoma
- Variability of the results, i.e., significance of mean IOP or IOP fluctuation as an independent risk factor for development or progression of glaucoma

One study was identified that examined the usefulness of a diurnal curve to monitor IOP fluctuation in patients with progressive glaucomatous damage despite "normal" IOP. An IOP >21 mmHg was found in 3 of 93 eyes and a range of IOPs >5mmHg was found in 33/93 eyes. The authors concluded that the IOP range may be more important than the peak because 35% of the progressing patients had a IOP range >5 mmHg compared to 3% of the patients having a peak IOP >21 mmHg. Results or discussion pertaining to a change in therapeutic management of the patients were not reported.

Table 5: Summary of Results for Noncomparative Studies in the MAS Analysis

Studies	Design	Risk Factor for Progression or Development of Glaucoma	Followup Duration	Measurement Schedule	Limitations
Studies Using an 8-Hour ("Office-hours") Diurnal Curve for IOP Measurement					
OHT (Malmo OHTS, 2005) (22)	Retrospective analysis of RCT (Level 4)	**Development** ✔ Level of IOP *(mean IOP or mean of maximum IOP or mean of randomly chosen IOP out of the 3 measurements)* ✖ Fluctuation (range)	Mean 8.5 years	Diurnal curve generated from **3** measurements every 3 months	Retrospective; not designed to examine IOP parameters. Scandinavian study - exfoliative glaucoma (a 2º OAG) more common in Scandinavian populations. Patients received treatment in RCT: timolol vs. placebo. Optimum number of measurements is unclear from literature.
Newly detected POAG (Bergea et al. 1999) (23)	Retrospective analysis of RCT (Level 4)	**Progression** ✔ Mean IOP ✖ Fluctuation (range)	24 months	Diurnal curve generated from 3 measurements every 2 months	Retrospective; not designed to examine IOP parameters. Scandinavian study - 55 eyes with exfoliative glaucoma and 21 with POAG. Patients received treatment in RCT:1º laser trabeculoplasty vs. drugs. Optimum number of measurements is unclear from literature.
Studies Using a >8-Hour Diurnal Curve for IOP Measurements					
Newly diagnosed NTG (Choi et al.,2007) (24)	Retrospective chart review (Level 4)	**Development** ✖ Mean IOP ✖ Fluctuation (range)	none	Every 2 hours between noon and 10am, except for between midnight and 6am when it was every 3 hours.	Study design – retrospective chart review. Patients had no previous or current antiglaucoma drug use. Study population was Korean – NTG more prevalent in Korean and Japanese populations.
Chronic POAG & NTG (Jonas et al., 2007) (25)	Subset of a registry study(Level 4)	**Progression** <u>Chronic POAG</u> ✖ Mean IOP ✖ Fluctuation (range) <u>Chronic NTG</u> ✔ Mean IOP ✖ Fluctuation (range)	Median 51.5 months; range 5.4 to 124.9 months	At least 2 IOP curves with measurements at 5pm, 9pm, midnight, 7am and noon.	Study design – registry subgroup. Patients treated by one or a combination of different topical IOP lowering drugs.
Studies Using Serial Single IOP Measurements					
Advanced POAG & Uncontrolled IOP (AGIS, 2008) (15)	Retrospective subset analysis of patients from RCT (Level 4)	**Progression** ✖ Mean IOP ✔ Fluctuation (SD)	Mean (SD) 7.2(2.2) years	3 months after intervention and every 6 months thereafter	SD used as a surrogate for fluctuation since no diurnal curve was conducted. Study design – retrospective subset Patients participated in RCT of surgical procedures.
Untreated OHT (DIGS, 2008) (16)	Retrospective subset analysis (Level 4)	**Development** ✔ Mean IOP' ✖ Fluctuation (SD)	Converters: Mean 82.2 months Nonconverters: Mean 86.3 months	Annually	SD used as a surrogate for fluctuation since no diurnal curve was conducted. Study design – retrospective subset Patients untreated at baseline and during followup.
Newly diagnosed POAG (EMGT,2007) (26)	Retrospective analysis of all eyes from RCT (Level 4)	**Progression** ✔ Mean IOP' ✖ Fluctuation (SD)	Median 8 years (range 0.1 to 11.1 years)	Every 3 months after time of inclusion to time of progression or last followup visit.	SD used as a surrogate for fluctuation since no diurnal curve was conducted. Study design – retrospective analysis Patients participated in RCT of surgical procedures.

IOP refers to intraocular pressure; OAG, open angle glaucoma; OHT, ocular hypertension; POAG, primary open angle glaucoma; RCT, randomized controlled trial; SD, standard deviation; VF, visual field

GRADE Quality of the Evidence

The quality of evidence for the use of diurnal curves in estimating the development or progression of glaucoma was examined using the GRADE Working Group criteria for interventions (Table 6). Overall, the GRADE quality was very low.

Table 6: Quality Assessment of Studies

No. of Studies	Design	Limitations	Indirectness	Inconsistency	Publication Bias	Quality
Studies Using an 8-Hour ("Office-hours") Diurnal Curve for IOP Measurement						
2 studies: 1. OHT (Malmo OHTS, 2005) 2. Newly detected OAG (Bergea et al. 1999)	Retrospective analysis of RCT	Retrospective Level 4; not designed to examine IOP parameters Patients received treatment in both studies: timolol vs. placebo 1º laser trabeculoplasty vs. drugs All patients underwent a diurnal curve generated from 3 measurements (every 2 or 3 months) for both studies. Optimum number of measurements is unclear from literature. **Low**	Both studies from Scandinavia. Exfoliative glaucoma (a 2º OAG) more common in Scandinavian populations. OAG study had 55 eyes with exfoliative glaucoma and 21 with POAG. **Low → Very Low**	No serious inconsistency **OHT – 1 study** Level of IOP (mean IOP, mean of maximum IOP, or mean of randomly chosen IOP out of the 3 measurements) a significant risk factor for VF progression, not fluctuation (range). **OAG – 1 study** Mean IOP but not fluctuation (range) a significant risk factor for VF progression (regression using quintiles)	Unlikely Possible, but not considered sufficient to downgrade quality of evidence.	**Very Low**
Studies Using a >8-Hour Diurnal Curve for IOP Measurements						
2 studies: 1. newly diagnosed NTG (Choi et al.,2007) 2. Chronic POAG & NTG combination (Jonas et al., 2007)	Retrospective chart review Subset of a registry study	Study designs – registry subgroup and retrospective chart review (Level 4). Patients treated by one or a combination of different topical IOP lowering drugs in chronic POAG/NTG study. Newly diagnosed NTG study had no previous or current antiglaucoma drug use. **Low**	No serious uncertainties	**Newly Diagnosed NTG** Both mean IOP and fluctuation (range) not significantly associated with VF progression or optic disc worsening. **Chronic POAG/NTG Combination** **Chronic POAG** Neither mean IOP nor fluctuation (range) significantly associated with VF progression. **Chronic NTG** Mean IOP but not fluctuation (range) significantly associated with VF progression. **Low → Very Low**	Unlikely Possible, but not considered sufficient to downgrade quality of evidence.	**Very Low**

No. of Studies	Design	Limitations	Indirectness	Inconsistency	Publication Bias	Quality
Studies Using Serial Single IOP Measurements						
3 studies: 1. Advanced POAG & Uncontrolled IOP (AGIS, 2008) 2. Untreated OHT (DIGS, 2008) 3. Newly diagnosed POAG (EMGT,2007)	Retrospective subset analysis of patients from RCT for AGIS and DIGS studies. Retrospective analysis of all eyes from EMGT.	Study designs – retrospective (Level 4) Patients in AGIS and EMGT participated in studies of surgical procedures. Patients in DIGS untreated at baseline and during followup. **Low**	No serious uncertainties	**<u>Advanced POAG & Uncontrolled IOP (AGIS)</u>** Fluctuation (SD) but not mean IOP significantly associated with VF progression. **<u>Untreated OHT (DIGS)</u>** Mean IOP but not fluctuation (SD) significantly associated with conversion to POAG **<u>Newly Diagnosed POAG (EMGT)</u>** Mean IOP but not fluctuation (SD) significantly associated with VF progression. **Low → Very Low**	Unlikely Possible, but not considered sufficient to downgrade quality of evidence.	**Very Low**
Studies on Diurnal Tension Curves for Glaucoma Suspects or Patients with Progressive Glaucoma Despite Normal Single Office IOP Measurements						
1 study	Retrospective case series	Study design (Level 4) Patients treated with drugs on day of measurements. Results or discussion pertaining to a change in therapeutic management of the patients were not reported **Low**	No serious uncertainties	1 study **Low → Very Low**	Unlikely Possible, but not considered sufficient to downgrade quality of evidence.	**Very Low**

IOP refers to intraocular pressure; OAG, open angle glaucoma; OHT, ocular hypertension; POAG, primary open angle glaucoma; RCT, randomized controlled trial; SD, standard deviation; VF, visual field

Conclusion

No studies were identified that directly compared diurnal curves with single IOP measurements to assess IOP fluctuation as a risk factor for progression or development of glaucoma.

There is very low quality evidence (retrospective studies, patients on different treatments) for the use of a diurnal tension curve or single measurements to assess short or long-term IOP fluctuation or mean as a risk factor for the development or progression of glaucoma.

There is very low quality evidence (expert opinion) whether the use of a diurnal tension curve is beneficial for glaucoma suspects or patients with progressive glaucoma, despite normal single office IOP measurements, and leads to a more effective disease management strategy.

Status in Ontario

Schedule of Benefits

- IOP measurement is currently billed under G435A-Tonometry ($5.10). This is limited to a single IOP measurement per day.
- There is a code (G-426) for glaucoma provocative tests, including water drinking tests ($9.70). According to an expert consultant, the water drinking test is not an accepted practice in North America or Europe to predict the IOP peak during an IOP measurement curve.
- A new fee code proposal was submitted to Provider Services for multiple IOP measurements per day (starting no later than 8am and running for a minimum of 12 hours) (Proposed fee $75).
- A fee code for a diurnal curve measurement exists in Quebec (0819 - $75), Saskatchewan (332S - $64.80) and British Columbia (22023 - $33.91 or 2018/2019 - $46.38).
- The ophthalmology section of the Alberta Medical Association are preparing a submission for a diurnal curve fee code.

Target Population

- According to a glaucoma specialist in Ontario:
    a) Diurnal tension curves would be limited to a glaucoma suspect to assess the risk for the development of glaucoma and in a progressive glaucoma patient despite normal single office IOP measurements.
    b) The estimated number of patients who would be candidates for a minimum 12-hour diurnal curve at a glaucoma specialty centre would be at most ~ 16 per month.
    c) A general ophthalmologist may perform ~ 5 diurnal tension curves per year.
- The estimated number of candidates at other glaucoma specialty centres in the province is unknown.
- The feasibility or acceptability of a minimum 12-hour diurnal curve to patients with glaucoma is not reported or discussed in the literature.
- According to an expert consultant, the usual course of treatment for a patient who experiences progression of their glaucoma despite normal single office IOPs (without the use of a diurnal tension curve) is to treat presumptively with another treatment or surgery. Furthermore, if the IOP is in mid-teens or higher, set a lower target therapy

Prevalence of Glaucoma in the Literature

- The prevalence of POAG ranges from 1.1% to 3.0% in Western populations and from 4.2% to 8.8% in populations of African descent. (3)
- An Italian study found the overall prevalence of ocular hypertension, POAG, and NTG to be 2.1%, 1.4% and 0.6% respectively. (6)

Guidelines

Canadian Ophthalmological Society Evidence-Based Clinical Practice Guidelines for the Management of Glaucoma in the Adult Eye

The following criteria were used by the Canadian Ophthalmological Society for assigning levels of evidence to the published studies. (5)

Studies of Prognosis
Level 1
(i) Inception cohort of patients with the condition of interest, but free of the outcome of interest
(ii) Reproducible inclusion/exclusion criteria
(iii) Follow-up of at least 80% of subjects
(iv) Statistical adjustment for extraneous prognostic factors (confounders)
(v) Reproducible description of outcome measures
Level 2
Meets criterion (i) above, plus 3 of the other 4 criteria
Level 3
Meets criterion (i) above, plus 2 of the other criteria
Level 4
Meets criterion (i) above, plus 1 of the other criteria

Progression

Assessing disease severity is important to determine which tests might be most useful for each individual. Patients with glaucoma should be monitored with both structural and functional tests, as progression can be detected by either method alone **[Level 2]**.

It is recommended that a correlation between structural and functional changes be sought in suspected progression, even though it is more common for a change to be detected with one or the other independently **[Level 1]**.

The clinician's response to a new progressive event should be to confirm the change with a repeat test. VFs may need to be performed more frequently during periods of apparent progression. Ultimately, it is most important to calculate the rate of progression over time **[Consensus]**.

In order to establish a good baseline and to detect possible rapid progression, several visual fields should be performed at regular intervals in the first 2 years **[Consensus]**.

Stage each eye of the patient as normal, suspect, early, moderate or advanced glaucoma based on optic nerve and (or) VF exam **[Consensus]**.

Set upper limit of initial target IOP range for each eye at first visit and then re-evaluate at each visit based on stability/change in structure and function of the optic nerve (i.e., optic nerve head exam with or without additional imaging information as well as VF data) **[Consensus]**.

Monitoring of patients should include documentation of the IOP (method and time measured), patient confirmation of and frequency of medications used, as well as the time of their last medication administration **[Consensus]**.

Economic Analysis

DISCLAIMER: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

Nonhospital: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

Downstream costs: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

Study Question

The objective of this economic analysis was to report costs associated with diurnal IOP measurements for glaucoma and intraocular hypertension, specifically for cases of POAG and NTG in Ontario.

Economic Literature Review

A literature search was performed on July 29th, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, and EconLit for studies published from 1950 (MEDLINE) to week 03, 2010 (EMBASE, MEDLINE). Included studies were those with full economic evaluations describing both costs and consequences of IOP measurements (serial and diurnal) for glaucoma and intraocular hypertension; with the same set of search keywords used as for the effectiveness systematic review.

According to the systematic review performed, there were no health economic evaluations found comparing the relative cost-effectiveness of IOP measurements for the populations of interest (i.e. POAG and NTG glaucoma patients, and those at risk of developing POAG or NTG).

Ontario-Based Cost Impact Analysis

The annual volume of POAG and NTG cases in Ontario was estimated from the prevalence of glaucoma as reported by Statistics Canada in 2008/09 and the relative proportions of POAG and NTG cases reported by Bonomi et al. 1998.(6;30) The estimated number of glaucoma patients in Ontario in fiscal 2008/09 is summarized in Table 7 by age group, where approximately 5% of the total cases were expected to benefit from diurnal IOP measurements as elicited from expert consultation. Using the

number of cases reported in Table 7, the expected number of patients to benefit from diurnal IOP measurements in Ontario in 2008/09 was approximately 6,708 POAG cases, with a 95% confidence interval of 5,314 to 8,103 cases; and 2,875 NTG cases, with a 95% confidence interval of 2,277 to 3,473 cases.

Table 7: Prevalence of Glaucoma in Ontario 2008/09

Age	Observed			Expected to benefit ~ 5%		
	N patients	Low 95% CI	High 95% CI	N patients	Low 95% CI	High 95% CI
45 to 64 years	45,335	30,612	60,058	2,267	1,531	3,003
65 to 84 years	115,166	97,346	132,987	5,758	4,867	6,649
85 years and over	31,164	23,862	38,465	1,558	1,193	1,923
Total	191,665	151,820	231,510	9,583	7,591	11,576

Source: CANSIM Canadian Community Health Survey (CCHS) 2008/09(30)

The incremental cost associated with providing diurnal IOP measurements for POAG and NTG patients was calculated from two strategies: A) annual diurnal IOP curve measurements taken for a minimum of 12 hours, starting no later than 08:00, or 8 or more measurements over 12-24 hours; and B) current care, which consisted of serial IOP measurements performed 3 times annually. These strategies were taken from expert consultation and were consistent with the treatment schedules found in the literature of the systematic effectiveness review. For both strategies (A and B), a physician assessment fee code of A234 ("Consultations and Visits - Ophthalmology - Partial assessment") was used for each measurement, as listed in the Ontario Schedule of Benefits.(31) A procedure fee code of G435 ("Diagnostic and Therapeutic Procedure - Ophthalmology – Tonometry") was used for the current care strategy (B), whereas an new, currently unlisted fee code was used for the prospective diurnal IOP measurements; the latter fee code was obtained from consultations with the MOHLTC. The total cost for each strategy is summarized in Table 8.

Table 8: Physician fee codes associated with diurnal and serial IOP curve measurement strategies

Strategy A - Diurnal IOP curve measurement				
OHIP code	**Description**	**Professional Fee**	**Frequency (per year)**	**Cost**
A234	Consultations and Visits - Ophthalmology - Partial assessment	$25.10	1	$25.10
NEW	Diurnal IOP measurement for a minimum of 12 hours, starting no later than 08:00; or 8 or more measurements over 12-24 hours	$75.00	1	$75.00
Total Cost		$100.10	1	$100.10
Strategy B - Serial single IOP measurement (current care)				
OHIP code	**Description**	**Professional Fee**	**Frequency (per year)**	**Cost**
A234	Consultations and Visits - Ophthalmology - Partial assessment	$25.10	3	$75.30
G435	Diagnostic and Therapeutic Procedure - Ophthalmology - Tonometry	$5.10	3	$15.30
Total Cost		$30.20	3	$90.60

Source: Ontario Health Insurance (OHIP) Schedule of Benefits and Fees (31)

Based on prevalence data from 2008/09, it was estimated that performing diurnal IOP measurements (strategy A) on POAG and NTG patients in Ontario would be more costly than serial IOP measurements (strategy B) by approximately $91K annually (95% confidence interval $72K to $110K), as shown in Table 9. Specifically, for POAG patients the incremental cost would be about $64K annually, and for NTG patients the incremental cost would be about $27K annually.

Table 9: Annual budget impact of diurnal IOP measurements versus current care (strategy A vs. B)

Description	POAG	NTG	Total	Total Low 95% CI	Total High 95% CI
Strategy A - Diurnal IOP curve measurement	$671.5K	$287.8K	$959.3K	$759.9K	$1158.7K
Strategy B - Serial single IOP measurement (current care)	$607.8K	$260.5K	$868.2K	$687.7K	$1048.7K
Incremental Cost Difference (A - B)	$63.7K	$27.3K	$91.0K	$72.1K	$110.0K

Appendices

Appendix 1: Literature Search Strategies

Search date: July 22, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, CINAHL, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1996 to July Week 2 2010>
Search Strategy:
---
1 exp Ocular Hypertension/ (15857)
2 (glaucoma* or (eye adj2 hypertension) or ocular hypertension or intraocular hypertension or intra-ocular hypertension).ti,ab. (17140)
3 1 or 2 (19976)
4 exp Tonometry, Ocular/ (1987)
5 (tonometer or tonometry or oculoplethysmography).ti,ab. (2945)
6 (Tono-Pen or Pneumatonometer or GAT).ti,ab. (1085)
7 exp circadian rhythm/ (24448)
8 (diurnal adj2 curve).ti,ab. (92)
9 (intravisit or intervisit or intra-visit or inter-visit).ti,ab. (51)
10 ((intra-ocular pressure or intraocular pressure or ocular pressure or IOP) adj2 (nocturnal or diurnal or measurement*or fluctuat* or varia* or mean or peak or range or sd or standard deviation or parameter*)).ti,ab. (2264)
11 or/4-10 (30544)
12 3 and 11 (3066)
13 limit 12 to (english language and humans and yr="2005 -Current") (1256)
14 limit 13 to (case reports or comment or editorial or letter) (105)
15 13 not 14 (1151)

Database: EMBASE <1980 to 2010 Week 28>
Search Strategy:
---
1 exp glaucoma/ (33236)
2 (glaucoma* or (eye adj2 hypertension) or ocular hypertension or intraocular hypertension or intra-ocular hypertension).ti,ab. (26154)
3 1 or 2 (36647)
4 exp oculoplethysmography/ (688)
5 exp tonometer/ or exp pressure measurement/ (54057)
6 (Tono-Pen or Pneumatonometer).ti,ab. (230)
7 exp circadian rhythm/ (35110)
8 (diurnal adj2 curve).ti,ab. (117)
9 (intravisit or intervisit or intra-visit or inter-visit).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (54)
10 ((intra-ocular pressure or intraocular pressure or ocular pressure or IOP) adj2 (nocturnal or diurnal or measurement*or fluctuat* or varia* or mean or peak or range or sd or standard deviation or parameter*)).ti,ab. (2770)
11 or/4-10 (89762)
12 3 and 11 (3703)
13 limit 12 to (human and english language and yr="2005 -Current") (1227)
14 limit 13 to (editorial or letter or note) (91)
15 case report/ (1113858)
16 13 not (14 or 15) (1088)

Appendix 2: Design of Studies Included in the Evidence-Based Analysis

Table 10: Design of Studies Included in the Evidence-Based Analysis

Design	Comparators in Parent RCT if Subset Analysis
Retrospective subset analysis of RCT (Malmo Ocular Hypertension Study [MOHS]) (22) 2005 Sweden	Timolol vs. placebo
Retrospective analysis of RCT (Bergea et al.) (23) 1999 Sweden	Surgery vs. pilocarpine
Observational (unclear if prospective or retrospective) (Jonas et al.) (25) 2007 Germany	NA
Retrospective chart review (Choi et al.) (24) 2007 Korea	NA
Retrospective subset analysis of an RCT (Advanced Glaucoma Intervention Study [AGIS]) (15) 2008 US	2 sequences of glaucoma surgery
Retrospective subset analysis of an observational study (Diagnostic Innovations in Glaucoma Study [DIGS]) (16) 2008 US	Diagnostic and monitoring techniques
Retrospective subset analysis of an RCT (Early Manifest Glaucoma Trial [EMGT]) (26) 2007 Sweden/US	Surgery plus betaxolol vs. no surgery/betaxolol

RCT refers to randomized controlled trial

Appendix 3: Results of Studies Included in the Evidence-Based Analysis

Table 11: Summary of Studies Using an 8-Hour ("Office-Hour") Diurnal Curve for IOP Measurement

Study, Year	Design	Population	Objective	IOP Parameters	Statistical Method	Timing of IOP Measurement	Results	Comment
Malmo OHTS, 2005 (22)	Retrospective analysis of RCT N=90 eyes	Ocular hypertension Participated in RCT for topical timolol vs. placebo	To study the effect of IOP fluctuations on the incidence of glaucomatous VF loss in patients with ocular hypertension.	Mean Range Peak	Cox multivariable analysis	Diurnal curve 8am, 11:30am and 3:30 pm obtained every 3 months.	Mean followup 8.5 years **Cox Multivariable Analysis:** Mean IOP of all measurements Risk 1.21 (1.09 to 1.38), P=0.005 Mean of daily range Risk 1.13 (0.80 to 1.60), P=0.49 **Cox Univariate Analysis (Different parameters for IOP level)** Mean of all IOP Risk 1.23 (1.08 to 1.39), P=0.0013 Mean of maximum IOP Risk 1.20 (1.07 to 1.36), P=0.0027 Mean of random IOP 1.22 (1.08 to 1.38), P=0.0017 **Cox Univariate Analyses (Different parameters for IOP variability)** Mean of daily range Risk (0.98 to 1.93), P=0.06 Maximum of all daily ranges Risk 1.04 (0.91 to 1.19), P=0.58 Range between minimum and maxi um IOP of all measurements Risk 1.02 (0.95 to 1.09), P=0.56	IOP measured during office hours. No published studies establish the optimum number of IOP measurements during office hours.

Study, Year	Design	Population	Objective	IOP Parameters	Statistical Method	Timing of IOP Measurement	Results	Comment
Bergea et al. 1999 (23)	Prospective? Secondary objective of a RCT. N=76 eyes 55 Exfoliative 21 Simple	Newly detected high pressure OAG. Participated in RCT comparing argon laser trabeculoplasty compared with pilocarpine.	To investigate the correlation of different parameters of IOP to visual field decay in open angle glaucoma.	Mean Range Peak	Hierarchical linear regression analysis and principal component analysis	Daytime diurnal curve (8am, 12pm and 3pm) obtained every second month	Followup period=24 months. 2 models were used. <u>Hierarchical Linear Regression Model (VF progression linear over time)</u> IOP peak or range P<0.05 <u>Hierarchical Regression with Partition into Quintiles (nonlinear VF progressions over time)</u> Mean IOP P<0.003	55% of patients had exfoliative glaucoma. Prior to risk analysis, the authors carried out principal-component analysis to avoid multicollinearity (avoid highly intercorrelated explanatory variables in the same model). This produced a number of multivariate regression models including different IOP parameters. Two of them included IOP range similar to the Malmo OHTS study. In 1 of the 2 regression models IOP range was combined with untreated baseline IOP and in the other with IOP % change (i.e., treatment effect calculated as the difference between untreated baseline IOP and mean of treated followup IOP divided by IOP at start). Therefore, the effects of followup IOP level and followup IOP fluctuation were not simultaneously tested in the same model. No published studies establish the optimum number of IOP measurements during office hours.

IOP refers to intraocular pressure; NTG, normal tension glaucoma; OAG, open angle glaucoma; RCT, randomized controlled trial; SD, standard deviation; VF, visual field

Table 12: Summary of Studies Using a 24-Hour Curve for IOP Measurement

Study, Year	Design	Population	Objective	IOP Parameters	Statistical Method	Timing of IOP Measurement	Results	Comment
Jonas et al. 2007 (25)	Unclear if retrospective or prospective observational analysis. 855 eyes	Chronic OAG NTG=174 eyes High pressure OAG=681 eyes	To evaluate whether the amplitude of day and night IOP profiles influence the rate of progression of chronic OAG.	Mean Fluctuation Peak	Multiple Cox proportional hazard regression	At least 2 IOP curves with measurements at 5pm, 9pm, midnight, 7am and noon.	Median followup=51.5 months; range 5.4 to 124.9 months 163/855 eyes showed progression. <u>High Pressure OAG</u> Progression significantly associated with age (P<0.001), not mean IOP or amplitude. <u>NTG</u> Progression significantly associated with higher mean IOP(P=0.04), but not amplitude (P=0.05).	All patients were on routine ophthalmic care including topical application of antiglaucoma drugs.
Choi et al. 2007 (24)	Retrospective chart review 113 eyes	NTG No previous or current use of antiglaucoma drugs	To investigate systemic and ocular hemodynamic risk factors for glaucomatous damage in eyes with NTG.	Mean Fluctuation Peak	Multivariate regression	Every 2 hours between 12pm and 10am, except for the period between 12am and 6am when measurements were every 3 hours.	Mean IOP, peak IOP and fluctuation were not significantly associated with VF or optic disc worsening (p>0.05).	Patients on hypertension or other hemodynamically active drugs not excluded.

IOP refers to intraocular pressure; NTG, normal tension glaucoma; OAG, open angle glaucoma; RCT, randomized controlled trial; SD, standard deviation; VF, visual field

Table 13: Summary of Studies Using Single Measurements (No Diurnal or 24-Hour Curve) for IOP Measurement

Study, Year	Design	Population	Objective	IOP Parameters	Statistical Method	Timing of IOP Measurement	Results	Comment
AGIS, 2008 (15)	Retrospective subset analysis N=301 eyes (only eyes that underwent 1 surgical intervention included in analysis)	Advanced glaucoma Uncontrolled IOP at maximum therapy Participated in RCT and underwent argon laser trabeculoplasty or trabeculectomy.	Clarify relationship between IOP parameters and VF progression.	Fluctuation(SD) Mean	Multivariate logistic regression	3 months after intervention and every 6 months thereafter	Mean(SD) followup 7.2(2.2) years IOP fluctuation OR (95%CI) 1.39 (1.09-1.79); P=0.009 Mean IOP 1.12 (0.98-1.27); P=0.09 (Multivariate logistic regression requires assumption of linear trend). Because of a weak correlation between mean IOP and SD, (0.03, p=0.006), mean IOP divided into terciles to evaluate presence of interaction between mean and SD Fluctuation significantly associated with VF progression in the low mean IOP group (P=0.002) but not the high mean IOP group (P=0.2)	SD used as surrogate for fluctuation since no diurnal tension curves were obtained. Only IOPs after surgery and up to time of first evidence of VF worsening (if any) used in calculation of mean/SD of IOP.
DIGS, 2008 (16)	Retrospective subset analysis N=252 eyes (selected cohort from DIGS)	Untreated ocular hypertension Untreated patients who participated in a longitudinal study designed to evaluate optic nerve structure and visual function in early or suspected glaucoma.	Investigate whether long term IOP fluctuation is a risk factor for conversion from ocular hypertension to glaucoma.	Fluctuation(SD) Mean	Multivariable Cox proportional hazards model	Annual followup visit.	Mean followup until conversion to glaucoma 82.8 months (nonconverters 86.3 months). Mean IOP predictive of conversion (adjusted HR 1.20 per 1 mmHg higher; 95%CI 1.06-1.36; P=0.005). IOP fluctuation not significantly associated with conversion (adjusted HR 1.08 per mmHg higher; 95% CI 0.79-1.48); P=0.620).	None of the patients received ocular hypotensive drugs at baseline and were left untreated during followup.
EMGT, 2007 (26)	Retrospective analysis N=255 eyes (all patients in trial whether treated or not)	Untreated newly detected glaucoma Participated in RCT comparing trabeculoplasty compared to no treatment.	Examine role of IOP fluctuation as an independent risk factor for glaucoma progression.	Fluctuation (SD) Mean	Cox regression with time dependent variables	3 months after assignment to treatment to time of progression or last followup visit.	Median followup 8 years (range 0.1-11.1 years) <u>Treatment and Control Groups Combined (mmHg) Hazard ratio (95%CI)</u> Mean IOP 1.11 (1.06-1.17), P<0.0001 IOP Fluctuation 1.00 (0.81-1.24), P=0.999 <u>Treatment Group</u> Mean IOP 1.12 (1.01-1.24), P=0.041 Fluctuation 1.16 (0.75-1.80), P=0.515 <u>Control Group</u> Mean IOP 1.10 (1.01-1.19), P=0.025 Fluctuation 0.94 (0.73-1.21), P=0.638	-

HR refers to hazard ratio; IOP, intraocular pressure; NTG, normal tension glaucoma; OAG, open angle glaucoma; OR, odds ratio; RCT, randomized controlled trial; SD, standard deviation; VF, visual field

References

(1) Tielsch JM. The epidemiology and control of open angle glaucoma: a population-based perspective. Annu Rev Public Health 1996; 17:121-36.

(2) United States Preventative Task Force. Screening for glaucoma: recommendation statement. Ann Fam Med 2005; 3(2):171-2.

(3) Mukesh BN, McCarty CA, Rait JL, Taylor HR. Five year incidence of open angle glaucoma: the visual impairment project. Ophthalmology 2002; 109(6):1047-51.

(4) Elolia R, Stokes J. Monograph series on aging-related diseases: XI Glaucoma. Chronic Dis Can 2000; 19(4):1-24.

(5) Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline Expert Committee. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of glaucoma in the adult eye. Can J Ophthalmol 2009; 44(Suppl 1):S7-S54.

(6) Bonomi L, Marchini G, Marraffa M, Bernadi P, De Franco I, Perfetti S et al. Prevalence of glaucoma and intraocular pressure distribution in a defined population: the Egna-Neumarkt Study. Ophthalmology 1998; 105(2):209-15.

(7) Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002; 120(6):701-13.

(8) Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002; 120(10):1268-79.

(9) AGIS (Advanced Glaucoma Intervention Study) Investigators. The Advanced Glaucoma Intervention Study (AGIS): the relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000; 130(4):429-40.

(10) Sultan MB, Mansberger SL, Lee PP. Understanding the importance of IOP variables in glaucoma: a systematic review. Surv Ophthalmol 2009; 54(6):643-62.

(11) Singh K, Shrivastava A. Intraocular pressure fluctuations: How much do they matter? Curr Opin Ophthalmol 2009; 20(2):84-7.

(12) Wilson MR, Singh K. Intraocular pressure: does it measure up? Open Ophthalmol J 2009; 3:32-7.

(13) David R, Zangwill L, Briscoe D, Dagan M, Yagev R, Yasur Y. Dirunal intraocular pressure variations: an analysis of 690 diurnal curves. Br J Ophthalmol 1992; 76(5):280-3.

(14) Barkana Y, Anis S, Liebmann J, Tello C, Ritch R. Clinical utility of intraocular pressure monitoring outside of normal office hours in patients with glaucoma. Arch Ophthalmol 2006; 124(6):793-7.

(15) Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. Ophthalmology 2008; 115(7):1123-9.

(16) Medeiros FA, Weinreb RN, Zangwill LM, Alencar LM, Sample PA, Vasile C et al. Long-term intraocular pressure fluctuations and risk of conversion from ocular hypertension to glaucoma. Ophthalmology 2008; 115(6):934-40.

(17) Malerbi FK, Hatanaka M, Vessani RM, Susanna J. Intraocular pressure variability in patients who reached target intraocular pressure. Br J Ophthalmol 2005; 89(5):540-2.

(18) Kumar RS, De Guzman MHP, Ong PY, Goldberg I. Does peak intraocular pressure measured by water drinking test reflect peak circadian levels? A pilot study. Clin Experiment Ophthalmol 2008; 36(4):312-5.

(19) Susanna R, Jr., Vessani RM, Sakata L, Zacarias LC, Hatanaka M. The relation between intraocular pressure peak in the water drinking test and visual field progression in glaucoma. Br J Ophthalmol 2005; 89(10):1298-301.

(20) GRADE Working Group. Grading quality of evidence and strength of recommendations. Br Med J 2004; 328(7454):1490-4.

(21) Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: Swedish Council on Technology Assessment in Health Care. 1996 81 p. SBU Report No. 119E.

(22) Bengtsson B, Heijl A. Diurnal IOP fluctuation: Not an independent risk factor for glaucomatous visual field loss in high-risk ocular hypertension. Graefes Arch Clin Exp Ophthalmol 2005; 243(6):513-8.

(23) Bergea B, Bodin L, Svedbergh B. Impact of intraocular pressure regulation on visual fields in open angle glaucoma. Ophthalmology 1999; 106(5):997-1005.

(24) Choi J, Kyung HK, Jeong J, Cho H-S, Chang HL, Kook MS. Circadian fluctuation of mean ocular perfusion pressure is a consistent risk factor for normal-tension glaucoma. Invest Ophthalmol Vis Sci 2007; 48(1):104-11.

(25) Jonas JB, Budde WM, Stroux A, Oberacher-Velten IM, Junemann A. Diurnal intraocular pressure profiles and progression of chronic open-angle glaucoma. Eye 2007; 21(7):948-51.

(26) Bengtsson B, Leske MC, Hyman L, Heijl A, Early Manifest Glaucoma Trial Group. Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial. Ophthalmology 2007; 114(2):205-9.

(27) Bergea B, Bodin L, Svedbergh B. Primary argon laser trabeculoplasty vs pilocarpine II. Long-term effects on intraocular pressure and facility of outflow. Acta Ophthalmol (Copenh) 1994; 72(2):145-54.

(28) Collaer N, Zeyen T, Caprioli J. Sequential office pressure measurements in the management of glaucoma. J Glaucoma 2005; 14(3):196-200.

(29) Asrani S. Diurnal intraocular pressure fluctuations. Asian J Ophthalmol 2005; 7(2):45.

(30) Statistics Canada. Canadian Community Health Survey 2008/09 - Healthy Aging [Internet]. [updated 2009; cited 2010 Nov 18]. Available from: http://cansim2.statcan.gc.ca/cgi-win/cnsmcgi.exe?Lang=E&CNSM-Fi=CII/CII_1-eng.htm

(31) Ontario Ministry of Health and Long-Term Care. Ontario Health Insurance Schedule of Benefits and Fees [Internet]. [updated 2010; cited 2010 Nov 18]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/sob_mn.html