Primary open-angle glaucoma and ocular hypertension : cost-effectiveness of early detection and treatment

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Primary open-angle glaucoma and ocular hypertension

Cost-effectiveness
of early detection and treatment

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Primary open-angle glaucoma and ocular hypertension

Cost-effectiveness of early detection and treatment

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus,
Prof. mr. G.P.M.F. Mols
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op woensdag 16 januari 2008 om 14.00 uur

door

Andrea Peeters

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Prof. dr. O. van Schayck

Delen van dit onderzoek werden gefinancierd door het College voor Zorgverzekeringen (CvZ) te Diemen

I have heard many years of telling,
And many years should see some change.

The ball I threw while playing in the park
Has not yet reached the ground.

Dylan Thomas, *Should lanterns shine*

voor Ralf
voor Thomas

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Abbreviations

bid	twice daily
CI	confidence interval
EGPS	European Glaucoma Prevention Study
EMGT	Early Manifest Glaucoma Trial
IOP	intraocular pressure
mm Hg	millimeters of mercury
OH	ocular hypertension
OHTS	Ocular Hypertension Treatment Study
POAG	primary open-angle glaucoma
qd	once daily
RCT	randomized controlled trial
RR	relative risk
SD	standard deviation
tid	three times daily

1.

Introduction

In this thesis ocular hypertension (OH) and primary open-angle glaucoma (POAG) are the main subjects of study. This introduction gives a brief description of OH and POAG, an explanation of the study methods and a detailed outline of the thesis.

Ocular hypertension

Data from large epidemiologic studies indicate that the mean intraocular pressure (IOP) is approximately 16 mm Hg, with a standard deviation of 3 mm Hg.¹ The IOP distribution is skewed towards higher pressures, especially in individuals over the age of 40. The probability of glaucoma development increases with higher IOP levels.²⁻⁶ A value for the IOP of more than 21 mm Hg is used by clinicians to define patients with ocular hypertension (OH), even though below this level individuals still can develop glaucoma. Individuals with OH, by definition, have an elevated IOP and no detectable glaucomatous damage as assessed by standard clinical eye examination and additional visual field examination. They have no symptoms due to OH and they have an increased risk of developing POAG.⁷ The prevalence of ocular hypertension found in population studies in several European countries is 2.2%.⁸⁻¹⁰ Presently, the intraocular pressure is the only risk factor for POAG that is amenable to medical intervention.

Primary open-angle glaucoma

Primary open-angle glaucoma (POAG) is a progressive, chronic optic neuropathy in adults where intraocular pressure (IOP) and other currently unknown factors contribute to damage and in which, in the absence of other identifiable causes, there is a characteristic acquired atrophy of the optic nerve and a loss of retinal ganglion cells and their axons.¹¹ In open-angle glaucoma, by definition, the anterior chamber angle is open by gonioscopic appearance. When no underlying cause of an elevated IOP and a consequent glaucomatous damage can be found, glaucoma is classified as primary. In this thesis, primary open-angle glaucoma is referred to as glaucoma.

Diagnosis

An initial glaucoma evaluation includes a comprehensive eye evaluation, including history to establish risk factors, and physical examination. The IOP, the appearance of the optic nerve, and the status of visual field can be evaluated by tonometry, ophthalmoscopy and perimetry, retrospectively. In addition, there are several instruments available for optic nerve imaging which use computer algorithms, such as the scanning laser ophthalmoscope, the retinal nerve fiber analyser, and the optical coherence tomograph.

Prevalence and incidence

Primary open-angle glaucoma affects about 1-2% of the population, ranging from 0.2% in 40-50 years old to 4.7% in individuals aged above 80 years.^{8,10,12} The incidence rate is estimated to be 0.1% per year.¹³

Risk factors

Four important risk factors associated with glaucomatous optic neuropathy are the IOP, race (African or Hispanic/Latino descent), age, and family history of glaucoma.¹¹ The association between POAG and other potential risk factors like low diastolic perfusion pressures, diabetes, myopia, and systemic hypertension has not been demonstrated consistently.

Natural history

Glaucoma is a chronic, slowly progressive, generally bilateral but often asymmetrical disease.¹⁴ In the end stages glaucoma produces tunnel vision and finally blindness. In many patients there are no noticeable symptoms until the later stages of the disease. Glaucoma is therefore sometimes called the “silent blinder”.¹⁵ In the Baltimore Eye Survey about 50% of people with glaucoma were unaware they had the disease.¹⁶ Blindness caused by glaucoma is irreversible. The incidence of blindness is estimated to be about 1% per year in treated glaucoma patients and about 10% in untreated.¹⁷⁻²⁰

Treatment

Glaucoma can not be cured. Treatment can stop or delay its progression to blindness.¹¹ Therapy is directed towards lowering the intraocular pressure, which can be achieved by means of medication, laser or surgery. Patients are committed to regular medical check-ups. Glaucoma medication is applied topically and is required lifelong. It can cause ocular and systemic side-effects. The purpose of treatment is to preserve visual function while minimizing adverse effects of therapy, thereby enhancing the patient's health and quality of life, especially with regard to such issues as self-care, driving and working.¹¹

Several types of IOP lowering drugs are now available. The most often used drugs are beta-adrenergic antagonists (timolol, betaxolol), carbonic anhydrase inhibitors (dorzolamide, brinzolamide and acetazolamide), alpha2-adrenergic agonists (brimonidine, apraclonidine) and hypotensive lipids (bimatoprost, latanoprost, travoprost). They have a different pharmacokinetic and pharmacodynamic profile. Moreover, they differ in IOP lowering effects and adverse events.

Public health impact

Glaucoma is the second leading cause of world-wide blindness.²¹ It has been estimated that there will be 60.5 million people with glaucoma in 2010, increasing to 79.6 million by 2020, 74% of whom will have POAG. Bilateral blindness will be present in 4.5 million people with POAG in 2010, rising to 5.9 million people in 2020.²¹ Because of the health, social, and economic consequences of blindness, adequate glaucoma management is not only a concern of patients and their physicians, but of the entire society.¹⁵

Early detection and treatment

As stated above, glaucoma is a slowly progressive disease without symptoms during a long time period. Glaucoma is a good candidate for early detection and

treatment. The disease can be diagnosed without much burden for the patient and effective treatment exists. Moreover, preventive treatment of ocular hypertension is an option to reduce glaucoma blindness.

Methodology

The goal of the study presented in this thesis is to explore the clinical effects and cost-effectiveness of current OH and POAG management and to provide relevant information for clinically and socially important decisions regarding early detection and treatment of OH and POAG. In the studies different methodology tools are used. A systematic review of literature of clinical trials with a meta-analysis is used to evaluate the effect on the risk of conversion to glaucoma of medical IOP lowering in OH patients. A case-referent study was designed to study the impact of early detection on the prevention of glaucoma blindness. Simulation models, in which the clinical experience of glaucoma specialists and the currently available scientific evidence are combined, estimate the long-term health-effectiveness. Finally, the principles of cost-effectiveness analysis are applied for an evaluation of different strategies for OH and POAG management.²² For this purpose the corresponding costs have been identified and assigned in the decision models.

In the field of ophthalmology the use of modeling techniques and the methods of cost-effectiveness evaluation are increasingly applied. It is common that an economic evaluation is formulated in terms of a choice between competing alternatives. The basic tasks of any economic evaluation are to identify, measure, value, and compare the costs and consequences of the alternatives being considered.²² In a health economic assessment it is of importance that all costs related to detection, treatment, and management of the disease, as well as the outcomes of treatment, are taken into account.²³ When all relevant costs and all outcomes, including adverse events and treatment failures, are properly included in the evaluation, a seemingly expensive treatment strategy might ultimately turn out to be less costly than a seemingly less expensive alternative. Specific for the cost expenditure in glaucoma is that costs are being spent in advance, while health benefits predominantly occur in the long term. Long-term data are required to estimate therapy effects. Such data are, however, difficult to obtain. Clinical trials mostly have a limited follow-up and are guided by a strict protocol, so they do not give a true reflection of patient management in clinical practice. A combination of these data with observational clinical data might be a better approach to this problem. Modeling allows to combine data from different sources, such as data sets, the literature, systematic reviews or even expert opinion in a meaningful way. Models allow real life situations to be represented in a mathematical or statistical way. A wide range of diagnostic and treatment scenarios can be investigated by varying the influential factors. Moreover, real life situations can be simulated to avoid placing individuals at risk and long-term progression can be studied in limited time. Mathematical modeling is used widely in economic evaluation of pharmaceutical and health care technologies.²⁴ Such models, often complex, deal with structural assumptions and parameter estimates.

To provide modellers with scientific guidelines, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has recommended criteria for assessing the quality of models, addressing model structure, the data used as input, and model validation.²⁴ The models presented in this thesis comply with these criteria.

The decision analyses in this thesis are based on state-transition Markov models. A Markov model is a useful tool when a decision problem involves recurrent events and risk that is continuous over time. A Markov model is comprised of a set of mutually exclusive and collectively exhaustive health states.²⁵ Health states may be defined according to disease stages, treatment status, or a combination of the two. The events are represented in the model as transitions from one state to another. The members of a hypothetical population are allocated and subsequently repeatedly reallocated into these health states. The reallocation happens at fixed time intervals, known as the Markov cycle length according to the defined transition probabilities. For instance, with a known yearly probability for patients to develop a disease, yearly transitions of patients from a health state 'well' to a health state 'ill' can be simulated. Likewise, progression from an early stage to an advanced stage of a disease can be modelled. These transitions may differ per strategy. Transition probabilities will often be different for untreated patients compared to patients under treatment. To each health state specific values can be assigned, such as costs, associated with the required health care related to the particular state. The transitions are repeatedly simulated over a chosen time period. The distribution of the population over the health states per cycle determines the quantity of the accumulated costs. The defined health outcomes and the total cost expenditure over the modelled time period can be identified per modelled strategy and compared.

In Figure 1 a hypothetical example of a Markov model is given. In this example a conversion to a disease and the disease progression over time are modelled. Transitions to a health state 'dead' are incorporated as well. The health state 'dead' is an absorbing state, from where no more transitions are possible, in contradiction to the other health states. From the state 'well' transitions to the states 'early stage of illness' and 'dead' are possible, which models healthy individuals becoming ill or dying. In the given example the mortality rate is illness dependent, but it is independent of age and gender. In contrast, in two models in this thesis the mortality rate does depend on age and gender, but it is not connected to glaucoma. In those models the mortality rate is increasing with each cycle as the simulated population is becoming older.

Figure 1: On the left: Representation of a Markov model, as a flowchart, with four health-states: ‘well’, ‘early stage of illness’, ‘advanced stage of illness’, and ‘dead’, shown as circles. Possible state transitions are indicated by arrows, labelled with yearly transition probabilities. On the right: The proportion of the population in each state at the beginning of a cycle and the change of this proportion over time is shown. Initially, the entire population is situated in the state ‘well’. The distribution of patients among the health states in the subsequent cycles is determined by their distribution in the previous cycles and the transition probabilities between the states.

In the models presented in this thesis a decision tree structure is incorporated as well. This is used to model events which occur once only, like diagnosing of patients, or adjustments of medication after the initiation of therapy. In a decision tree the sequence of chance events and decisions over time is represented.²⁶ Each chance event is assigned a probability. Each path in the decision tree represents one possible sequence of chance and decision events.

Outline of the thesis

The feasibility of screening for glaucoma is a subject of a currently ongoing debate among ophthalmologists and health decision makers.²⁷ This is a complex problem and despite the recent advances in the diagnosis and treatment of glaucoma it is uncertain if glaucoma screening can be effectively and reliably achieved.²⁸ This thesis is directed to investigate issues connected to the early detection and treatment of ocular hypertension and glaucoma.

One of the puzzling controversies in glaucoma management is whether ocular hypertension should be treated or not, considering a different susceptibility of patients to tolerate high intraocular pressures and the uncertain rate of conversion to glaucoma and progression to blindness in treated and untreated patients.¹¹ We have estimated the effect of treatment on the conversion to glaucoma in patients with ocular hypertension and its progression in patients with early glaucoma through a systematic review of randomized clinical trials. This is described in Chapter 2. The results of this study help to decide whether patients with OH or early POAG should be treated.

The impact of early detection and subsequent treatment of OH or POAG on the occurrence of blindness has not been explicitly assessed in the literature. If treatment initiated at an early stage of the disease can prevent the progression to blindness one would expect that patients who did become blind due to glaucoma have not been diagnosed in time. These issues are investigated in a case-referent study, described in Chapter 3. The results of this study help to decide whether tests to detect OH and POAG at an early stage should be applied by ophthalmologists.

A realistic alternative for screening to discover and treat OH and POAG at an early stage is case-finding among patients visiting an ophthalmologist. Even though case-finding strategies are currently being applied by most ophthalmologists, the effects of such strategies to prevent glaucoma blindness are unknown. In Chapter 4 a cost-effectiveness evaluation of different case-finding strategies is given. A simulation model is used to compare the lifetime costs and effects of three different strategies. The results of this study help to decide which case-finding strategy should be applied by an ophthalmologist.

The emergence of new types of glaucoma drugs in the past years has offered better opportunities to medically treat patients but also caused a substantial rise of the therapy costs.²⁹⁻³¹ A broad spectrum of available drugs, which differ in costs and effects, which may or may not cause side-effects, which may also be combined, allows for a large variety of possible treatment strategies. In practice such strategies involve the use of target pressures, which are different for POAG and OH. In order to make progress in investigating optimal treatment strategies for OH, we here study the question of which drug should be used as a first treatment choice. In Chapters 5 and 6 an evaluation of two different strategies for the initiation of OH therapy by means of a simulation model is given. Initiation of OH therapy with a new topical agent (latanoprost) is compared to initiation by a beta-blocker (timolol). The short and long-term clinical consequences of these two strategies are described in detail in Chapter 5. In Chapter 6 a cost-effectiveness analysis of these two strategies is presented. The results of these studies help ophthalmologists to decide which initial OH medication therapy to apply.

Finally, in Chapter 7 the findings of this thesis are discussed and recommendations for further research are given.

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Chapter 1

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2.

Quantifying the effect of the reduction of intraocular pressure on the occurrence and progression of glaucoma

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Abstract

Objective: To estimate the effect of IOP lowering therapy on the incidence of primary open-angle glaucoma (POAG) in patients with ocular hypertension (OH) and on the progression in patients with glaucoma.

Design: Meta-analysis of randomized controlled trials.

Participants: Nine articles which included OH patients and one article which included early glaucoma patients.

Methods: An electronic search of the databases Medline, Embase and the Cochrane Register of Controlled Trials was conducted to identify articles for inclusion. The inclusion criteria were: articles written in English, French, German or Dutch; trials in OH or POAG; a randomized comparison of intraocular pressure (IOP) lowering intervention versus placebo or no treatment; visual field loss or optic disc changes as outcome; follow-up longer than 6 months. The methodological quality of the selected studies was evaluated by criteria of the Delphi list and the Cochrane Collaboration. In a meta-analysis performed for OH trials a pooled relative risk was calculated using a 'random effects model'. A meta-regression analysis was performed to assess the magnitude of the glaucoma risk reduction in OH patients per mm Hg of IOP reduction achieved through therapy.

Outcome measures: Conversion to glaucoma or its progression.

Results: The search resulted in nine OH trials and one POAG trial, which met the inclusion criteria. All individual OH studies show a positive effect of IOP lowering on a reduction of the incidence rate of glaucoma. The calculated pooled relative risk is 0.61 (95% confidence interval 0.45-0.83). A meta-regression model shows a decrease of the relative risk of conversion to glaucoma by 14% with each mm Hg of extra IOP reduction ($p = 0.045$). The only trial, which included glaucoma patients, shows a protective effect of hypotensive therapy in early glaucoma.

Conclusions: There is sufficient evidence that IOP lowering therapy in patients with ocular hypertension reduces the risk of conversion to glaucoma. The relative risk decreases more with larger IOP reduction. The protective effect of IOP lowering on glaucoma progression is shown by one trial which included patients with early visual field loss.

Introduction

An elevated intraocular pressure (IOP) is an important risk factor for a conversion to glaucoma in patients with ocular hypertension (OH) and a prognostic factor in patients with primary open-angle glaucoma (POAG).¹ Medication, laser and surgery are used to lower the IOP. The final goal of therapy is to prevent or delay damage to the optic nerve and thereby to prevent functional limitations and blindness.

In the past, trials have been carried out which show that lowering the IOP in patients with glaucoma is beneficial for the prevention of severe visual field loss and the usefulness of glaucoma treatment is not questioned.²⁻⁶ In these trials a comparison is made between different types of hypotensive treatment. The effect of treatment versus no treatment is particularly of interest for OH patients and patients with early glaucoma. The susceptibility of the optic nerve to IOP-related damage varies among individuals and for many patients treatment may not be considered necessary.¹

The efficacy of early detection and treatment in connection with prevention of advanced stages of glaucoma with severe visual loss or blindness is closely associated with the effectiveness of treatment of OH and early POAG. A level of IOP achieved by treatment plays a role in this as well. In the current glaucoma management an ophthalmologist strives to achieve for each patient an IOP level by which protection against optic nerve damage is achieved. The estimated upper limit of such IOP level is considered 'target pressure'. For OH patients a target pressure may be viewed as a threshold recommended for initiation of treatment.⁷ Therefore, it is of interest to investigate to what extent a larger IOP reduction in OH patients influences the risk of conversion to glaucoma.

In the present study the currently available scientific evidence concerning the benefit of treatment in OH and early glaucoma is systematically analysed. A quantification of the effect of IOP lowering in OH patients on the occurrence of glaucoma is performed by combining data of several comparable randomized controlled trials in a meta-analysis. Nine OH studies, including two so far largest trials, the Ocular Hypertension Treatment Study (OHTS)⁸ and the European Glaucoma Prevention Study (EGPS)⁹ are included in this meta-analysis. Meta-regression analysis based on the outcomes of these nine OH trials determines the magnitude of risk reduction of conversion of OH to glaucoma per each extra mm Hg of IOP reduction achieved through therapy.

Methods

Search strategy

Articles describing randomized controlled trials (RCT's) on treatment of patients with ocular hypertension or primary open-angle glaucoma were identified through a systematic search in the databases Medline, Embase, and the Cochrane Register of

Controlled Trials. For search in Medline the modified version, advised by the Cochrane Handbook, of the published search strategy of Dickersin was used.¹⁰ For search in Embase a strategy of Tulder et al was applied.¹¹

Keywords in connection with the disease were: “glaucoma” and “ocular hypertension”. Keywords in connection with the study outcome were: “visual field”, “dB”, “Humphreys”, “Friedman” and “perimetr*”. The ‘thesaurus’ of the databases and the ‘explode’ option were utilized. The original search of the databases was done until February 2004, but recently the search was updated. Subsequently the reference lists of the selected articles and of two meta-analysis articles^{12,13} were consulted until no further studies could be found. Also the result of a search conducted in connection with a meta-analysis performed earlier by the authors was checked.¹⁴

Selection of the studies; inclusion criteria

Two researches (JS and AP) selected independently potential articles to be included in the meta-analysis. By viewing the title, abstract and the medical subject heading (MeSH) of the articles, a first judgement of the eligibility was done. The potentially eligible publications were printed or photocopied for further evaluation. All selected articles had to fulfil the following inclusion criteria: 1) language: English, French, German or Dutch; 2) disease in question: OH or POAG; 3) randomized comparison: IOP lowering intervention versus placebo or no treatment; 4) study outcomes: visual field loss or optic disc changes; 5) follow-up longer than 6 months.

Quality Assessment and Data Abstraction

Methodological quality of the selected studies was evaluated by the criteria for evaluation of RCT's recommended by the Delphi list,¹⁵ the Cochrane Collaboration and criteria added by the authors (see Table 1). The quality items used for the quality assessment are given in Table 1. Two researchers (JS and AP) assessed the quality, independently. In case of different opinion a discussion followed until consensus was reached. For each trial several quality items, as shown in Table 1, were noted. Based on these trial features the quality of each study was rated. If an article qualified for an item, one point was given. The maximum quality score was 16. Next, the following data were collected on a standardized record form: number of patients, nature of the disease, interventions, nature of the study outcomes, methods for evaluating the optic disc and the visual field, mean pre- and post treatment IOP per trial arm or the change in IOP from baseline, and the incidence of glaucoma or its progression.

Table 1: Quality items included for the quality assessment, source of the quality item, and number of publications with a positive quality score per item in 10 trials identified in the systematic review

Item code	Source	Quality item	No. of publications scored 'yes'*
A	Delphi list ¹⁵	Was the randomization procedure concealed?	5
B	Delphi list	Were eligibility criteria specified?	9
C	Delphi list	Was the patient blinded?	4
D	Delphi list	Was the care provider blinded?	4
E	Delphi list	Was the outcome assessor blinded?	8
F	Delphi list	Were the groups similar at baseline regarding the most important prognostic indicators?	8
G	Cochrane Collaboration	Was there a selective loss to follow-up?	3
H	Delphi list	Did the analysis include an intention-to-treat analysis?	10
I	Cochrane Collaboration	Were other interventions comparable?	4
J	Considered for Delphi list	Is it unlikely that compliance may explain differences between groups?	0
K	Delphi list	Were point estimates and measures of variability presented for the primary outcome measures?	9
L	Added by authors	Was the follow-up period comparable?	9
M	Added by authors	Was there an explicit description of intervention?	10
N	Added by authors	Was the outcome assessment properly described?	8
O	Added by authors	Were side effects reported?	7
P	Considered for Delphi list	Was calculation of statistical power reported after treatment allocation?	6

* complementary answers were 'unknown' or 'no'

Data Analysis

The outcome of interest was defined as the cumulative incidence of glaucoma or its progression. A relative risk per study was calculated: the incidence in the intervention group divided by the incidence in the control group, with its 95% confidence interval. The relative risks of the individual studies were combined in a meta-analysis and a pooled relative risk was calculated using a 'random effects model'.¹⁶ Heterogeneity was assessed by judging the forest plot and by the Q-test and I2 statistic.¹⁷ To examine publication bias Egger's measure of publication bias was calculated.¹⁸

The interpretation of data from one study needs further clarification. In the European Glaucoma Prevention Study (EGPS) there was a major loss to follow-up and patients who reached a safety point (IOP > 35 mm Hg) were excluded from the trial. We assumed that patients lost to follow-up developed glaucoma according to the incidence of the group without treatment. Furthermore, because high IOP is often associated with conversion to glaucoma we considered patients who reached a safety endpoint as having developed glaucoma.

A meta-regression analysis was used to determine the glaucoma risk reduction per mm Hg of IOP reduction achieved through therapy. For this purpose the logarithm of the relative risk was modeled, weighted by the inverse of its variance, dependent on the difference in the end IOP. This was defined for each study as the end IOP in the control group minus end IOP in the intervention group (mm Hg).

In a sensitivity analysis, the robustness of the findings to different assumptions was examined. Also the impact of an exclusion of trials of poorer quality on the outcome of the meta-analysis was examined. The overall effect was calculated for the studies with a quality score of 10 points or more. An impact of an addition of a study with no treatment effect on the outcome of the meta-analysis was assessed by including a hypothetical study with 4000 patients and a relative risk of 1. Additionally, meta-analyses were performed with different relative risk values for the EGPS study (the calculations of these values are given in Table 2).

Results

4109 articles were identified. After screening the articles by title and abstract 1422 papers remained. From these finally, nine trials in OH patients and one trial in glaucoma patients met the inclusion criteria and were selected.^{8,9,19-26} (see Figure 1). Results from the OH trials were pooled in a meta-analysis. In Table 2 the basic characteristics of the selected studies and the quality score for each study are shown. Five OH trials and the glaucoma study had a score above 10 (maximum score was 16). These were also the largest and the most recent studies. There was no indication for significant heterogeneity between the studies ($Q = 15.19$ ($P = 0.085$), $I^2 = 47\%$). Nor was there an indication for presence of a publication bias, the P value of Eager's measure of publication bias was 0.31. Figure 2 gives the results of the meta-analysis. As seen in this figure, all individual studies in ocular hypertension showed a positive effect of IOP lowering by glaucoma medication on a reduction of the incidence rate of glaucoma. The calculated pooled relative risk is 0.61 (95% CI 0.45-0.83). The 95% confidence intervals of the studies include the overall effect estimate.

According to the meta-regression model there is a relationship between the difference in end IOP in the control group and the intervention group and the risk of conversion to glaucoma (see Figure 3). The relative risk of conversion to glaucoma decreases with an increase in difference in the achieved IOP reduction between the control group and the intervention group. With each mm Hg difference of the end IOP the relative risk of conversion to glaucoma decreases with 14%.

The Early Manifest Glaucoma Trial (EMGT) showed that lowering the IOP is beneficial in slowing glaucoma progression. When the cumulative incidence was calculated after 48 months, the relative risk was 0.61 (95% CI 0.45-0.84). When calculations were made after a median follow-up of 6 years, the relative risk was 0.73 (95% CI 0.57-0.92).

Figure 1: Flowchart of the selection of the studies

Sensitivity analysis

The calculations of the overall effect in the meta-analysis by the random and fixed effects models showed no substantial difference. The pooled relative risk calculated by the 'random effects model' was 0.61 (95% CI 0.45-0.83) whereas by the 'fixed effects model' this was 0.65 (95% CI 0.54-0.78). When only studies with a quality score higher than 10 (points) were included, the pooled relative risk was 0.63 (95%

CI 0.43-0.90). Inclusion of a hypothetical study, showing no treatment effect, in the meta-analysis did not change its conclusions. When a hypothetical study with 4000 patients, a relative risk 1, and an assumed glaucoma incidence of 10% was added, the pooled relative risk remained below 1, namely 0.80 (95% CI 0.71-0.92). Calculations of the overall effect with the higher value for the relative risk of the EGPS study did not influence the conclusions of the meta-analysis. An analysis with a 0.93 value (see Table 2) gave a pooled relative risk of 0.62 (95% CI 0.44-0.87). The value of 0.77 (see Table 2) gave a pooled relative risk of 0.60 (95% CI 0.45-0.80).

Figure 2: Meta-analysis of the relative risks of the nine ocular hypertension trials

Forest plot

Pooled relative risk: $RR = 0.61$ (95% CI 0.45-0.83); $Q = 15.19$, $P = 0.085$; $I^2 = 47\%$; p -publication bias 0.313. The square and the horizontal line for each study correspond to the point estimate and a 95% confidence interval. The area of the square reflects the weight of the study in the meta-analysis. The solid vertical line through $RR = 1$ corresponds to no effect of treatment. The diamond represents the pooled relative risk with 95% confidence interval.

EGPS = European Glaucoma Prevention Study; OHTS = Ocular Hypertension Treatment Study

Table 2: Baseline characteristics of the included studies, quality scores, and study outcomes

Trial	Group	Intervention	No. of patients	Endpoint reached	Cumulative incidence (%)	Endpoint	Relative risk (95% CI)	Follow-up (months)	IOP change (mm Hg)*	Quality score criteria (max. 16)	Quality criteria not fulfilled
OH trials											
EGPS group 2005 ⁹	Intervention	dorzolamide 2% tid	536	74	13.8	26 VF, 20 disc 28 unkn [†]	0.82 (0.62-1.09)	mean 60 (median 55)	23.4±1.53 – 19.3 decrease 4.1	14	g,j
	Control	placebo	541	91	16.8	38 VF, 22 disc 31 unkn [†]			23.5±1.68 – 20.4 decrease 3.1		
Kamal et al. 2003 ¹⁹	Intervention	betaxolol bid	182	15	8.2	15 VF	0.80 (0.41-1.53)	range 24 – 72 (median 60)	26.3±2.3 – 21.6±2.9 (p<0.01) decrease 4.7	14	i,j
	Control	placebo	174	18	10.3	18 VF			25.6±2.2 – 23.7±2.9 (p<0.0001) decrease 1.9		
Kass et al. 1989 ²⁰	Intervention	timolol 0.25% bid, one eye if IOP ≥ 20 timolol 0.5% bid, one eye	62	6	9.7	2 VF, 2 disc 2 VF+disc	0.60 (0.23-1.55)	> 60	26.4±4.4 – 21.6±3.7 (p<0.001) decrease 4.8	14	a,j
	Control	placebo (fellow eye)	62	10	16.1	2 VF, 0 disc 8 VF+disc			26.6±4.5 – 23.8±4.0 (p<0.001) decrease 2.8		
Kass et al. 2002 ⁸	Intervention	medication till TP ≤ 24 and > 20% reduction	817	36	4.4	15 VF, 18 disc 3 VF+disc	0.41 (0.28-0.59)	mean 60 (median 76.5)	24.9±2.6 – 19.3±2.2 decrease 5.6	12	c,d,i,j
	Control	no treatment	819	89	10.9	29 VF, 51 disc 9 VF+disc			24.9±2.7 – 23.9±2.9 decrease 1		

Trial	Group	Intervention	No. of patients reached	Cumulative incidence (%)	Endpoint	Relative risk (95% CI)	Follow-up (months)	IOP change (mm Hg)*	Quality score (max. 16)	Quality criteria not fulfilled
Heijl et al. 2000 ²¹	Intervention	timolol 0.5% bid	46	5	10.9	5 VF	0.60 (0.21-1.69)	mean 60	27.1 – 20.4 decrease 6.7	11 a,i,j,o,p
	Control	placebo	44	8	18.2	8 VF			26.2 – 25.2 decrease 1.0	
Schulzer et al. 1991 ²²	Intervention	timolol 0.25% or 0.5%	70	17	24.3	15 VF 2 disc	0.93 (0.53-1.64)	mean 72	26.3±3.49 – 21.8±3.22 decrease 4.5 (p<0.001)	9 a,c,d,g,i,j,o
	Control	no treatment	73	19	26	13 VF 6 disc			26.1±3.18 – 26.3±4.34 decrease -0.19 (p<0.001)	
Epstein et al. 1989 ²³	Intervention	timolol 0.5% bid	54	6	11.1	4 VF 2 disc	0.61 (0.24-1.56)	mean 56	24.0±1.3 – 20.2 decrease 3.8	9 c,d,e,g,j,i,p
	Control	no treatment	55	10	18.2	9 VF 1 disc		mean 51	23.9±1.6 – 23.4 decrease 0.5	
Becker et al. 1966 ²⁴	Intervention	topical epinephrine 2% bid	50	2	4.0	2 VF	0.29 (0.06-1.31)	48– 60	21.7 – 16.7 decrease 4.96	6 a,c,d,e,f,i,j,k,n,p
	Control	no treatment (fellow eye)	50	7	14.0	7 VF			21.0 – 19.74 decrease 1.26	
Shin et al. 1976 ²⁵	Intervention	epinephrine hydrochloride 1% or 2% bid	19	2	10.5	0 VF 2 disc	0.18 (0.05-0.71)	range 12 – 60 (mean 37.5±17.2)	end IOP difference between control and intervention group 6.25 ^{††}	6 a,b,c,d,f,i,j,n,o,p
	Control	no treatment (fellow eye)	19	11	57.9	11 VF and/or disc				

Trial	Group	Intervention	No. of patients	Endpoint reached	Cumulative incidence (%)	Endpoint	Relative risk (95% CI)	Follow-up (months)	IOP change (mm Hg)*	Quality score (max. 16)	Quality criteria not fulfilled
POAG trial											
Heijl et al 2002 ²⁶	Intervention	laser trabeculoplasty + betaxolol 0.5% bid; if IOP > 25 at 2 consecutive visits latanoprost 0.05% qd	129	39 at 48 months	30.2 at 48 months	EMGT progression criteria	0.61 (0.45-0.84) at 48 months	mean 72 (range 51-102)	at 3 months FU: 20.6±4.1 – 15.5 decrease 5.1 mean difference from baseline to all visits: -4.5±3.4	13	c,d,j
	Control	no treatment; if IOP > 35 at 2 consecutive visits latanoprost 0.05% qd	126	62 at 48 months	49.2 at 48 months	EMGT progression criteria	0.73 (0.57-0.92) after a median follow-up of 6 years	at 3 months FU: 20.9±4.1 - 20.8 decrease 0.1 mean difference from baseline to all visits: 0.0±1.9			

OH = ocular hypertension; POAG = primary open-angle glaucoma; VF = visual field; disc = optic disc; qd = 1/day; bid = 2/day; tid = 3/day; ukn = unknown; TP = target pressure
* Value plus standard deviation, if given.

† Unknown because the given endpoints were recalculated. The calculations were made as follows: (1) Patients lost to follow-up were included as developed glaucoma according to the incidence of the group without treatment and patients who reached a safety endpoint as having developed glaucoma => value 0.82. For the sensitivity analysis the following calculations were made: (2) Patients lost to follow-up were included as developed glaucoma according to the incidence of the group without treatment and patients who reached safety endpoints were not included => value 0.93. (3) Neither patients who were lost to follow-up nor patients with safety end points were included => value 0.77.
‡ Given in the paper.

Figure 3: Meta-regression analysis of the relative risks of the nine ocular hypertension trials, carried out in the logarithmic domain, dependent on the end intraocular pressure (IOP) difference between the control and the intervention group

p-interaction: 0.045; log RR = -0.025 - 0.15 "End IOP Difference"

Discussion

Our analysis shows that IOP lowering reduces the risk of glaucoma and also that a larger lowering of IOP is associated with a greater reduction of this risk. All studies included in the meta-analysis showed a beneficial effect of an IOP lowering therapy. The computed pooled relative risk was 0.61 (95% CI 0.45-0.83). The relative risks were calculated from the cumulative incidence. All studies had a follow-up up to 5-6 years. The meta-regression model showed that the relative risk of conversion to glaucoma decreases by 14% with each mm Hg of IOP reduction achieved through therapy.

The protective effect of pressure lowering treatment is consistent with the outcomes of a recently published meta-analysis performed by Maier et al.²⁷ The authors of this study performed a meta-analysis of time to event data and the computed hazard ratio in this study is 0.56 (95% CI 0.39-0.81). However, Maier et al. included only five OH trials in their analysis. In the present meta-analysis four more OH studies were added including the second largest trial in ocular hypertension, the European Glaucoma Prevention Study, the results of which were only published in 2005. Three of the remaining four studies use fellow eye as a control.^{20,24,25} This was an exclusion criterion by Maier et al. In addition, in the present study the outcomes of the nine individual trials were used to carry out a meta-regression analysis to relate the size of IOP reduction to the effect on the conversion to glaucoma.

The present systematic review is based on search of articles in the three most relevant databases (Medline, Embase and Cochrane). The validity of the search is

corroborated by the search results of Maier et al., who identified the same articles. The meta-analysis was performed for the OH trials. We have identified one trial only which included glaucoma patients, the Early Manifest Glaucoma Trial. We did not search for normal pressure glaucoma, considering the possible different pathogenesis of the normal- and high-pressure glaucoma, and a different therapy response. It must be noted that a proportion of patients in the EMGT study had normal pressure glaucoma, however, the subgroup analysis of the patients showed a protective effect of IOP lowering particularly for those patients with an increased intraocular pressure.²⁶

The trial interventions were limited to the use of topical medication in OH patients and a combination of topical medication with laser trabeculoplasty in glaucoma patients. As expected, surgery was not included in any of the trials, because it is not a primary treatment option for ocular hypertension or early glaucoma. We did not find any randomized controlled trials comparing treatment with no treatment conducted in patients with advanced glaucoma. This is to be expected, since avoiding treatment in such patients would be ethically inappropriate.

The OH studies with the most extreme positive outcomes, with the lowest relative risks, are the oldest studies with the lowest quality scores and with least weight in the meta-analysis. In three studies the relative risk was higher than the pooled estimate, but still lower than 1. The study with a relative risk closest to 1 (done by Schulzer et al.) scored 9 quality points. It included 143 patients. The Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study are the studies with most weight in the meta-analysis. These studies included 1636 and 1077 patients. The OHTS study is the largest study, which showed the effectiveness of reducing the IOP with topical medication in delaying or preventing the onset of POAG with statistical significance ($p < 0.0001$). The EGPS study failed to do so. This study showed somewhat unexpected results. The difference in IOP reduction between the treatment and control group was only 1 mm Hg during the course of the study and the IOP dropped substantially in the control group. As pointed out by Dr. Quigley, three significant differences with the OHTS study may explain the failure of the EGPS study to find a therapy benefit: (1) the use of dorzolamide therapy alone, regardless of IOP lowering with placebo control; (2) a major regression to the mean in IOP at 6 months; (3) selective loss to follow-up of persons with higher IOP.²⁸ It should be noted, that the observed, even though non-significant risk reduction in this study, is consistent with the expected effect of a 1 mm Hg difference in IOP, according to our meta-regression model.

By viewing the results of the individual studies, most striking are the outcomes of the trial done by Schulzer et al.. In this study, in spite of an end IOP difference of 4.5 mm Hg, the difference in the glaucoma development between the two trial arms was small ($RR = 0.93$ (95% CI 0.53-1.64)). It must be noted that glaucoma incidence was very high in this study (see Table 2). This could be explained by the fact that the population was at high risk of developing glaucoma. From the included patients 31% had a positive family history of glaucoma, 20% had a baseline entry

pressure of 30 mm Hg or greater, and 29% had a cup-to-disc ratio of 0.5 or greater at entry. The high-risk patients were represented equally in the intervention and control group. Moreover, the mean achieved IOP level in the treated group was 21.8 mm Hg, which is rather high for the high-risk patients. This study scored 9 quality points. When a separation of the studies into two groups with a quality score less than 10 points and 10 points or more was introduced in the regression model, this did not significantly change the outcomes of the meta-regression (p-interaction = 0.770).

The Early Manifest Glaucoma Trial showed a protective effect of immediate treatment, compared with no initial treatment or later treatment, in patients with early glaucoma. This trial included newly diagnosed and previously untreated open-angle glaucoma patients with early visual field loss. When the cumulative incidence was calculated after 48 months, the relative risk was 0.61 (95% CI 0.45-0.84). When calculations were made after a median follow-up of 6 years, the relative risk was 0.73 (95% CI 0.57-0.92). The authors of the study calculated patient-based risk of progression using a Cox proportional hazard regression model. The calculated hazard ratio after 6 years was 0.50 (95% CI 0.35-0.71). In the trial an initial randomization to treatment or no treatment was maintained only as long as progression did not occur. The study does not include long-term follow-up of untreated patients beyond EMGT progression. The EMGT multivariate analyses showed that the risk decreased about 10% with each millimeter mercury of IOP reduction from baseline, which seems consistent with the results of our meta-regression.²⁹

Conclusion

There is sufficient scientific evidence that topical hypotensive therapy reduces the risk of conversion to glaucoma in ocular hypertension and a progression of visual field loss in early glaucoma. The evidence is provided by a number of well-conducted randomized controlled trials. Moreover, the risk of conversion to glaucoma in patients with ocular hypertension decreases with approximately 14% per each mm Hg of extra IOP reduction.

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3.

The effect of early detection of ocular hypertension and primary open-angle glaucoma on the occurrence of blindness *A case-referent study*

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Abstract

Objective: To establish the effectiveness of early detection and treatment of ocular hypertension (OH) and primary open-angle glaucoma (POAG) in the ophthalmic practice on the prevention of glaucoma blindness.

Design: A case-referent study.

Methods: Cases are patients who became blind due to glaucoma in at least one eye. Referents are patients with an exudative form of age-related macular degeneration (AMD) and a Snellen visual acuity < 0.3 in at least one eye. An exposure to tests by which OH and glaucoma can be detected (tonometry and ophthalmoscopy) prior to the diagnosis was retrieved from the medical charts of the cases and referents. Two glaucoma specialists did the retrieval of data from the medical records, independent of each other and unaware whether the record was of a case or a referent. They were asked to give the amount of certainty with which they judged whether an examination could be considered a 'screening' moment and thus not based on patients symptoms on a six point scale from 'certainly' to 'certainly not'. If early detection and treatment is effective in preventing glaucoma blindness it is to be expected that the frequency of these examinations is lower among cases compared to referents that represent the frequency of such testing in the general population. The relative risk, expressing the effect of early detection on glaucoma-related blindness, adjusted for potential confounders was estimated in a logistic regression analysis. Diabetes mellitus, hypertension, myopia, family history of glaucoma, year of the diagnosis and age were taken as potential confounders.

Results: Fewer cases than referents were screened by ophthalmologists for ocular hypertension and early glaucoma within 20 years prior to their diagnosis. The crude relative risk (RR) is 0.57 (90% confidence interval 0.31-1.05), when adjusted for potential confounders the RR is 0.46 (90% confidence interval 0.22-1.00).

Conclusion: The application of tonometry and ophthalmoscopy as screening tests for early detection of ocular hypertension and glaucoma by ophthalmologists is likely to lead to a reduction of glaucoma blindness.

Introduction

Primary open-angle glaucoma (POAG) is a chronic optic neuropathy in which the progressive loss of the retinal ganglion cells leads to characteristic structural changes at the head of the optic nerve and to functional loss to the visual field.¹ This process is insidious and takes place over a relatively long time period. In many patients there are no noticeable symptoms until patients lose their central vision. An elevated intraocular pressure (IOP) defines ocular hypertension (OH) and is a major risk factor for a conversion to glaucoma and a prognostic factor for the occurrence of visual field loss. Treatment is aimed to lower the IOP.

In spite of the fact that glaucoma is an important public health problem there is no screening programme for OH and POAG.² However, early detection in the form of case-finding takes place in ophthalmologic practice. The efficacy of early detection by case-finding and consequent treatment to prevent glaucoma blindness has not yet been investigated. Due to the need of a large sample size, long follow-up and ethical considerations, a randomized clinical trial or a prospective cohort study are not well suited for this purpose. Another type of epidemiological study, a case-referent study, can give an estimation of the effect of screening or case-finding if the number of screening examinations received prior to the date of diagnosis for cases and referents are assessed.³ This type of study allows a direct estimation of the effect size.⁴ A case-referent study is relatively easy to conduct with fewer costs since fewer patients need to be included and there is no need for a follow-up since cases already have reached the outcome that one wishes to prevent with screening or case-finding. In other fields of medicine case-referent studies have been used to evaluate the efficacy of screening programmes on the occurrence of death.^{5,6}

Glaucoma meets many criteria for screening.² One of the criteria is that the targeted disease has a pre-clinical stage which is detectable by suitable screening tests. A further prerequisite is that there are effective treatments that reduce the progression to the end stage of the disease. An elevated IOP can be detected by tonometry.⁷ The early glaucomatous structural changes of the optic nerve head can be detected by ophthalmoscopy before significant visual field loss occurs.⁸ There are effective treatments to lower the intra-ocular pressure that prevent a conversion to glaucoma or its progression.⁹⁻¹¹

If early detection and a subsequent application of an efficacious therapy can reduce the conversion or progression rate of the disease, then it is likely that testing for early detection is beneficial for the prevention of glaucoma-related blindness. In this paper a case-referent study is presented in which the effect of early detection of OH and POAG by case-finding in ophthalmologic practice on the occurrence of glaucoma blindness is estimated.

Methods

Study setting

Cases and referents were ophthalmic patients treated at the University Hospital Maastricht. The hospital research ethics board (REB) approved the conduct of this study. All patients were informed about the study and consented to their enrolment. The study adhered to the tenets of the Declaration of Helsinki.

Identification of cases and referents

For identifying potential cases first all consecutive patients who underwent a 10-2 Humphrey visual field testing (Humphrey perimetry, Carl Zeiss Meditec, Dublin CA) during two years, from 01-01-2000 until 19-02-2002, at the University Hospital Maastricht were selected. The print-outs of the visual field and basic patient information were abstracted directly from the Humphrey hardware by the use of a software program PeriData (PeriData Software GmbH). Next, patients were selected who met the inclusion criteria. Cases had to meet the following criteria: (1) diagnosis primary open-angle glaucoma (2) functioning visual field in at least one eye restricted to 10 degrees (3) resident of the chosen region (4) born between 1920-1940 (5) treated for glaucoma at the University Hospital Maastricht. The final selection of the study participants was based on patients' approval with the participation in the study and on the availability of the data. First, the medical charts of all potential participants were collected. If patients were referred from another hospital, a copy of their medical record was requested. If a record could not be found, if the notes were incomplete, or if the diagnosis preceded the first date on the medical chart patients were not included.

Referents had to meet the following criteria: (1) a diagnosis exudative form of age related macular degeneration (AMD) (2) visual acuity < 0.3 due to MD in at least one eye (3) resident of the chosen region (4) born between 1920-1940 (5) treated for macular degeneration at the University Hospital Maastricht. First, all consecutive patients who underwent fluorescein angiography (FAG) at the University Hospital Maastricht from 01-01-1997 until 31-12-2002 were identified. Thereafter, the same procedure as described by the cases was used for the final selection of referents.

Patients were initially approached by mail. The letters, printed in large print, in which the nature of the study was explained, were signed by the treating ophthalmologist. Patients were asked to sign their approval of enrollment in the study. Patients who did not respond received a reminder. Patients who did not respond to the reminder were approached by phone.

Data collection

An exposure to tests for early detection prior to the diagnosis POAG or AMD was ascertained by reviewing the medical records of the study participants. The tests for detection were defined as tonometry and ophthalmoscopy. A diagnosis OH was considered detection for POAG patients. If an IOP of 22 mm Hg or more was found

the date of this finding was taken as the date of the diagnosis. Testing had to be performed in a time period when progression in glaucoma patients could have been stopped or slowed down by treatment. Testing had to take place within 20 years preceding the date of the diagnosis. For the cases testing was not considered a 'screening' moment if the tests were performed due to complaints associated with glaucoma or if it took place within one year before the occurrence of blindness. For the referents testing was not considered a 'screening' moment if the tests were performed due to complaints of AMD. For each participant the information on medical history and notes made during the outpatients visits were photocopied from the charts. Two glaucoma specialists (CW and HB) were asked to review the photocopies and state whether an examination could be considered as screening or was based on patient's symptoms. The judgment was scored on a six point ordinal scale: 'certainly'; 'very probably'; 'probably'; 'probably not'; 'very probably not'; 'certainly not'. They were kept unaware of whether a participant was a case or a referent.

Further patient data that were retrieved from the medical charts were: age, sex, year of the diagnosis (POAG or AMD) and myopia (spherical equivalent < -4.0 D). In addition, presence of diabetes mellitus, hypertension, and a positive family history of glaucoma were assessed by means of a questionnaire. This questionnaire was sent by mail, printed in large letters.

Data analysis

The effect of early detection of OH and POAG on glaucoma blindness was expressed as a relative risk (RR). The ratio of the frequency of testing for OH and POAG prior to the diagnosis POAG among the cases was divided by the ratio of the frequency of such testing prior to the diagnosis AMD among the referents. A RR below 1 would then indicate that the testing for early detection of OH and POAG is less likely among the cases. Next, the calculated RR was adjusted for potential confounders in a logistic regression model. The following variables were taken as potential confounders: diabetes mellitus, hypertension, myopia, family history of glaucoma, year of the diagnosis and age. For the analyses the judgement of the ophthalmologist, whether the performed testing could be considered as screening, which was more conservative (leading to a RR closest to 1) was chosen. The analyses were performed for two different cut-off points on the ordinal scale. First the options 'certainly', 'very probably', and 'probably' were considered positive and then only the options 'certainly' and 'very probably'.

Table 1: Number of potential cases and referents, reasons for exclusion and the final number of the study participants

	Cases	Referents
Patients considered for the study (based on visual field or fluorescein angiography)	151	252
Patients who met the inclusion criteria	83	186
Reasons for no participation in the study:		
- no informed consent	17	41
- no additional information from a referring hospital	18	9
- incomplete additional information from a referring hospital	3	4
- untraceable medical chart	-	5
- diagnosis before the history of the medical chart	4	3
- diagnosis of glaucoma prior to the diagnosis of MD	-	14
Total number of study participants	41	110

Table 2: Baseline characteristics of cases and referents

	Cases (n = 41)	Referents (n = 110)
Mean age at diagnosis (years $\pm$ SD))	63.5 ($\pm$ 5.9)	70.0 ($\pm$ 5.0)
Men	17 (41 %)	57 (46 %)
Myopia	26 (63 %)	48 (44 %)
Family history of glaucoma	7 (17 %)	14 (13 %)
Diabetes mellitus	7 (17 %)	15 (14 %)
Hypertension	7 (17 %)	21 (19 %)

The results

In Table 1 an overview is given of number of patients initially considered for the study, the reasons for non-inclusion and the final number of patients who were enrolled. Finally, 41 cases and 110 referents were included. The baseline characteristics of these patients are given in Table 2. Cases were younger when diagnosed, with a mean age of 63 years, compared to 70 years in referents. The mean year of the diagnosis was 1992 (SD $\pm$ 6.2), among the cases and 1997 (SD $\pm$ 3.8) among the referents. A history of tests for early detection by tonometry and/or ophthalmoscopy was less common among cases, namely 16 (39%), than among referents, 58 (53%) ($p = 0.13$). The results of the analysis are given in Table 3. The crude effect measure (not adjusted for possible confounding) was 0.57 (90% confidence interval 0.31-1.05). After adjustment for all listed potential confounders in a logistic regression model the RR became 0.46 (90% confidence interval 0.22-1.00). When in the analysis the cut-off point for the judgement whether testing could be considered a 'screening' moment was shifted and only the options 'certainly' and 'very probably' were taken as positive, then the unadjusted RR became 0.40 (90% confidence interval 0.21-0.74), and the RR adjusted for all potential confounders was 0.34 (90% confidence interval 0.16-0.72).

Table 3: Results of the case-referent study - relative risk of the application of the examinations for early detection of glaucoma among the cases and referents, unadjusted and adjusted for potential confounders, for two different cut-off points of the certainty that the performed examinations were applied as an early detection

Crude effect	Relative risk (RR) cut-off point 1**	Relative risk (RR) cut-off point 2***
Unadjusted for confounding	0.57 (90% CI 0.31-1.05)	0.40 (90% CI 0.21-0.74)
Adjusted for the listed potential confounders*	0.46 (90% CI 0.22-1.00)	0.34 (90% CI 0.16-0.72)

* potential confounders: diabetes mellitus, systemic hypertension, myopia, family history of glaucoma, year of the diagnosis, age

** options 'certainly', 'very probably', and 'probably' taken for the confirmation that testing was applied as an early detection

*** options 'certainly' and 'very probably' taken for the confirmation that testing was applied as an early detection

Discussion

In this paper a case-referent study is presented which was designed to investigate if early detection of OH and POAG by means of case-finding by the ophthalmologist is beneficial for the prevention of glaucoma-related blindness. The relative risk adjusted for possible confounding is 0.46 (90% confidence interval 0.22-1.00). When for more certainty was chosen in whether testing could be considered a 'screening moment', the relative risk, after adjustments for confounding, became 0.34 (90% confidence interval 0.16-0.72). This suggests that early detection of OH and POAG by means of case-finding by the ophthalmologist reduces the risk of glaucoma blindness to about one half or more of the risk when no case-finding is done.

The calculation of the relative risk is based on a proportion of individuals who underwent testing by tonometry and/or ophthalmoscopy prior to their diagnosis, not based on patient's symptoms. The argumentation why this should have an impact on the occurrence of blindness is that when a performance of these tests by which OH and early POAG can be detected is not based on the disease symptoms, one can assume that the disease is diagnosed and treated in an early stage. If treatment of OH and early glaucoma is effective in blindness prevention then patients diagnosed in time will not progress to blindness. To obtain a reasonable estimate of the true effect it is essential that the proportion of individuals who underwent tonometry and ophthalmoscopy among the referents is a valid estimate of the proportion of individuals with these examinations in the general population from which the blind glaucoma patients come.

The choice of the referents is fundamental and has to fulfill two criteria.¹² Firstly, the referents must come from the same general population as the cases. For this reason referents were chosen from the same hospital and the same region as the cases. It is plausible that if a referent would have become a glaucoma patient he would have been included in the study as a case because he would have been treated

in the same hospital. Secondly, the referents' disease and disease stage should not be related to the examinations under study. Blindness due to exudative macular degeneration is not associated with the tests for early detection of glaucoma. Although AMD can be detected by ophthalmoscopy, this does not influence the course of the disease and the occurrence of blindness since there is, or until recently there was not, an effective treatment for it. To prevent bias the testing was only considered a 'screening' moment if the tests were not related to the symptoms of AMD that may have led these patients to visit an ophthalmologist.

Another precaution taken to minimize bias was blinding of the ophthalmologists (who had to indicate whether testing was done on indication or not) to whether a patient was a case or a referent.

The confounders for which the crude effect has been adjusted, i.e. diabetes mellitus, hypertension, myopia, family history of glaucoma and age are (potential) risk factors for glaucoma. Additionally, year of the diagnosis and also age may be related to the aspect of time. Cases have been diagnosed earlier than referents. This is to be expected because the rate of blindness is slower in patients with glaucoma than in patients with AMD. The time period may be associated with detection, because in the past people used to visit an ophthalmologist more often than nowadays e.g. for a prescription of spectacles. Age may be associated with detection because older people visit an ophthalmologist more often than younger persons.

Conclusions

The results of the case-referent study show that fewer blind glaucoma patients underwent tests for early detection of ocular hypertension and glaucoma than referents, which represent such testing in the general population. This supports the hypothesis that early detection and treatment has a positive effect on the prevention of glaucoma blindness. The outcomes of the present study emphasize the need for the assessment of IOP and an optic nerve examination in each patient visiting an ophthalmologist.

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Cost-effectiveness of early detection and treatment of ocular hypertension and primary open-angle glaucoma by the ophthalmologist

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Abstract

Purpose: To determine the most cost-effective case-finding strategy for the ophthalmologist to detect and treat ocular hypertension (OH) and primary open-angle glaucoma (POAG) at an early stage to prevent blindness.

Design: A Markov cost-effectiveness simulation model.

Methods: Three case-finding strategies are analyzed and compared. The simulated cohort consists of all initial patients of at least 40 years old visiting an ophthalmic practice. All patients undergo ophthalmoscopy, but tonometry is routinely performed to: (1) all initial patients, (2) high-risk patients only, or (3) no one. The population characteristics are based on data of 1 000 initial patients. Transition probabilities are taken from the literature. The (direct) costs of diagnosis and treatment represent those for The Netherlands. The time-horizon of the model is 20 years. An annual discount rate of 4% is used.

Main outcome measures: Costs, proportion of patients becoming blind, years of blindness.

Results: The costliest strategy (1) leads to least blindness. The incremental cost-effectiveness ratio, which shows extra costs per year of vision saved in comparison to the cheapest strategy (3), is lower for strategy (1) than for strategy (2). It amounts to € 1 707, not including extra costs due to blindness (e.g. associated with the use of disability facilities). When such costs exceed € 1 707 per patient per year, which is most likely, then strategy (1) becomes cost saving.

Conclusions: It is most cost-effective to routinely perform tonometry to all initial ophthalmic patients to prevent blindness due to glaucoma.

Introduction

Primary open angle glaucoma (POAG) is an important public health problem, being the second leading cause of bilateral blindness worldwide.¹ It is characterized by progressive optic nerve atrophy leading to visual field damage and possibly blindness. The natural history of POAG is though variable; some people develop significant visual problems, while others do not.² An elevated intraocular pressure (IOP) defines ocular hypertension (OH) and is a major risk factor for POAG. Through IOP lowering treatment the risk of glaucoma and its progression can be reduced.^{3,4}

In the past it has often been suggested that a screening program should be set up, but because of high costs and unknown effectiveness it has never been systematically introduced.⁵ In the last two decades new technologies have been introduced that permit earlier detection of structural and functional damage due to glaucoma. New treatments, such as hypotensive lipids and selective laser trabeculoplasty, allow for safer and more effective IOP reduction. Several well conducted clinical trials showed the effectiveness of treatment.^{3,4} These new developments, and a possibly increasing prevalence of POAG due to aging, bring along the necessity to re-evaluate screening.⁶ However, the feasibility and efficacy of a screening program still can be questioned. Only recently the US Preventive Services Task Force concluded that there is still insufficient evidence to recommend for or against a screening program for glaucoma.^{7,8}

An alternative for screening to discover and treat OH and POAG at an early stage is case-finding among patients visiting an ophthalmologist. The advantages compared to screening in the general population are the use of an existing infrastructure, the high probability for discovery by means of a complete ophthalmic examination and the direct initiation of treatment without loss to follow-up. Moreover, the prevalence of OH, POAG, and risk factors for glaucoma, is higher among patients visiting an ophthalmologist than in the general population.

In many countries ophthalmologists routinely apply strategies to detect OH and POAG. However, the effect of these strategies to prevent glaucoma blindness is unknown. The cost-effectiveness is unknown as well. This study aims to investigate the effects, costs, and cost-effectiveness of different case-finding strategies that can be applied by an ophthalmologist in daily practice to detect and treat OH and POAG at an early stage to prevent glaucoma blindness.

Method

Three case-finding strategies, which differ with respect to the group of patients routinely receiving tonometry, are analyzed and compared using a Markov cost-effectiveness simulation model. In the model all initial ophthalmic patients undergo ophthalmoscopy to detect a glaucomatous optic nerve, but the three strategies differ by whether tonometry is routinely performed to: (1) all initial patients, (2) high-risk

patients only, or (3) no one. In case of positive results of testing with ophthalmoscopy and/or tonometry, perimetry is performed to complete the assessment of the correct diagnosis. These different diagnostic strategies lead to different proportions of patients being diagnosed and treated for OH or POAG. The long-term consequences of these three strategies are then evaluated.

The population characteristics are based on data gathered from the charts of 1 000 initial patients visiting an ophthalmic practice. The transition probabilities are taken from the literature. The (direct) costs of diagnosis and treatment represent those for The Netherlands. The time-horizon of the model is 20 years and an annual discount rate of 4% is used. The analysis is performed from a societal perspective.

The Model

It is modeled that a cohort of initial patients visiting an ophthalmologist, having a certain prevalence of OH and POAG, undergoes testing to detect these disorders. The use of the diagnostic tests is strategy dependent, as described above, and so per strategy different proportions of patients are specified for observation, treatment, or discharge. Subsequently a 20-year follow-up is modeled, while the progression of patients returning for regular visits, but also that of the discharged patients is being tracked. Per strategy blindness due to glaucoma is determined and the corresponding costs are computed.

The cohort simulated in the model corresponds to initial patients of at least 40 years old visiting an ophthalmic practice. In the Netherlands the general practitioner refers the majority of such patients. The age and sex distribution, and the prevalence of OH and POAG are jointly taken into account. In the model the high-risk group is defined to consist of patients reporting a positive family history of glaucoma. Such patients have an increased risk of having glaucoma.^{9,10}

The model consists of two parts. Part one models the diagnostic process; part two models the disease progression over time. In part one, the known sensitivity and specificity of ophthalmoscopy and tonometry are used to calculate proportions of patients receiving the diagnosis OH or POAG for each strategy. This leads to a strategy dependent distribution of the patient cohort over the set of health states. These health states are defined by the true condition of a patient, by the obtained diagnosis and by the assigned therapy (see Figure 1). The therapy assignment corresponds to the clinical practice, where IOP level, the presence of risk factors, and severity of the disease play a role. Patients diagnosed as OH are either put under observation or given medical treatment with monotherapy. In the strategy ‘tonometry all’ 50% of the OH patients starts medication directly after the diagnosis is made. The rest is kept under observation and receives treatment only if conversion to POAG occurs. In the strategy ‘tonometry high-risk group’ all patients diagnosed as OH are at risk and therefore require medication. POAG patients start

therapy with monotherapy in all strategies; a small proportion undergoes laser or surgery directly. Missed OH and POAG patients are discharged.

In part two of the model transitions between health states can take place. Here the development of OH in normotensives, the development of POAG from OH, and the progression of POAG to blindness is modeled. Also, undiagnosed patients are tracked and can be rediscovered. A distinction is made between patients completely discharged and patients still visiting the ophthalmologist regularly for some other ophthalmic condition. The latter group of patients has a higher chance of OH/POAG detection. For patients under therapy every 6 months an outpatient visit is modeled to take place and the proportion of patients showing progression is modeled to undergo a therapy switch. The therapy sequence is based on recommendations of the American Academy of Ophthalmology; its chronological order is monotherapy, combination therapy, laser, and surgery.¹¹ The end stage of the disease is blindness. Patients under treatment develop blindness only after surgery, when there are no further treatment possibilities. Discharged patients can also eventually develop blindness without treatment. Patients who become blind continue to use combination therapy and to visit an ophthalmologist once in two years. The false positives, patients unjustly positively diagnosed, continue to use monotherapy medication.

The model is built and analyzed using the software package 'Decision Analysis by TreeAge' (Data), version 3.5. It has the structure of a Markov model and it has a time horizon of 20 years, consisting of 40 cycles of 6 months each. This choice of cycle length reflects the common time between the consecutive outpatient visits of the glaucoma patients. The diagnostic process is implemented as the first cycle only, the disease progression over time involves the other cycles. At the end of each cycle transitions between the health states take place. These transitions include age and sex dependent survival probabilities, probabilities concerning the discovery of undiagnosed patients, and the probabilities related to the development or progression of OH and POAG. These probabilities are independent of the three strategies being evaluated.

Figure 1: Part two of the simulation model: transitions among the health states

The health state 'dead' (not shown) can be entered from all other states. After the diagnosis was made, in part one of the model, all health states except 'blind' and 'dead' can be entered. The shown scheme is a simplified reproduction of the model. In the model a distinction is namely made between undiscovered patients completely discharged and patients still visiting the ophthalmologist regularly for some other ophthalmic condition. A distinction is also made in the form of medication, namely monotherapy or combination therapy. Another health state, not shown, is 'false positives on monotherapy'.

Cost assignment

The direct medical costs are assigned as once-only costs and state dependent costs. The once-only costs are the costs of the diagnostic process and the costs for laser treatment and surgery. The state dependent costs are the costs of outpatient visits and medication. These costs are assigned to the health states and reflect the treatment requirements related to 6 months of treatment of a particular state. The costs for diagnosis apply to all patients. The costs for treatment apply to diagnosed patients only.

Outcomes

The outcomes of the analysis concern: 1) costs, 2) proportion of patients becoming blind, 3) years of blindness.

The Data

The data and their sources are presented in Tables 1-3. The age distribution and the OH/POAG prevalence for the population have been determined from the charts of 1 000 initial patients, consecutively visiting a general ophthalmic practice in Maastricht (Medisch Centrum Maastricht Annadal - MCMA), starting from January 1999.¹² The global characteristics of the data are consistent with the indications from the literature.¹³⁻¹⁵ The values for sensitivity and specificity of the diagnostic tests were taken from the literature. The starting therapy assignment for discovered patients is consistent with the opinion of the glaucoma specialists, the recommendations of the American Academy of Ophthalmology and the European Glaucoma Society.^{11,16} In part two of the model the 6 months transition probabilities are calculated from the yearly transition probabilities, which are obtained as follows. The age and sex dependent survival probabilities are taken from data provided by the Dutch Central Bureau for Statistics (CBS).¹⁷ The modeled disease progression is based on the literature, mainly on the long-term follow-up studies and on therapy trials.^{3,18-37} The unit prices related to the outpatient visits, laser trabeculoplasty and surgery are as determined at the University Hospital Maastricht. This was done according to the micro costing method.³⁸ The prices of medical drugs represent the prices in the Netherlands (incl. VAT). The prices of monotherapy and combination therapy are based on the average use of the individual drugs in the Netherlands, combining up to three drugs in the combination therapy. The frequency of the health care use is modeled in accordance with the specialists' opinion and the recommendations of the American Academy of Ophthalmology. The costs due to blindness in connection with the usage of disability facilities in the Netherlands could not be retrieved.

Chapter 4

Table 1: Parameters used in the simulation model

Parameter	Lower bound	Baseline	Upper bound	Source
A. Proportions				
Se tonometry ^a	0.90	1	-	54-56
Se ophthalmoscopy	0.60	0.80	1	5,57-61
Sp tonometry	0.90	1	-	54-56
Sp ophthalmoscopy	0.80	0.90	1	5,57-61
Screen positive OH ^b				5,57-61
strategy (1)	0.91	1	-	
strategy (2)	0.20	0.28	0.36	
strategy (3)	0	0.10	0.20	
Screen positive POAG ^b				5,57-61
strategy (1)	0.96	1	-	
strategy (2)	0.67	0.84	1	
strategy (3)	0.60	0.80	1	
Screen positive 'normal' ^b				5,57-61
strategy (1)	-	0	0.05	
strategy (2)	-	0	0.012	
strategy (3)	-	0	0.01	
Discovered OH patients with check-up only				Estimate
strategy (1)	0.40	0.50	0.60	
strategy (2)	-	0	-	
strategy (3)	0.40	0.50	0.60	
Patients with regular visits due to other condition	0.4	0.5	0.7	14, clinical data
POAG patients with direct laser assignment	0	0.02	0.05	39, estimate
POAG patients with direct surgery assignment	0	0.02	0.05	39, estimate
B. Yearly probability estimates				
Discovery of OH in 'visitors'				5,57-61
strategy (1)	-	0.95	-	
strategy (2)	-	0.10	-	
strategy (3)	-	0.10	-	
Discovery of OH in 'discharged' ^c				62, clinical data
strategy (1)	0.01	0.05	0.10	
strategy (2)	0.0028	0.014	0.028	
strategy (3)	0.001	0.005	0.01	
Discovery of POAG in 'discharged' ^c				62, clinical data
strategy (1)	0.01	0.05	0.10	
strategy (2)	0.0084	0.042	0.084	
strategy (3)	0.008	0.04	0.08	
OH development in discharged 'normals'	0.002	0.003	0.006	18,19
POAG development in discharged OH patients	0.02	0.05	0.10	3,18,20-24
Blindness development in untreated POAG patients	0.05	0.133	0.2	5,63,64
POAG development in OH patients with check-up only	0.015	0.02	0.07	3,23
Switch to combination therapy in OH patients on monotherapy	0.08	0.095	0.11	3,25,26
Switch to combination therapy in POAG patients on monotherapy	0.20	0.213	0.25	25-27
POAG development in OH patients on combination therapy	0.037	0.054	0.089	3,24,28
Switch to laser in POAG patients on combination therapy	0.32	0.49	0.74	25,39
Success laser 0-1 years after the intervention ^d	0.65	0.70	0.75	29-33
Success laser >1 year after the intervention ^d	0.85	0.87	0.90	29-33
Success surgery 0-5 years after the intervention ^e	-	0.94	-	34-37
Success surgery 5-10 years after the intervention ^e	-	0.95	-	34-37
Success surgery >10 years after the intervention ^e	-	0.975	-	34-37
Discovery of POAG in 'visitors'	-	0.95	-	5,60,61

a Values reflect IOP measurement by the Goldmann applanation tonometer (golden standard) to diagnose patients with IOP > 21 mm Hg.

b Per strategy the proportions of the correct diagnoses have been calculated, using the following assumption. In case of a positive outcome of at least one of the performed tests a patient undergoes further examinations and will be correctly diagnosed within the first 6 months. Values for perimetry were not required for the calculations, even if perimetry contributes to the achievement of a correct diagnosis. Perimetry is performed in case of positive results of testing with ophthalmoscopy and/or tonometry.

c The probability of visiting an ophthalmologist has been multiplied by the probability of being diagnosed. **d** The complementary probability to 'success laser' is the probability to switch to surgery.

e The complementary probability to 'success surgery' is the probability to become blind.

Strategy (1) = 'tonometry all'; Strategy (2) = 'tonometry high-risk group' (the values shown are valid if 20% of OH and POAG and 5% of the rest of the patients report a positive family history of glaucoma); Strategy (3) = 'tonometry no one'; Discovery = probability of discovering undiagnosed patients in part two of the model; Visitors = patients visiting the ophthalmologist regularly due to other ophthalmic condition than OH or POAG; Discharged = patients being discharged after the diagnostic process (part one of the model) is completed; Monotherapy = receiving 1 medication; Combination therapy = receiving more than 1 medication; Normal = has neither OH nor POAG

Table 2: OH and POAG prevalence among initial ophthalmic patients¹²

Age category	OH	POAG	Normal ^a
40 - 49 years	16.7 %	0 %	83.3 %
50 - 59 years	2.2 %	1 %	96.8 %
60 - 69 years	5.3 %	1 %	93.7 %
70 - 79 years	7.9 %	4 %	88.1 %
80+ years	5.2 %	6.9 %	87.9 %
All age-categories	6.7 %	2.4 %	90.9 %

a normal = has neither OH nor POAG

Table 3: Prices (2001) and frequency of the health care use

Resource	Patient type	Frequency	Unit price (€)
Outpatient visit ^a			23
	OH patients with check-up only	1 / year	
	OH patients on monotherapy	1 / year	
	OH patients on combination therapy	1 / year	
	POAG patients on monotherapy	2 / year	
	POAG patients on combination therapy	2 / year	
	POAG patients post laser ^b	2 / year	
	POAG patients post surgery ^c	2 / year	
	blind	0.5 / year	
Perimetry			77
	OH patients on monotherapy	0.2 / year	
	OH patients on combination therapy	0.33 / year	
	POAG patients on monotherapy	1 / year	
	POAG patients on combination therapy	1 / year	
	POAG patients post laser	1 / year	
	POAG patients post surgery	1 / year	
Argon laser therapy	POAG patients (by indication)	1	267
Surgery	POAG patients (by indication)	1	1 282
Monotherapy	patients on monotherapy	daily	158 / year ⁶⁵
Combination therapy	patients on combination therapy	daily	358 / year ⁶⁵
Transportation	all patients	per visit	3

a 10 minutes consult: included are visus control, tonometry, ophthalmoscopy (the first consult costs 26 € if tonometry is included, and 24 € without tonometry)

b plus 1 extra consult after the intervention

c plus 10 extra consults after the intervention

Results

Table 4 gives the expected costs and outcomes per initial ophthalmic patient due to OH and POAG within a period of 20 years. Not surprisingly, both strategies ‘tonometry all’ and ‘tonometry high risk group’ cost more than ‘tonometry no one’ but also avert more blindness. The strategy ‘tonometry all’ is the most expensive one, with least blindness. For this strategy the incremental costs to prevent blindness in comparison with ‘tonometry no one’ are € 7 778 to prevent one person from becoming blind and € 1 707 per year of vision saved. For strategy ‘tonometry high risk group’ the incremental costs to prevent blindness are higher. These outcomes do not include extra costs due to blindness, e.g. in connection with the usage of disability facilities. Since such costs are likely to exceed € 1 707 per year, inclusion of such costs makes the strategy ‘tonometry all’ cheapest and most effective.

The sensitivity analysis shows that in strategy ‘tonometry all’ the occurrence of blindness is always lowest and in strategy ‘tonometry no one’ always highest. The incremental costs to prevent blindness are always lower for the strategy ‘tonometry all’ than ‘tonometry high-risk group’. These results show the robustness of the conclusions.

In a one-way sensitivity analysis the lower and upper bound values of all parameters for which ranges are given were used. Alteration of glaucoma incidence among undiscovered OH patients has the largest impact on the results of the cost-effectiveness analysis. The incremental costs per year of vision saved for strategy ‘tonometry all’ are € 4 670, when glaucoma incidence among discharged OH patients is lowest and € 564 when it is highest. Alteration of blindness incidence among untreated glaucoma patients gives incremental costs per year of vision saved € 3 900, when it is lowest, and € 1 240, when it is highest. A two-way sensitivity analysis, which uses the lower values of both above-mentioned parameters, gives the incremental costs € 12 250 per year of vision saved. Alteration of the health care costs, with all unit prices raised by 10% and 30%, has no substantial effect on the outcomes of the cost-effectiveness analysis (data not shown). Neither does an alteration of the cohort characteristics and of the sensitivity and specificity of the diagnostic tests (data not shown).

Table 4: Results of the cost-effectiveness analysis of three different strategies for early detection and treatment of OH and POAG among initial ophthalmic patients

	Strategy ‘tonometry all’	Strategy ‘tonometry high- risk group’	Strategy ‘tonometry no one’
Costs ^a (€)	295	265	225
Proportion of patients not becoming blind ^a	0.993	0.986	0.984
Years of blindness ^a	0.021	0.053	0.062
Incremental cost-effectiveness ratio ^b (extra costs to prevent 1 person from becoming blind)	7 778	20 000	-
Incremental cost-effectiveness ratio ^b (extra costs per year of vision saved)	1 707	4 444	-

^a expected costs and effects per initial ophthalmic patient due to ocular hypertension or glaucoma within 20 years (costs and years in blindness have been discounted by 4%)

^b the incremental cost-effectiveness ratio shows extra costs per effect in comparison with the strategy ‘tonometry no one’ (ratio between the difference in costs and the difference in effects)

Discussion

This study evaluates the long-term consequences of three case-finding strategies, which differ with respect to the group of patients receiving tonometry. For this purpose a simulation model was used. Although a randomized clinical trial would be of interest, it is almost impossible to conduct. Beside the ethical objections such trial would inevitably give large expenses because of the low prevalence of glaucoma and its slow progression to blindness. An advantage of modeling is the possibility to simulate and compare several strategies. Another advantage is the possibil-

ity to integrate current research results and examine the influence of alteration of different parameters.

The figures incorporated in the model are based on information from different sources. This could give uncertainty about the exact value of the figures. A sensitivity analysis was performed to assess the impact of variation of the uncertain quantities in the model on the outcomes of the cost-effectiveness analysis. The conclusions were robust to these uncertainties.

To validate the simulation model strategy ‘tonometry all’, which represents more or less the current practice, was studied in more detail. The model shows that on average over a period of 20 years, each year 5.2% of glaucoma patients undergoes laser therapy and 2.7% surgery. A questionnaire, distributed among glaucoma patients in randomly chosen practices in the Netherlands, showed comparable results.³⁹ Per year 4.8% of patients had laser therapy and 2% surgery. The model was further validated by comparing the incidence of glaucoma blindness to those reported in the literature. Two longitudinal studies were conducted in patients from a clinic.^{40,41} The incidence rate of blindness in these studies was 1.05% and 0.95% per year, respectively. The model shows an incidence rate of blindness 0.90% per year.

The costs seem to be comparable to those reported in the literature. One study assessed the annual resource use and costs of patients in the Netherlands.⁴² The mean costs per glaucoma patient were € 469 (converted and using the retail price index). In the simulation model this is € 454. Another study calculated the direct treatment costs for newly diagnosed OH or POAG patients in Germany.⁴³ The mean costs per OH/POAG patient for one year of treatment were about € 324 (converted and using the retail price index). The same authors calculated the costs for France and the United Kingdom.⁴⁴ This was € 387 and € 560, respectively. Other published glaucoma cost studies show comparable estimates for yearly costs in Europe and Canada.⁴⁵⁻⁴⁷ In the U.S. the published yearly costs ranged from € 486 for early stage of the disease to € 1960 for patients with end-stage disease.⁴⁸ Differences in unit costs, in medication prices, in the assignment of laser therapy and surgery, can explain some variations in the costs. However, raising the costs in our study did not affect its conclusions.

The outcomes show that strategy ‘tonometry all’ is the most preferable in relation to blindness prevention. This strategy is most costly, but prevents most blindness. The incremental costs to prevent blindness when compared to ‘tonometry no one’ are small. For strategy ‘tonometry high risk group’ the incremental costs are higher. Even if the financing would be limited, it would be more preferable to perform tonometry in all patients, and not in high-risk group only, because strategy ‘tonometry all’ dominates strategy ‘tonometry high risk group’ in the extended sense.³⁸ The costs due to blindness from glaucoma could not be retrieved. If such yearly costs exceed € 1 707, then performing tonometry in all patients becomes cost saving. This is likely the case because blindness is accompanied by the utilization of disability

facilities. In the Netherlands a common help in the household for disabled people (12 hours a week) has a yearly cost of € 5 300. The costs of blindness may vary per country depending on the care and support given. A study conducted in the United Kingdom, which took the societal perspective, estimated the costs of blindness for people with age related macular degeneration.⁴⁹ The costs of blindness in this study were € 10 134 (€ 2 159- € 26 847) in the first year and € 9 883 (€ 2 080-€ 26 376) in the second and subsequent years (converted and using the retail price index). The same paper gives an overview of the estimates of the cost of blindness for UK, Scotland, Australia, USA and Switzerland. The yearly costs due to blindness in these countries probably exceed € 1 707.

At first glance it is not obvious why strategy ‘tonometry all’ is the most cost-effective because in general, approaching a high-risk group would give a higher yield of case-finding. However, in strategy ‘tonometry all’ not every detected OH patient is treated, as current guidelines advice only treatment in case of a presence of a risk factor. Those who are not treated at once are followed for the occurrence of glaucoma. Those who develop glaucoma are treated at an early stage; thereby blindness can still be prevented, and the costly treatment of those OH patients who never develop POAG can be avoided. When the proportion of high-risk patients receiving treatment was made similar to that in strategy ‘tonometry all’, the results became more alike, confirming that monitoring of OH patients without direct treatment contributes to a favorable cost-effectiveness ratio of strategy ‘tonometry all’.

The impact of not using the ophthalmoscope to detect POAG has not been addressed. In daily practice ophthalmoscopy cannot be left out of the first ophthalmic examination. Its use is needed for the diagnosis of many diseases. Tonometry could be left out more easily since there is often no indication for it, except for the early detection of OH or POAG. The use of perimetry, costly and time consuming, is unlikely an option for case-finding. In the model patients undergo perimetry on indication, to confirm the diagnosis.

A positive family history of glaucoma was appointed as an indication for being at risk of having glaucoma. It is an established risk factor and it is easy to assess in daily practice.¹¹ It has been estimated that about 20% of the OH and POAG patients and 5% of others in the ophthalmic patients population report a positive family history of glaucoma.^{10,50} The simulations show that even if these proportions are much higher strategy ‘tonometry all’ remains the most cost-effective (data not shown).

Note that normal tension glaucoma (NTG) is not included in this study. The role of IOP in its pathogenesis and the response to therapeutic lowering of IOP is different in comparison with high-tension glaucoma. Moreover, this disorder cannot be primarily detected by tonometry. As a consequence, inclusion of NTG in the study has no impact on the outcomes of the cost-effectiveness analysis, because the incremental costs and the incremental effects do not change. When NTG is in-

cluded, the proportion of patients prevented from blindness due to glaucoma is slightly lower than calculated.

The indirect costs have not been used in the presented analysis, because glaucoma effects mainly elderly and the consequences in terms of potential loss of production are limited.⁵¹ No cost-utility analysis has been performed. An estimate for the utility for blindness is 0.6.⁵² The estimated incremental costs per quality-adjusted life-year (QALY) for strategy 'tonometry all' are then approximately € 2 850. According to the guidelines in the Netherlands a 4% discount rate is used. Because of the current international recommendation of 3%, an extra analysis was performed.^{38,53} If using a 3% discount rate, the incremental costs per year of vision saved for 'tonometry all' are € 1 550.

Conclusion

The strategy 'tonometry all' is the most preferable strategy for blindness prevention, with € 1 707 extra costs per year of vision saved when compared to strategy 'tonometry no one'. When costs associated with the use of disability facilities due to blindness exceed € 1 707 per patient per year, which is most likely, then strategy 'tonometry all' becomes cost saving. We conclude that it is most cost-effective to routinely perform tonometry to all initial ophthalmic patients to prevent blindness due to glaucoma.

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5.

The clinical impact of two different strategies for initiating therapy in patients with ocular hypertension

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Abstract

Objective: To assess the impact of two strategies for initiating therapy in ocular hypertension on intraocular pressure, drug use, and eventual blindness due to glaucoma.

Design: A simulation model.

Methods: Two strategies are modelled. In strategy (1) therapy is started with timolol, in strategy (2) with latanoprost. By Monte Carlo simulation the IOP lowering effect of the specific drugs is applied to a hypothetical cohort of OH patients, characterized by an initial IOP distribution. Depending on the achieved IOP and occurrence of side effects, the prescribed therapy can be maintained or therapy switches occur, at most four times. The adjustment of therapy to reach the target pressure involves consecutively monotherapy, combination therapy, and laser. Switches to different types of monotherapy and combination therapy are included. Four drugs are used: latanoprost, timolol, brimonidine, and dorzolamide. After 15 months of therapy adjustments a lifelong follow-up with possible conversion to glaucoma and to blindness is modeled (Markov model). Conversion rates depend on the achieved IOP. The parameters in the model are based on the literature, the cohort characteristics on the data of 1 000 patients. The analyses were performed for a cohort with a sampled and fixed initial IOP (25 and 30 mm Hg).

Outcome measures: 1) drug distribution after 15 months 2) IOP after 15 months 3) blindness through glaucoma within a lifelong follow-up.

Results: Treatment goal was achieved in both strategies in 90% by monotherapy. For a cohort with an initial IOP 30 mm Hg this was 60%. The originally prescribed medication was maintained in 66% in strategy (1) and in 77% in strategy (2). IOP decreased with approximately 34%, from 25.4 mm Hg (sampled mean) to 16.7 mm Hg in strategy (1) and to 16.5 mm Hg in strategy (2). The computed blindness per person within 18.7 years of life expectancy was 0.0923 years in strategy (1) and 0.0870 years in strategy (2), which corresponds to approximately 1 month. The difference between strategies corresponds to 2 days spent in blindness per patient.

Conclusion: Concerning the clinical effects of the two strategies, the differences are quite small. This is largely caused by the key concept of a target pressure, which underlies both strategies.

Introduction

The introduction of new IOP lowering drugs in the last decades has contributed to a change of the drug prescription pattern for ocular hypertension (OH) and glaucoma.¹⁻³ An ophthalmologist can choose from a broad spectrum of hypotensive drugs. The IOP lowering effect, the ease of application, the occurrence of side-effects, contraindications, and costs, are all important factors in drug choice. For many years, non-selective beta-blockers such as timolol have been the first choice in treatment. However, the use of beta-blockers is decreasing and hypotensive lipids, such as latanoprost, are becoming the most commonly prescribed drugs. One may question whether latanoprost should be the first choice in OH therapy instead of timolol. Latanoprost gives only a slightly better IOP lowering effect than timolol.⁴ The cost price of latanoprost is, however, considerably higher than that of timolol. In the literature mostly a head-to-head comparison can be found between treatment with hypotensive lipids and treatment with timolol, based on the achieved IOP level. One study compared the effectiveness of treatment on the glaucoma progression as well, however, based on IOP reduction through timolol only and hypotensive lipids only.⁵ Such a comparison does not take into account essential aspects of patient management. In daily practice, therapies often get adjusted, even repeatedly. For each patient a target pressure is defined and a best fitting therapy is searched for, a therapy that achieves an optimal IOP reduction with minimal adverse events. The goal of each treatment strategy is to reach the same target pressure. Therefore, one may expect that such strategies will give similar clinical results. In this paper a simulation model is presented, which was used to quantitatively assess the clinical effects of initiating OH therapy with timolol or with latanoprost. The details of therapy adjustments have been taken into account. The model is set up to compare the two strategies with respect to their impact on the IOP, drug use, and blindness due to glaucoma. Our analysis is focused on the difference in the clinical effects due to a different first therapy choice, followed by similar steps for therapy adjustments, for a cohort of OH patients as they enter an ophthalmic practice.

Methods

General design

Two strategies for the initiation and adjustment of OH medication are modelled and compared. In strategy (1) therapy is started with timolol and in strategy (2) with latanoprost. By using a Monte Carlo simulation the IOP lowering effect of the specific drugs is applied to a hypothetical cohort of OH patients. This cohort is characterized by the initial IOP and age distributions. The adjustment of therapy in order to reach the target pressure is modelled as in the ophthalmic practice. Patients start therapy with a topical agent and return for evaluation. In case of adverse events, or unsatisfactory IOP decrease, therapy is adjusted and a new evaluation follows. Therapy switches are modelled at most four times. Therapies involve monotherapy, combination therapy and laser. Four drugs, representatives of four

major generic classes, are used: timolol (beta-blockers), latanoprost (hypotensive lipids), brimonidine (α 2-adrenergic agonists), and dorzolamide (topical carbonic anhydrase inhibitors). The modelled IOP lowering effects are specific for each drug and for each drug combination. Effects correspond to timolol 0.5%, latanoprost 0.005%, dorzolamide 2%, brimonidine 0.2%. Contraindication to timolol is taken into account. Once the therapy adjustments are completed, which covers at most 15 months of therapy, per strategy the achieved new IOP distribution and the drug distribution within the cohort are determined. Subsequently by using a Markov model also a lifelong follow-up of the cohort and the disease progression over time are modelled. A conversion to glaucoma and to blindness can take place. Yearly conversion rates are dependent on the achieved IOP level. Per strategy the eventual years of blindness are determined. The time horizon of the model is based on the life expectancy of patients. The parameters used in the model are based on the literature. The IOP lowering effect of the specific drugs is based on a meta-analysis of randomized clinical trials.⁴ The estimates of other parameters are based on clinical trials and long-term follow-up studies. Glaucoma specialists were consulted to decide which medication should be used in case of a therapy switch. The characteristics of the simulated cohort are based on the data of 1 000 ophthalmic patients.

The model

The model is built by use of software package ‘Decision Analysis by TreeAge’ (Data), version 3.5. Input data and their sources are shown in Tables 1-3 and Figure 1. In addition, the survival probabilities are taken from data provided by the Dutch Central Bureau for Statistics (CBS).³³ Conversion to blindness is based on an assumption that 1% of glaucoma patients per year become blind.^{34,35} The simulated cohort consists of initial OH patients (without glaucomatous changes of the optic nerve head or visual field loss) of at least 40 years old. Mean age is 64.5 years. Initial IOP within this population includes values from 22 to 35 mm Hg. Mean initial IOP value is 25.36 mm Hg.

Figure 1: The IOP dependent yearly incidence of POAG in OH patients under treatment²¹⁻³²

Table 1: The initial IOP distribution of the simulated cohort⁶

IOP (mm Hg)	Proportion
22	0.17
23	0.16
24	0.15
25	0.13
26	0.11
27	0.08
28	0.05
29	0.04
30	0.03
31	0.02
32	0.02
33	0.02
34	0.01
35	0.01

Two treatment strategies are set up as follows. In strategy ‘start with timolol’ patients start therapy with timolol unless contraindicated, in which case latanoprost is used. In strategy ‘start with latanoprost’ all patients start therapy with latanoprost. Both latanoprost and timolol are used in each strategy. A switch from latanoprost to timolol and vice versa is possible. In case of a therapy switch first latanoprost and timolol are used, brimonidine, and dorzolamide afterwards. Laser treatment follows only if there are no more treatment options through medication. Contraindication to timolol is taken into account at all places in the model where this drug is applied. The corresponding proportion of patients receives another medication.

Table 2: IOP reduction through therapy used in the simulation model^{4,7-11}

Intervention	IOP reduction (%) (mean $\pm$ SD)
Timolol (0.5%)	26.5 $\pm$ 14
Latanoprost (0.005%)	29.5 $\pm$ 13.4
Dorzolamide (2%)	19.5 $\pm$ 13.5
Brimonidine (0.2%)	21 $\pm$ 13.1
Timolol + latanoprost (add on)	20.5 $\pm$ 13.9
Timolol + dorzolamide (add on)	18 $\pm$ 12
1 drug + 1 drug or laser (add on)	18 $\pm$ 12
2 drugs + 1 drug or laser (add on)	10 $\pm$ 5
3 drugs + laser (add on)	8 $\pm$ 4
Laser	30 $\pm$ 12

Table 3: Parameters used in the simulation model¹²⁻²⁰

Parameter	Proportion (lower bound)	Proportion (baseline)	Proportion (upper bound)
Contraindication timolol	0.1	0.2	0.3
Side effect* timolol	0.05	0.1	0.3
Side effect* latanoprost	0.01	0.03	0.1
Side effect* dorzolamide	0.05	0.15	0.25
Side effect* brimonidine	0.05	0.15	0.25

* any side effects of medication that cause a therapy change

Therapy adjustment is modelled within the structure of a decision tree. A simplified impression of the tree is given in Figure 2. Always three months after a prescription

of a medication an evaluation is modelled to take place. For each simulated patient a new IOP, achieved by the IOP lowering effect of the prescribed drug, and an occurrence of side effects are modelled probabilistically. A patient then either maintains the prescribed medication, or a therapy change follows with a subsequent new evaluation. Criteria for treatment adjustments are as follows. 1) If serious side effects occur, the drug is replaced with another one, regardless of the achieved IOP level. 2) In the absence of side effects the treatment assignment depends on the achieved IOP level as follows: a) If the achieved IOP is less than or equal to 21 mm Hg, medication is not changed. b) If the achieved IOP is higher than 21 mm Hg and the IOP reduction is more than 20% of the original IOP level another drug is added. c) If the achieved IOP is higher than 21 mm Hg and the IOP reduction is less than 20% of the original IOP level, the currently used medication is substituted by another one. Laser treatment is assigned in the same way as a new drug, as an addition to the medication or as a replacement of it. Occurrence of side effects is independent of age or IOP.

Figure 2: Visual representation of the therapy adjustments applied during the first 15 months of treatment

* if target IOP reached or if all 4 steps have been evaluated, then continuation therapy

[†] with respect to baseline IOP

Subsequent lifelong follow-up is implemented as a Markov model. In a Markov model a set of independent states is defined and patients switch from one state to another at a regular interval (cycle) according to the transition probabilities. The following health states can be entered: 'glaucoma', 'blindness' and 'death'. Age and sex dependent survival probabilities, an IOP dependent (per mm Hg) glaucoma incidence rate, and a yearly probability of becoming blind from glaucoma are included. In the model sex has been distributed equally. Transitions to the health states can take place always at the end of a 6 months cycle. The choice of the cycle length reflects the common time between consecutive outpatient visits.

Analysis

The analyses were performed for an initial IOP sampled from the distribution and additionally for the fixed values of the initial IOP: 25 and 30 mm Hg. The following outcomes were determined: 1) drug distribution after 15 months after initiation of therapy 2) IOP distribution and mean IOP within the cohort after 15 months after initiation of therapy 3) blindness through glaucoma within a lifetime follow-up. A sensitivity analysis was conducted for the outcomes of mean IOP and blindness. For this purpose the parameters for contraindication to timolol, the occurrence of side-effects, and the IOP lowering effect of timolol and latanoprost were varied. Also analyses were conducted after an elimination of the IOP lowering effect of brimonidine, dorzolamide, and laser. In addition, for the outcome of blindness, a comparison was made with a simulated 'no-treatment' option.

Results

Drug use after 15 months after initiation of therapy

The drug distribution within the cohort after the therapy adjustment is given in Table 4. In both strategies approximately 90% of the simulated patients use monotherapy. In a cohort of patients with an initial IOP of 30 mm Hg this is about 60%. The proportion of patients using initially prescribed medication is different per strategy. In strategy 'start with timolol' 53% of patients use monotherapy timolol and 32% monotherapy latanoprost. It must be noted that in this strategy it is modeled that 20% of patients start therapy with latanoprost because of contraindication to timolol. Thus about 66% maintain the originally prescribed timolol. In strategy 'start with latanoprost' 77.1% maintains the prescribed monotherapy latanoprost. The proportion of patients receiving combination therapy and/or laser treatment is similar for both strategies, even in the cohort of patients with IOP of 30 mm Hg.

Table 4: Drug use 15 months after the initiation of OH therapy with timolol or with latanoprost, per strategy, for different values of the initial IOP

	Strategy 'start with timolol'			Strategy 'start with latanoprost'		
	IOP sample	IOP 25 mm Hg	IOP 30 mm Hg	IOP sample	IOP 25 mm Hg	IOP 30 mm Hg
Monotherapy						
timolol	53.0 %	55.8 %	28.8 %	8.0 %	10.2 %	7.6 %
latanoprost	32.0 %	35.8 %	23.8 %	77.1 %	81.8 %	47.5 %
brimonidine or dorzolamide	5.8 %	7.1 %	7.8 %	5.8 %	6.9 %	7.9 %
Combination of 2 drugs						
timolol+latanoprost	2.0 %	0.0 %	9.3 %	3.4 %	0.0 %	16.1 %
timolol+dorzolamide	1.5 %	0.0 %	7.3 %	-	-	-
dorzolamide+ brimonidine	0.4 %	0.0 %	1.7 %	0.4 %	0.0 %	1.6 %
timolol+(dorzolamide or brimonidine)	0.0 %	0.0 %	0.1 %	1.2 %	0.0 %	5.1 %
latanoprost+(dorzolamide or brimonidine)	3.0 %	0.0 %	12.8 %	1.4 %	0.0 %	6.6 %
Combination of 3 drugs						
various combinations of timolol, latanoprost, dorzolamide, brimonidine	1.2 %	0.0 %	4.3 %	1.2 %	0.0 %	4.1 %
Laser treatment	1.9 %	1.2 %	5.8 %	2.1 %	1.2 %	5.7 %

IOP after 15 months of treatment

In Figure 3, for the cohort with sampled IOP, an IOP distribution after therapy adjustment is given for both strategies. The patterns of distribution seem superimposable. Nevertheless, values of 19 mm Hg and higher are more frequent in strategy ‘start with timolol’, 30% against 27%, and complementary values of 18 mm Hg and lower are more frequent in strategy ‘start with latanoprost’, 73% against 70%. The mean IOP values are shown in Table 5. The initial IOP decreased with approximately 34% from 25.4 mm Hg (sampled mean) to 16.7 (± 0.017) mm Hg in strategy ‘start with timolol’ and to 16.5 (± 0.013) mm Hg in strategy ‘start with latanoprost’. In a cohort of patients with an initial IOP of 30 mm Hg the IOP decrease in both strategies was about 69%, to 17.5 mm Hg.

Figure 3: IOP distribution after 15 months of treatment per strategy, for a cohort with a sampled initial IOP

Years of blindness due to glaucoma

In Table 5 for each strategy the expected years of blindness due to glaucoma per patient are given. The computed time with blindness per patient is 0.0923 (33.7 days) years in strategy ‘start with timolol’ and 0.0870 (31.8 days) years in strategy ‘start with latanoprost’. This corresponds to approximately 1 month of blindness per patient, over a period of 18.7 years, which is the computed mean life expectancy in the cohort. The difference between the strategies is 2 days of blindness, a difference of about 6%. For reference, a ‘no treatment’ simulation (0% IOP reduction through medication and laser) shows 0.492 expected years of blindness per patient, which corresponds to approximately 6 months of blindness.

Sensitivity analysis

In a one-way sensitivity analysis the parameters for contraindication to timolol and occurrence of side-effects have been varied within the given ranges, as given in Table 3. This had however, minimal impact on the mean IOP or blindness (data not shown). In Table 5 other results of the sensitivity analysis are shown. The IOP lowering effects of timolol and latanoprost were varied within the range of a 95% confidence interval around the given value, in which the lower and upper bounds for both drugs represent about 2% more or less IOP reduction.⁴ A two-way sensitivity analysis with 2% less IOP reduction through timolol and 2% more IOP reduction through latanoprost shows a difference in blindness, which corresponds to 5 days per patient, in favor of strategy 'start with latanoprost'.

Table 5: Treatment effects of two different strategies for initiating OH therapy, (1) 'start with timolol' or (2) 'start with latanoprost', for different values of the initial IOP

	Initial IOP = sample		Initial IOP = 25 mm Hg		Initial IOP = 30 mm Hg	
	Strategy (1)	Strategy (2)	Strategy (1)	Strategy (2)	Strategy (1)	Strategy (2)
	(timolol)	(latanoprost)	(timolol)	(latanoprost)	(timolol)	(latanoprost)
IOP change through medication after 15 months of therapy (mm Hg)						
Basic analysis	16.66	16.52	16.88	16.74	17.49	17.49
	± 0.017*	± 0.013	± 0.016	± 0.014	± 0.008	± 0.011
Sensitivity analysis						
0% IOP reduction through laser	16.73	16.57	16.92	16.77	17.67	17.67
	± 0.005	± 0.016	± 0.020	± 0.018	± 0.014	± 0.010
0% IOP reduction through laser, dorzolamide en brimonidine	17.02	16.84	17.17	17.00	18.35	18.27
	± 0.014	± 0.024	± 0.019	± 0.019	± 0.014	± 0.018
2% less IOP reduction through timolol and 2% more IOP reduction through latanoprost	16.66	16.22	16.85	16.42	17.36	17.29
	± 0.019	± 0.022	± 0.011	± 0.011	± 0.008	± 0.001
Blindness through glaucoma [†] (years of blindness)						
Basic analysis	0.0923	0.0870	0.0977	0.0924	0.1175	0.1173
	± 0.0012	± 0.0010	± 0.0011	± 0.0011	± 0.0008	± 0.0012
Sensitivity analysis						
0% IOP reduction through all medication and laser (no treatment)	0.4924	0.4924	0.4555	0.4555	0.7741	0.7741
	± 0.0031	± 0.0031	± 0.0038	± 0.0038	± 0.0059	± 0.0059
0% IOP reduction through laser	0.0969	0.0923	0.1003	0.0953	0.1301	0.1299
	± 0.0013	± 0.0022	± 0.0007	± 0.0013	± 0.0013	± 0.0009
0% IOP reduction through laser, dorzolamide en brimonidine	0.1092	0.1040	0.1107	0.1047	0.1546	0.1535
	± 0.0021	± 0.0020	± 0.0004	± 0.0002	± 0.0023	± 0.0024
2% less IOP reduction through timolol and 2% more IOP reduction through latanoprost	0.0934	0.0807	0.0982	0.0854	0.1160	0.1130
	± 0.0015	± 0.0017	± 0.0007	± 0.0007	± 0.0012	± 0.0012

* standard deviation for the average, computed from 5 Monte Carlo simulations of size 20 000 each

[†] mean expected time spent in blindness per person within 18.7 years of life expectancy

Discussion

The difference in impact on IOP or blindness of the two analyzed treatment strategies was minimal. The model shows that from the clinical point of view it does not matter by which medication therapy should be initiated. Many OH patients can reach their target pressure with *any* first choice medication, whether timolol or latanoprost. For them, glaucoma development and blindness will be acceptably small; only slight differences will apply. For patients with a high initial IOP a similar situation arises, since treatment adjustments are also aimed to reach the target pressure. If the target pressure is achieved, clinical effects of the different strategies will again be very similar. Otherwise more therapy adjustments will occur to achieve a best possible treatment and the effect of the initial choice largely cancels out.

The choice for a simulation model requires some attention. The alternative of a clinical trial would inevitably be associated with large expenses, particularly due to a long follow-up. One of the advantages of modeling is the ability to predict events in the long-term. A simulation of a lifetime follow-up of a cohort of patients can be performed. Hence, in a short time period long-term results can be assessed. Another advantage is that different scenarios can be constructed by changing the influential factors. A model also allows a real life simulation, such as no treatment strategy, without placing patients at risk. Moreover, by applying a Monte Carlo simulation, which is run 100 000 times, a reliable estimate of the clinical result of a strategy given the underlying variation is obtained (see the calculated standard deviations given in Table 5).

The parameters used in the model are taken from different sources and do not represent an exact value. We have attempted to use the best available data from the literature. A range of values was tested to determine the robustness of the qualitative conclusions drawn from the analysis. The outcomes of the sensitivity analysis did not alter the conclusions of the study.

To validate the model a process known as “debugging” the tree was applied, to avoid modeling or programming errors.³⁶ Also, a comparison was made with clinical outcomes of OH treatment, as known from the literature. The design of the Ocular Hypertension Treatment Study (OHTS) corresponds well with the modelled therapy approach.³⁷ In the OHTS study therapy was initiated with a topical agent and medication was subsequently changed and/or added, if required, until the treatment goals were met or the participant was receiving the maximum tolerated topical medical therapy. In the OHTS study the baseline pressure was 24.9 ± 2.7 mm Hg. In the modelled cohort this was 25.4 ± 3.0 mm Hg. The model showed approximately 34% IOP reduction through medication. In the OHTS study the IOP reduction in the medication group was smaller, namely $22.5 \pm 9.9\%$. There are several explanations for this. Firstly, the treatment goals of the studies differ in the target pressure criterion, this being 24 mm Hg in the OHTS study and 21 mm Hg in the model. Secondly, in the OHTS study the average IOP across follow-up visits is

given, whereas the model outcomes show a mean IOP value after the therapy adjustments are completed. Thirdly, when treatment of the OHTS study participants started, the treatment choice was limited, as some of the hypotensive drugs, were not available yet.

In the model no difference is made between beginning and advanced glaucoma. The yearly estimate for blindness applies to all glaucoma patients. This might be slightly overestimated. The IOP reduction through various medications is taken from a meta analysis of randomized clinical trials.⁴ The age and IOP distributions within the cohort of initial OH patients were selected from the charts of 1 000 initial patients, consecutively visiting a regional non-referral ophthalmic practice in Maastricht (Medisch Centrum Maastricht Annadal - MCMA), starting from January 1999. The global characteristics of these distributions have been verified to be consistent with the literature.³⁸⁻⁴⁰

In summary, we believe that our model approaches the clinical practice closely, uses the optimal current data, and produces results that are reliable.

Conclusions

Concerning the clinical effects of the two strategies of initiating OH therapy with latanoprost or with timolol, the differences are quite small. This is largely caused by the key concept of a target pressure, which underlies both treatment strategies. As it turns out, this target pressure can be achieved fairly easily by both strategies for many patients.

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Latanoprost versus timolol as first choice
therapy in patients with ocular hypertension
A cost-effectiveness analysis

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Abstract

Objective: To determine the long term cost-effectiveness of treatment of ocular hypertension (OH) with latanoprost compared to timolol.

Design: A cost-effectiveness simulation model.

Methods: Two strategies are modelled. In strategy (1) therapy is started with timolol, in strategy (2) with latanoprost. By Monte Carlo simulation the IOP lowering effect of the specific drugs is applied to a hypothetical cohort of OH patients, characterized by an initial IOP distribution. Depending on the achieved IOP and occurrence of side effects the prescribed therapy can be maintained or changed, at most four times. In a short term decision analytic model the adjustment of therapy to reach the target pressure involves consecutively monotherapy, combination therapy, and laser. Switches to different types of monotherapy and combination therapy are included. Four drugs are used: latanoprost, timolol, brimonidine, and dorzolamide. After 15 months of therapy adjustments a lifelong follow-up with possible conversion to glaucoma and to blindness is modeled (Markov model). Conversion rates depend on the achieved IOP. The direct medical costs are assigned. The parameters in the model are based on the literature and on the data of 1 000 patients. The analyses were performed with a sampled initial IOP and with fixed values of 25 and 30 mm Hg.

Outcome measures: 1) mean IOP after 15 months of therapy 2) mean expected costs after 15 months of therapy 3) blindness through glaucoma within a lifetime follow-up 4) mean expected lifetime costs.

Results: The IOP decreased from 25.4 mm Hg (sampled mean) to 16.7 mm Hg in strategy (1) and to 16.5 mm Hg in strategy (2). In strategy (1) the mean expected time spent in blindness per patient within 18.7 years of life expectancy is 0.0334 years and the lifetime costs are € 3 514 and in strategy (2) 0.0318 years and € 4 397, respectively (4% discount used). The computed extra costs per year of vision saved for strategy (2) in comparison with strategy (1) amount to € 537 000. For patients with an initial IOP of 30 mm Hg this is € 7 068 000. These cost-effectiveness ratios are increasing with age, from € 222 632 for the 40-years old to € 1 057 025 for the 70-years old.

Conclusion: It is computed, with the current cost price of latanoprost, that for saving one year of vision about € 537 000 extra is needed when therapy in OH patients is initiated with this drug compared to initiation with timolol.

Introduction

The approach towards treatment of ocular hypertension (OH) and primary open-angle glaucoma (POAG) has changed in recent years. This is partly due to the introduction of new hypotensive agents, but also because of publication of the results of several randomized trials, which show the benefit of treatment in OH patients or in patients with early glaucoma.¹⁻³ Recent research in various European countries indicates an increased number of treated patients, more aggressive treatment, and a change in therapy prescription pattern.^{4,7} The rising costs in glaucoma treatment can only be justified if associated with an adequate reduction in visual disability. The aim of therapy is to reduce increased intraocular pressure (IOP), a major risk factor in the development of glaucoma, and so prevent future visual deterioration and thus blindness.

Nowadays, hypotensive lipids are becoming the most commonly prescribed class of glaucoma drugs.⁶ Of these, latanoprost reduces IOP most and is currently often used as the drug of first choice instead of the beta-blocker timolol. However, its hypotensive effect is only slightly better than that of timolol,⁸ whereas the costs are much higher. Considering the costs and effects of these agents one may question whether it is cost-effective to change the initiation of therapy with timolol to latanoprost in OH patients. In the clinical trials an evaluation of the effectiveness of a specific glaucoma drug is based on its IOP lowering effect as monotherapy. However, it is important to realize, that patient management in the clinical practice often involves therapy switches and even combined therapies, in order to reach a target pressure for each patient.

In the present study, two strategies of initiating therapy in patients with ocular hypertension, starting with latanoprost or starting with timolol are modelled and evaluated for effects and costs. The two strategies are modelled as in the ophthalmic practice, including therapy adjustments, to reach a target pressure. Considering that this is the aim of both treatment strategies, one may expect small difference in the achieved IOP reduction. Which strategy is more cost-effective, may thus depend on whether the achieved difference in IOP will translate, in the long-term, in a reduction of glaucoma development and blindness that will outweigh the cost expenditure for OH medication. This study is performed from the societal perspective.

Methods

General design

Two strategies for the initiation and adjustment of OH medication are modelled and compared. In a previous study we have already assessed the short and long-term clinical effects of these strategies. In the present study we have assigned direct medical costs of treatment and calculated the incremental costs and effects of the two strategies, according to the standards of a cost-effectiveness analysis.^{9,10} We use the same model as described earlier (paper submitted for publication).

In strategy (1) therapy is started with timolol and in strategy (2) with latanoprost. By using a Monte Carlo simulation the IOP lowering effect of the specific drugs is applied to a hypothetical cohort of OH patients. This cohort is characterized by the initial IOP and age distributions. First the adjustment of therapy is modelled. Patients start therapy with a topical agent and return for evaluation. In case of adverse events, or unsatisfactory IOP decrease, therapy is adjusted and a new evaluation follows. Therapy switches are modelled at most four times. Therapies involve different types of monotherapy, combination therapy, and laser. Four drugs are used, representing four major generic classes: timolol (beta-blockers), latanoprost (hypotensive lipids), brimonidine (α 2-adrenergic agonists), and dorzolamide (topical carbonic anhydrase inhibitors). The modelled IOP lowering effects are specific for each drug and for each drug combination. Effects correspond to timolol 0.5%, latanoprost 0.005%, dorzolamide 2%, brimonidine 0.2%. Contraindication to timolol is taken into account. Once the therapy adjustments are completed, which covers at most 15 months of therapy, the achieved new IOP distribution and the drug distribution within the cohort are determined per strategy. Subsequently by using a Markov model a lifelong follow-up and the disease progression over time are modelled. A conversion to glaucoma and to blindness can take place. Yearly conversion is dependent on the IOP achieved after 15 months of treatment. Per strategy the eventual years of blindness are determined. The time horizon of the model is based on the life expectancy of patients. The IOP reductions through therapy, side-effects and contraindication of medication, glaucoma incidence and blindness development are based on the literature. The age and initial IOP distributions are based on the data of 1 000 ophthalmic patients. Glaucoma specialists were consulted to decide which medication should be used in case of a therapy switch.

The hypothetical cohort consists of initial OH patients (without glaucomatous changes of the optic nerve head or visual field loss) of at least 40 years old. Mean age is 64.5 years. Initial IOP within this population includes values from 22 to 35 mm Hg. Mean initial IOP value is 25.4 mm Hg.

The therapy adjustments (decision model)

Therapy adjustment is modelled within the structure of a decision tree. The output of this decision model forms the input for the Markov model, which covers the lifelong follow-up. A simplified impression of the models is given in Figure 1. Two treatment strategies are set up as follows. In strategy 'start with timolol' patients start therapy with timolol unless contraindicated, in which case latanoprost is used. In strategy 'start with latanoprost' all patients start therapy with latanoprost. Both latanoprost and timolol are used in each strategy. A switch from latanoprost to timolol and vice versa is possible. In case of a therapy switch first latanoprost and timolol are used, followed by brimonidine, and dorzolamide. Laser treatment follows only if there are no more treatment options through medication. Contraindication to timolol is taken into account at all places in the model where this drug is applied. The corresponding proportion of patients with contraindication receives different medication.

Every three months after a prescription of a medication an evaluation is modelled to take place. For each simulated patient a new IOP, achieved by the IOP lowering effect of the prescribed drug, and an occurrence of side effects are modelled probabilistically. A patient then either maintains the prescribed medication, or a therapy change follows with a subsequent new evaluation. Criteria for treatment adjustments are as follows. 1) If serious side effects occur, the drug is replaced with another one, regardless of the achieved IOP level. 2) In the absence of side effects the treatment assignment depends on the achieved IOP level as follows: a) If the achieved IOP is less than or equal to 21 mm Hg, medication is not changed. b) If the achieved IOP is higher than 21 mm Hg and the IOP reduction is more than 20% of the original IOP level another drug is added. c) If the achieved IOP is higher than 21 mm Hg and the IOP reduction is less than 20% of the original IOP level, the currently used medication is substituted by another one. Laser treatment is assigned in the same way as a new drug, as an addition to the medication or as a replacement of it. Occurrence of side effects is independent of age or IOP.

The lifelong follow-up (Markov model)

The lifelong follow-up is implemented within the structure of a Markov model. In a Markov model a set of independent states is defined and patients switch from one state to another at a regular interval (cycle) according to the transition probabilities. For all possible outcomes of medication assignment health states are defined, which can be entered. This takes place after the therapy adjustments are finished. At the end of the first 15 months period each simulated patient has his specific IOP achieved through therapy and a specific medication prescription. The initial health states are entered according to this specific medication. Subsequently during the follow-up the following health states can be entered: 'death', 'glaucoma', and 'blindness'. Age and sex dependent survival probabilities, an IOP dependent (per mm Hg) glaucoma incidence rate, and a yearly probability of becoming blind from glaucoma are included. In the model sex has been distributed equally. Transitions to the health states can take place always at the end of a 6 months cycle. The cycle length reflects the common time between consecutive outpatient visits.

Figure 1: Visual representation of the therapy adjustments applied during the first 15 months of treatment (decision model) and the subsequent lifelong follow-up (Markov model)

* if target IOP reached or if all 4 steps have been evaluated, then continuation therapy

[†] with respect to baseline IOP

The shown scheme is a simplified reproduction of the model. In the Markov model there are more health states than shown in the figure. A distinction is namely made between different types of monotherapy or combination therapy. There is a health state defined for each specific type of a drug (latanoprost, timolol, brimonidine, dorzolamide) and the possible combinations of these. In the graphical scheme of the Markov model 'X' represents health state 'dead'.

Cost assignment

The health care costs are assigned as once-only costs and state dependent costs. The once-only costs are the costs of outpatient visits, medication and laser therapy, related to the first 15 months of treatment. For each simulated patient these costs are added up. The state dependent costs are the costs related to OH and POAG treatment during life time follow-up in the Markov model. These costs are assigned to the health states and reflect the treatment requirements related to 6 months of treatment of a particular state. For each OH patient the costs involve the costs of outpatient visits and the specific costs of the prescribed medication. Once a conversion to POAG takes place, then POAG costs are assigned. These are the same for all patients and represent the average costs of a glaucoma patient in the Netherlands, including the costs of outpatient visits, perimetry, laser trabeculoplasty, surgery, and medication.

Model input

Input data and their sources are shown in Tables 1-4 and Figure 2. The age and IOP distribution for the population have been determined from the charts of 1 000 initial patients, consecutively visiting a general ophthalmic practice in Maastricht (Medisch Centrum Maastricht Annadal - MCMA), starting from January 1999. The prices of medical drugs represent the prices in the Netherlands (incl. VAT). The unit prices related to outpatient visits and laser trabeculoplasty are as determined at the University Hospital Maastricht. This was done according to the micro costing method.⁹ The average treatment costs of a POAG patient were taken from a previous study of the authors (Eye advance online publication, 24 November 2006; doi:10.1038/sj.eye.6702637). The frequency of the health care use is modeled in accordance with the specialists' opinion and the recommendations of the American Academy of Ophthalmology.¹¹ The survival probabilities are taken from data provided by the Dutch Central Bureau for Statistics (CBS).¹² Conversion to blindness is based on an assumption that 1% of glaucoma patients per year become blind.^{13,14}

Figure 2: The IOP dependent yearly incidence of POAG in OH patients under treatment^{1,2,45-54}

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Table 1: Initial IOP of the simulated cohort³⁰

IOP (mm Hg)	Proportion
22	0.17
23	0.16
24	0.15
25	0.13
26	0.11
27	0.08
28	0.05
29	0.04
30	0.03
31	0.02
32	0.02
33	0.02
34	0.01
35	0.01

Table 2: IOP reduction by therapy used in the simulation model^{8,31-35}

Intervention	IOP reduction (%) (mean $\pm$ SD)
Timolol (0.5%)	26.5 $\pm$ 14
Latanoprost (0.005%)	29.5 $\pm$ 13.4
Dorzolamide (2%)	19.5 $\pm$ 13.5
Brimonidine (0.2%)	21 $\pm$ 13.1
Timolol + latanoprost (add on)	20.5 $\pm$ 13.9
Timolol + dorzolamide (add on)	18 $\pm$ 12
1 drug + 1 drug or laser (add on)	18 $\pm$ 12
2 drugs + 1 drug or laser (add on)	10 $\pm$ 5
3 drugs + laser (add on)	8 $\pm$ 4
Laser	30 $\pm$ 12

Table 3: Parameters used in the simulation model^{23,36-43}

Parameter	Proportion (lower bound)	Proportion (baseline)	Proportion (upper bound)
Contraindication timolol	0.1	0.2	0.3
Side effect* timolol	0.05	0.1	0.3
Side effect* latanoprost	0.01	0.03	0.1
Side effect* dorzolamide	0.05	0.15	0.25
Side effect* brimonidine	0.05	0.15	0.25

* any side effects of medication that cause a therapy change

Table 4: The cost prices of medication and the health care unit prices (2001)⁴⁴

	Cost price
Timolol (0.5%)	5.10 € / month
Latanoprost (0.005%)	18.67 € / month
Dorzolamide (2%)	12.86 € / month
Brimonidine (0.2%)	14.32 € / month
Timolol + latanoprost (add on)	22.79 € / month
Timolol + dorzolamide (add on)	17.59 € / month
Outpatient visit (15 min)	27.57 €
Outpatient visit (10 min)	23.85 €
Perimetry	80.93 €
Laser	279.42 €
Transportation (per visit)	2.9 €
Glaucoma therapy*	450 € / year

* average costs of a glaucoma patient including outpatient visits, medication, perimetry, laser, and surgery

Analysis

A Monte Carlo simulation was used to sample from the age, sex, and initial IOP distributions within the cohort, and the distributions of IOP reduction through specific medication and/or laser. The analyses were performed for an initial IOP sampled from the distribution and additionally for the fixed values of the initial IOP: 25 and 30 mm Hg. The following outcomes were determined per strategy: 1) mean IOP within the cohort after 15 months after initiation of therapy 2) mean expected costs after 15 months of therapy 3) blindness through glaucoma within the lifetime follow-up 4) mean expected lifetime costs. The analysis was performed with a discount rate of 4%, for both costs and effects, and without a discount. A subgroup and sensitivity analyses were performed for the fixed values of the initial IOP: 25 and 30 mm Hg, with a 4% discount rate. In a subgroup analysis the expected costs and years of blindness per strategy were determined apart for patients aged 40, 50, 60 and 70 years. In a one-way sensitivity analysis the contraindication for timolol, the side effects of medication, the cost of glaucoma therapy and the cost price of latanoprost have been varied. A two-way sensitivity analysis was carried out for the IOP lowering effect of timolol and latanoprost.

Results

Outcomes after 15 months of treatment: IOP and expected costs

The initial IOP decreased with approximately 34% from 25.4 mm Hg (sampled mean) to 16.7 (± 0.017) mm Hg in strategy ‘start with timolol’ and to 16.5 (± 0.013) mm Hg in strategy ‘start with latanoprost’. For patients with a fixed initial IOP of 30 mm Hg the IOP decrease was about 69%, in both strategies to about 17.5 mm Hg. The calculated costs per patient 15 months after initiation of therapy were € 367 (± 0.66) in strategy ‘start with timolol’ and € 469 (± 0.39) in strategy ‘start with latanoprost’. For patients with an initial IOP of 30 mm Hg these costs were € 441 (± 0.33) and € 496 (± 0.53), respectively.

Outcomes within a lifetime follow-up: blindness due to glaucoma and expected costs

In Table 5 for each strategy years of blindness due to glaucoma and expected lifetime costs per patient are given. The computed time with blindness per patient is 0.0923 (33.7 days) years in strategy ‘start with timolol’ and 0.0870 (31.8 days) years in strategy ‘start with latanoprost’ (without discount). This corresponds to approximately 1 month of blindness per patient, over a period of 18.7 years, which is the computed mean life expectancy in the cohort. The difference between the strategies is 2 days of blindness, a difference of about 6%, in favor of strategy ‘start with latanoprost’. For reference, a ‘no treatment’ simulation (0% IOP reduction through medication and laser) showed 0.492 expected years of blindness per patient, which corresponds to approximately 6 months.

Table 5: Results of the cost-effectiveness analysis of two different strategies for initiating treatment of ocular hypertension (analyses with sampled and fixed values of the initial IOP)

	Strategy ‘start with timolol’	Strategy ‘start with latanoprost’
4% discount (costs and effects)		
Initial IOP sampled		
costs (€)	3 514 ± 13.670***	4 397 ± 15.014
years of blindness*	0.0334 ± 0.0004	0.0318 ± 0.0004
incremental C/E**	-	536 852
Initial IOP = 25 mm Hg		
costs (€)	3 396 ± 4.056	4 304 ± 4.378
years of blindness	0.0361 ± 0.0004	0.0344 ± 0.0003
incremental C/E	-	547 276
Initial IOP = 30 mm Hg		
costs (€)	4 215 ± 6.394	4 583 ± 10.708
years of blindness	0.04301 ± 0.0002	0.04296 ± 0.0004
incremental C/E	-	7 068 037
0% discount (costs and effects)		
Initial IOP sampled		
costs (€)	5 456 ± 23.929	6 794 ± 27.790
years of blindness	0.0923 ± 0.0012	0.0870 ± 0.0010
incremental C/E	-	253 011
Initial IOP = 25 mm Hg		
costs (€)	5 269 ± 18.760	6 628 ± 17.188
years of blindness	0.0977 ± 0.0011	0.0924 ± 0.0011
incremental C/E	-	254 150
Initial IOP = 30 mm Hg		
costs (€)	6 556 ± 18.142	7 099 ± 13.767
years of blindness	0.1175 ± 0.0008	0.1173 ± 0.0012
incremental C/E	-	2 009 703

The values represent the expected lifetime costs and effects for a treated OH patient (an average computed from 5 Monte Carlo simulations of size 20 000 each); * mean expected time spent in blindness per person within 18.7 years of life expectancy; ** the incremental cost-effectiveness ratio shows extra costs per year of vision saved when starting therapy with latanoprost compared to starting with timolol; *** standard deviation for the average, computed from 5 Monte Carlo simulations of size 20 000 each

The calculated expected lifetime costs include the costs of the first 15 months of therapy as well. The lifetime costs are lower for strategy ‘start with timolol’ than for strategy ‘start with latanoprost’, namely € 5 456 against € 6 794 (€ 3 514 against

€ 4 397 discounted). For patients with an initial IOP of 30 mm Hg the difference in costs is smaller, namely € 6 556 against € 7 099 (€ 4 215 against € 4 583 discounted). The outcomes of the subgroup analysis are given in Table 6. The difference in costs and effects between the strategies becomes smaller with an increasing age.

Sensitivity analyses

The outcomes of the sensitivity analyses are partially shown in Table 6. The variation of the transition probabilities of contraindication for timolol and side effects of medication within the given ranges (see Table 3) had hardly any influence on the outcomes (data not shown). Lowering the costs of glaucoma therapy from € 450/year to € 350/year, or increasing it to € 600/year, gives only a slight decrease or increase of the lifetime costs in both strategies, about 0.8-1.5%. Analyses with a reduced price of latanoprost, from € 18.7/month to € 10/month and € 6/month, show a marked reduction and vanishing of the cost difference between the strategies. With a reduced price of latanoprost, for patients with an initial IOP of 30 mm Hg, in strategy 'start with latanoprost' the lifetime costs are lower than in strategy 'start with timolol'. The IOP lowering effects of timolol and latanoprost were varied within the range of a 95% confidence interval around the given value, in which the lower and upper bounds for both drugs represent about 2% more or less IOP reduction.⁸ A two-way sensitivity analysis with 2% more IOP reduction through latanoprost and 2% less IOP reduction through timolol shows better blindness prevention for a cohort with an initial IOP 25 mm Hg in strategy 'start with latanoprost', and with an initial IOP 30 mm Hg in both strategies.

Cost-effectiveness

According to the simulations strategy 'start with timolol' is cheaper than strategy 'start with latanoprost' but yields more years of blindness. In tables 5 and 6 the incremental cost-effectiveness ratios are given. These are calculated as a ratio between the difference in costs and the difference in effects between the two strategies and represent extra costs per year of vision saved when initiating therapy with latanoprost compared to initiating with timolol. If therapy is initiated with latanoprost the computed extra costs per year of vision saved in comparison to initiation with timolol amount to € 537 000. An analysis with a fixed initial IOP of 30 mm Hg shows a reduced difference in costs and almost no difference in blindness between the two strategies. For such patients extra costs per year of vision saved become much higher and amount to € 7 068 000.

The subgroup analyses per 10-years age categories show that extra costs per year of vision saved when initiating therapy with latanoprost compared to timolol, are increasing with age, from € 222 632 for the 40-years old to € 1 057 025 for the 70-years old. When the price of latanoprost is reduced, the cost-effectiveness ratio becomes smaller and drops even to € 44 095, if the price is € 6/month. For patients with a fixed IOP of 30 mm Hg strategy 'start with latanoprost' then becomes cost saving.

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Table 6: Results of the subgroup and sensitivity analyses

	Initial IOP = 25 mm Hg		Initial IOP = 30 mm Hg	
4% discount (costs and effects)	Strategy 'start with timolol'	Strategy 'start with latanoprost'	Strategy 'start with timolol'	Strategy 'start with latanoprost'
A. Subgroup analysis				
Age: 40 years				
costs (€)	5 414 ± 1.364***	6 797 ± 2.222	6 712 ± 7.813	7 261 ± 7.620
years of blindness*	0.1218 ± 0.0006	0.1156 ± 0.0007	0.1453 ± 0.0004	0.1447 ± 0.0003
incremental C/E**	-	222 632	-	912 363
Age: 50 years				
costs (€)	4 716 ± 2.157	5 942 ± 4.177	5 866 ± 9.311	6 356 ± 14.177
years of blindness	0.0749 ± 0.0005	0.0712 ± 0.0004	0.0892 ± 0.0002	0.0893 ± 0.0004
incremental C/E	-	334 809	-	- 8 786 078****
Age: 60 years				
costs (€)	3 848 ± 5.543	4 874 ± 4.547	4 804 ± 9.425	5 219 ± 5.903
years of blindness	0.0380 ± 0.0002	0.0361 ± 0.0003	0.0454 ± 0.0003	0.0452 ± 0.0003
incremental C/E	-	552 352	-	3 320 995
Age: 70 years				
costs (€)	2 885 ± 4.400	3 668 ± 1.688	3 607 ± 5.437	3 929 ± 1.861
years of blindness	0.0145 ± 0.0001	0.0138 ± 0.0001	0.0175 ± 0.0001	0.0175 ± 0.0000
incremental C/E	-	1 057 025	-	18 182 688
B. Sensitivity analysis				
Cost glaucoma therapy				
350 € / year				
costs (€)	3 347 ± 8.779	4 253 ± 7.471	4165 ± 5.290	4530 ± 9.849
years of blindness	0.0361 ± 0.0002	0.0343 ± 0.0003	0.0428 ± 0.0006	0.0427 ± 0.0005
incremental C/E	-	506 138	-	3 453 151
Cost glaucoma therapy				
600 € / year				
costs (€)	3 446 ± 10.226	4 340 ± 8.563	4303 ± 2.503	4671 ± 8.284
years of blindness	0.0353 ± 0.0003	0.0336 ± 0.0002	0.0429 ± 0.0002	0.0429 ± 0.0002
incremental C/E	-	528 171	-	5 226 625
Cost latanoprost 0.005%				
10 € / month				
costs (€)	2 964 ± 9.027	3 326 ± 11.926	3 666 ± 6.358	3 756 ± 6.301
years of blindness	0.0360 ± 0.0003	0.0339 ± 0.0004	0.0425 ± 0.0001	0.0425 ± 0.0001
incremental C/E	-	174 394	-	-2 271 388****
Cost latanoprost 0.005%				
6 € / month				
costs (€)	2 751 ± 5.945	2 828 ± 5.806	3 368 ± 3.385	3 307 ± 4.260
years of blindness	0.0359 ± 0.0003	0.0341 ± 0.0003	0.0428 ± 0.0003	0.0426 ± 0.0002
incremental C/E	-	44 095	-	- 324 031*****
IOP reduction: timolol 2% less				
and latanoprost 2% more				
costs (€)	3 467 ± 7.314	4 344 ± 13.292	4 324 ± 12.942	4 626 ± 9.037
years of blindness	0.0360 ± 0.0003	0.0313 ± 0.0002	0.0423 ± 0.0003	0.0414 ± 0.0002
incremental C/E		186 068	-	317 103

The values represent the expected lifetime costs and effects for a treated OH patient (an average computed from 5 Monte Carlo simulations of size 20 000 each).

* mean expected time spent in blindness per person within 18.7 years of life expectancy

** incremental cost-effectiveness ratio shows extra costs per year of vision saved when starting therapy with latanoprost compared to starting with timolol

*** standard deviation for the average, computed from 5 Monte Carlo simulations of size 20 000 each

**** higher costs, less effect in strategy 'start with latanoprost'

***** lower costs, more effect in strategy 'start with latanoprost'

Discussion

The results of the modeling study show that initiating therapy in OH patients with latanoprost brings along extremely high incremental costs, € 537 000 extra for saving one year of vision when compared to initiating therapy with timolol. If treatment with latanoprost only and timolol only would be compared, there would undoubtedly be a significant difference in treatment effects between those two drugs. However, a comparison of clinically based strategies, where different first therapy choice is followed by similar steps for therapy adjustments to achieve a target pressure, shows minimal difference in the achieved IOP and blindness through glaucoma between the two analyzed strategies. The computed cost difference on the other hand, is large. As the IOP reduction is similar in both strategies, with a consequence that only slight differences occur in glaucoma development and blindness, the corresponding glaucoma costs will be comparable in both strategies as well. The different OH therapy costs are thus responsible for the main cost difference, as confirmed by the results of the sensitivity analysis.

Many OH patients can reach their target pressure with timolol as well as with latanoprost. Patients whose target pressure cannot be easily reached and controlled with monotherapy need more therapy adjustments including combination therapy or laser treatment. This is however, the case in both strategies and the costs for these patients will thus be comparable. Long-term use of monotherapy with latanoprost is a largest contributor to the higher cost expenditure in the strategy 'start with latanoprost'. When starting therapy with latanoprost, the less expensive, but fairly enough sufficient, alternative for patients who can easily reach a target pressure with both drugs is not considered. This is the underlying reason why the strategy 'start with latanoprost' is not preferable from the cost-effectiveness point of view, in comparison to the strategy 'start with timolol'. The modelled simulations show that even for young OH patients, who have a longest life expectancy and thus most time to develop glaucoma and blindness, it is not cost-effective to initiate therapy with latanoprost.

A simulation model was used to analyze the two treatment strategies. Since we were able to incorporate data of recent, adequately performed, randomized clinical trials we believe that the results of our modelled strategies validly represent the current practice. Moreover, the long-term effects of the strategies could be assessed in a short time period. Another advantage of modeling is the evaluation of different modifications of the strategies as well, by changing the key parameters in the

model. By applying a Monte Carlo simulation, which is run 100 000 times, a reliable estimate of the clinical result of a strategy given the underlying variation is obtained (see the calculated standard deviations given in Tables 5 and 6). Extensive sensitivity analyses were performed to establish the impact of a variation of the uncertain values in the model on the outcomes and the study conclusions. It showed that these conclusions were robust. Only a reduction of the cost of latanoprost leads to a favorable cost-effectiveness ratio for the strategy ‘start with latanoprost’.

To avoid modeling or programming errors a process known as ‘debugging’ the tree was applied.¹⁵ Further, a comparison was made with the facts known from the literature. The model showed approximately 34% IOP reduction through medication and laser. In the Ocular Hypertension Treatment Study (OHTS), the design of which corresponds well with the modelled therapy approach, this was $22.5 \pm 9.9\%$. However, the target pressure criterion differs, this being 24 mm Hg in the OHTS study and 21 mm Hg in the model. Laser treatment was not applied in the OHTS study participants. Further in the OHTS study the average IOP across follow-up visits is given, whereas the model gives a mean IOP value after the therapy adjustments. Lastly, the treatment choice was limited, when the OHTS study participants started their therapy. The yearly estimate for blindness might be slightly overestimated in the model, because no difference is made between beginning and advanced glaucoma. The age and IOP distributions of the population are verified to be consistent with the literature.^{16,17,18} IOP values above 35 mm Hg were not addressed in the model, because such values are very likely to be already associated with glaucoma. The IOP reduction through specific medication is based on the best current data, namely on a meta-analysis of randomized controlled trials.⁸

There have been some studies published, addressing the cost-effectiveness of various treatments with glaucoma drugs.^{19,20} However, no sensible comparison of our results with these studies can be made, because they include treatment of glaucoma and ocular hypertension. The drug persistency in glaucoma treatment is different than in ocular hypertension. Moreover, these studies use IOP as an outcome measure. In one epidemiological study, by using a questionnaire in 1513 patients, a drug use in ocular hypertension in Belgium was established.²¹ This was done in 1992 and 96% of patients were using a topical beta-blocker, many other types of ocular hypotensive drugs were not available yet. A median value of five years showed that in 77% the drug therapy involved only one drug. In the model about 66% of patients maintain the originally prescribed timolol after 15 months of treatment. Another cross-sectional study in France, with retrospective data collection for the preceding 5 years, found that 82.6% of patients with ocular hypertension were using monotherapy medication.²² The majority of patients were using a beta-blocker. In the model approximately 90% of patients uses monotherapy medication. In the same study the annual treatment costs for OH patients were € 275, € 376 and € 476 for patients with 0, 1, and 2 treatment changes. In the model the mean costs calculated for 12 months of treatment were approximately € 295 for strategy ‘start with timolol’ and € 375 for strategy ‘start with latanoprost’. The proportion of patients with no treatment change in the model was 68% in strategy

‘start with timolol’ and 77.1% in strategy ‘start with latanoprost’. The average treatment costs of a POAG patient used in the model match with the outcomes of other glaucoma cost studies.²³⁻²⁹ The costs due to blindness in connection with the usage of disability facilities in the Netherlands could not be retrieved. Even if these costs would be added, this should not influence the outcome of the study, because there is almost no difference in blindness between the two analyzed strategies. In the model a 4% discount is rate used, while internationally a 3% rate is recommended.⁹ This was done due to the guidelines in the Netherlands, however, if 3% is used no substantial changes occur (data not shown). No utility analysis has been performed. The main purpose of the study was to assess and compare the impact of two different approaches of starting medication in OH patients. In summary we believe that the results of our modeling study can be regarded as reliable, since our model approaches clinical practice closely, we used recent estimates of treatment efficacy, and the intermediate results are in general consistent with existing reports.

Conclusions

Initiating therapy in OH patients with latanoprost brings along extremely high incremental costs to prevent blindness when compared to initiating therapy with timolol. Given the current cost price of latanoprost, saving one year of vision would incur € 537 000 of expenditures. These incremental costs are even higher for patients with a high initial IOP and are increasing with age.

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7.

General discussion

In this thesis the clinical effects and cost-effectiveness of early detection and treatment of ocular hypertension (OH) and primary open-angle glaucoma (POAG) are studied. The main questions investigated are closely linked to clinical practice and are the following. (1) Should patients with OH or early POAG be treated? (2) Is early detection and treatment of OH and POAG by an ophthalmologist beneficial for the prevention of blindness? (3) Which case-finding strategy applied in the ophthalmic practice is the most cost-effective? (4) What is the clinical impact of initiation of OH treatment with a new type of glaucoma medication in comparison with the medication used so far? (5) Is such a strategy of initiating OH treatment with a new type of medication cost-effective in comparison with the existing strategy?

In studying cost-effectiveness it is difficult to take all the costs and effects properly into account because glaucoma is an irreversible slowly progressive disease and a long-term follow-up is required. In view of the absence of long-term empirical data, meta-analysis and simulation models have been used to acquire insight in these issues. Two outcome measures are of most interest for clinical practice: (1) the conversion from OH (i.e. an increased intraocular pressure (IOP) in the absence of structural and functional damage) to POAG, and (2) the eventual progression of POAG to blindness. Costs are associated with medical diagnosis and treatment on one side, and with blindness related impairment on the other side.

Figure 1. Framework for the illustration of the glaucoma related research in this thesis

In Figure 1 a framework is presented which illustrates the research in the various chapters of this thesis, and clarifies their interrelationships. Currently, treatment of glaucoma is aimed at its main risk factor: an increased intraocular pressure. The IOP plays a key role in its diagnosis and detection on the one hand, whereas lower-

ing of the IOP is the only effective treatment at present on the other hand. Future developments, for instance in the area of neuroprotection, may lead to different treatment strategies.

The effectiveness of OH treatment

For many decades now, lowering of the IOP is the cornerstone of glaucoma treatment. Even though it is widely recognized that an elevated IOP contributes to glaucomatous optic neuropathy, there is great inter-individual variation in the susceptibility of the optic nerve to IOP-related damage.¹ The Baltimore Eye Survey, which is a population-based study, indicates that only one-tenth or less of patients with an elevated IOP have glaucomatous field loss.² Whether the IOP should be lowered in patients with ocular hypertension has repeatedly been a subject of discussion among ophthalmologists. The study described in Chapter 2 in this thesis has started in 2001. At that time, only the results of a few randomized trials were available which included OH patients. These studies were small in size and gave no conclusive scientific evidence on the effect of OH treatment. A major step forward has been the publication of the results of the Ocular Hypertension Treatment Study in 2002.³ There it was shown that topical ocular hypotensive medication is effective in delaying or preventing the onset of POAG in individuals with an elevated IOP.³ In 2005 the results of another major study, the European Glaucoma Prevention Study, became available.⁴ This study has also shown a protective effect of OH treatment although it failed to confirm this at a statistically significant level.

In this thesis, a *quantification* of the effect of IOP reduction in OH patients on the occurrence of glaucoma is given in Chapter 2, in which the results of a meta-analysis of OH trials are described. An advantage of this meta-analytical approach is that by combining data of several comparable studies, the results of a large number of patients can be included, and relatively small effects can be detected or excluded with confidence.⁵ The pooled relative risk, expressing the protective effect of IOP lowering therapy on the conversion of OH to POAG, is estimated as 0.61 (95% confidence interval 0.45 to 0.83). Additional regression analysis shows that a larger medically achieved decrease in IOP is associated with a larger reduction of the risk of conversion from OH to glaucoma. By using a meta-regression model it is estimated that the relative risk of conversion to glaucoma decreases by 14% with each mm Hg of IOP reduction.

The OH trials included in the meta-analysis all have a limited follow-up, with a maximum of 6 years. Therefore, these trials cannot directly be used to assess the impact of OH treatment on the prevention of glaucoma blindness. Clearly, time aspects need to be addressed when studying such long-term effects of treatment. Ocular hypertension is rare under the age of 40 and glaucoma mostly affects elderly people. Also, it is a slowly progressive disease, so many patients will not live long enough to reach the end stage and become blind. To properly take such time related

issues into account, it is necessary to consider age and corresponding mortality rates, which change over time and are gender dependent.

In the absence of empirical data, the simulation model presented in Chapters 5 and 6 allows one to investigate time related issues as mentioned above. In this model the simulated cohort is based on the demographic characteristics of initial patients visiting an ophthalmic practice. Two strategies are modelled for initiating OH treatment with two different types of medication; the outcome measure is glaucoma blindness. For both treatment strategies, the expected time of blindness per patient is found to correspond with approximately 1 month over a period of 18.7 years, which is the mean life expectancy in the cohort. In a simulation where patients were only treated after conversion to glaucoma, the expected time of blindness per patient corresponds to approximately 6 months. These results indicate that OH treatment is beneficial for the prevention of glaucoma blindness in a population where age distribution resembles that of patients visiting an ophthalmic practice.

Currently, therapy for OH patients is mostly recommended when IOP is above 29 mm Hg or when IOP exceeds 21 mm Hg in the presence of other risk factors for POAG.⁶ However, most patients enrolled in the OH trials included in the meta-analysis had an initial IOP between 24 mm Hg and 32 mm Hg and only some had additional risk factors. This implies that future research may be conducted on this topic. Also, for *elder* patients it may well turn out that the adverse effects of treatment counterbalance the expected gain in blindness prevention, so that age dependent treatment strategies may be developed.

Cost-effectiveness of early detection and treatment of OH and POAG

A cost-effectiveness analysis is a form of economic evaluation where both the costs and the consequences of health programmes or treatments are examined.⁷ As a consequence of changes in knowledge, facilities, equipment and costs over time, the existing programmes may once in a while need to be re-evaluated, and new strategies may be developed and compared with existing ones.

Within health care an identification and a comparison of strategies for detection and/or treatment are of interest. In the past, medical treatment options in glaucoma management were limited. The economic evaluations were generally focused on the efficacy of different diagnostic tools for OH and POAG detection⁸ and on the evaluation of different screening strategies in the general population.^{9,10} The feasibility and efficacy of a screening program is still an issue of ongoing debate and screening in the general population is not recommended at present.¹¹ However, in the last decades many new developments in the field of glaucoma took place, including new technologies that permit earlier detection of glaucomatous structural and functional damage, and new hypotensive treatments, which allow for safer and more effective IOP reduction. In a number of well-conducted clinical trials the effectiveness of treatment has been investigated and target pressures are now play-

ing a key part in modern therapy strategies. However, new technologies and strategies also bring along higher costs and the economic evaluation has shifted towards the cost-effectiveness of treatment.

Treatment nowadays has become more complex through the availability of a broad spectrum of hypotensive agents, and different combinations of these. These drugs differ in their IOP lowering effects, topical and systemic side-effects, and costs. New diagnostic technologies allow for a better distinction of various stages of glaucoma progression. This is favourable for early detection of OH and POAG and also for a set up of more sophisticated treatment strategies. Also utility scores may be measured and defined for different degrees of vision loss. By adjusting life expectancy with the utility scores, quality-adjusted life years (QALYs) can be calculated, which has become an increasingly popular outcome measure for resource allocation.¹² However, utility scores do carry an element of subjectivity and are not easy to assess consistently, and the impact of the loss of vision of one eye is largely influenced by the remaining functionality of the other eye. In the recently published cost-utility analysis of the Ocular Hypertension Treatment Study,¹³ the impact of OH treatment is evaluated in terms of QALYs for a simulated cohort of patients with an initial IOP of ≥ 24 mm Hg. In the present thesis we have instead considered years of blindness as the main outcome measure.

In Chapters 4 and 6, two cost-effectiveness evaluations are presented: an evaluation of different case-finding strategies to detect OH and POAG by an ophthalmologist, and an evaluation of different strategies for the initiation of OH treatment. Both models include treatment of OH and POAG, and the main outcome measure is blindness due to glaucoma. In the model in which the case-finding strategies are simulated, an interaction of both *detection and treatment* is taken into account. In the other presented model, initiation of OH treatment followed by *therapy adjustments* based on clinical practice is simulated. This differs from other evaluations of the new generation of hypotensive drugs which mostly involve a head-to-head comparison of two different agents.^{14,15}

As already mentioned above, screening for glaucoma in the general population is not recommended at present. In 1968 Wilson and Jungner proposed criteria for new screening programs, adopted by the World Health Organization, which should be fulfilled before their introduction in practice.¹⁶ The most important criteria are the following. (1) The condition sought should be an important health problem for the individual and community. (2) The natural history of the disease should be adequately understood. (3) There should be an early pre-clinical phase during which the individuals with the disease can be identified. (4) There should be appropriate, acceptable, and reasonably accurate screening tests. (5) There should be an agreed policy on whom to treat as patients. (6) There should be an accepted and effective treatment which should be more effective in preventing morbidity when initiated early. (7) The costs of case finding should be economically balanced in relation to possible expenditure on medical care as a whole. Glaucoma meets many of these criteria, but not completely. Criteria 1, 3 and 4 are fulfilled, even though the screen-

ing tests are amenable to further improvement. Criteria 2, 5, 6 and 7 are partially fulfilled and subject of ongoing discussion.

The outcomes of Chapter 4 express the consequences of ophthalmic care versus no care, dependent on the yield of case-finding in the ophthalmic practice. The most preferable strategy for glaucoma-related blindness prevention is to perform tonometry to all initial ophthalmic patients. When costs associated with the use of disability facilities due to blindness exceed € 1 707 per patient per year, which is most likely, this strategy not only is effective in blindness prevention but in fact becomes cost saving. This outcome is consistent with the findings of the performed systematic review in Chapter 2 and the case-referent study described in Chapter 3, which indicate that early treatment of OH and POAG is effective in preventing blindness due to glaucoma.

In addition, it can be noted that there are several other factors than IOP (e.g., blood supply to the optic nerve, substances toxic to the optic nerve or retina, axonal or ganglion cell metabolism, and the lamina cribrosa extracellular matrix), that may play a role in the progressive optic neuropathy of POAG.¹ If one were able to identify subgroups of patients who are more susceptible to high intraocular pressure than others, treatment strategies could be applied which take this into account. This would positively influence the cost-effectiveness of the chosen strategies through an improved balancing of monitoring and treatment.

The outcomes of the model presented in Chapters 5 and 6 show that it is not preferable to start OH therapy with latanoprost, which gives more IOP reduction but is also more expensive, instead of timolol. Due to the concept of a target pressure, which underlies both strategies, the eventual difference in the clinical effects of the two strategies is small. When therapy is started with latanoprost, the extra costs needed for saving one year of vision in comparison with starting with timolol are very high, namely € 537 000. A different future cost price of latanoprost may affect this outcome.

Conclusions and recommendations

The research conducted in this thesis shows that: (1) topical hypotensive therapy reduces the risk of conversion to POAG in OH and a progression of visual field loss in early glaucoma, (2) early detection and treatment of OH and POAG is likely to be beneficial in the prevention of blindness, (3) it is most cost-effective to routinely perform tonometry to all initial ophthalmic patients to prevent blindness due to glaucoma, (4) the differences in the clinical effects of the two strategies of initiating OH therapy, with latanoprost or with timolol, are quite small, (5) given the current cost price of latanoprost, initiating therapy in OH patients with this agent brings along extremely high incremental costs to prevent blindness when compared to initiating therapy with timolol.

Further research topics that are suggested by the outcomes of the performed studies are the following. (1) To establish more accurate guidelines for when to start OH treatment based on the IOP level, the presence of other risk factors and life expectancy, related to the expected gain in the prevention of blindness. (2) To identify subgroups of patients to which treatment strategies can be tailored. This may involve aspects such as the initial IOP level, risk factors, prognostic factors, severity of the disease at the moment of diagnosis, and life expectancy. (3) To identify the most cost-effective strategies for such different subgroups of patients.

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Summary

In this thesis, both the clinical effectiveness and the cost-effectiveness of detection and treatment of patients with ocular hypertension (OH) and primary open-angle glaucoma (POAG) are investigated. POAG, further referred to as glaucoma, is a progressive chronic eye disease which can ultimately lead to blindness. It has a considerable public health impact, being the second leading cause of world-wide blindness (cataract being the first). The etiology of glaucoma is unknown. It mostly affects elderly people. Individuals with ocular hypertension are at risk to develop glaucoma. In these individuals the intraocular pressure (IOP) is increased above values which clinicians consider safe. A chronic increased intraocular pressure as such causes no symptoms and can only be detected if tonometry is performed. The probability of developing glaucoma increases with higher IOP values. Other known risk factors are race, age, and family history of glaucoma.

Glaucoma is characterized by damage of the optic nerve. This leads to impairment of visual function. The disease manifests itself mostly by defects in the peripheral visual field first. Patients may not notice this for a long period. At later stages glaucoma may progress to tunnel vision and irreversible blindness. Although glaucoma cannot be cured, its progression can be reduced by treatment. As the rate of progression of the disease is higher at high IOP levels, therapy is directed towards lowering the IOP. In clinical trials it was shown that IOP lowering therapy reduces the risk of conversion to glaucoma in OH patients (Ocular Hypertension Treatment Study) and that it has a protective effect on a progression in POAG patients (Early Manifest Glaucoma Trial, Advanced Glaucoma Intervention Study). However, individuals vary in their ability to sustain increased IOP. Not all OH patients develop glaucoma. On the other hand, some glaucoma patients show progression despite a lowering of the intraocular pressure. IOP is therefore not the only factor that plays a role in the pathogenesis and progression of glaucoma. Other factors involved in the glaucomatous optic neuropathy are not well researched yet. IOP is at present the only factor manageable by treatment. Therapy involves hypotensive medication, laser treatment and surgery. The main therapeutic goal is to preserve visual function and to prevent the end stage of the disease. To achieve this goal it is

important that patients are detected in time. There are several tests available for diagnosing glaucoma. The IOP can be measured, the head of the optic nerve can be visualised, and the status of the visual field can be examined. Mostly a combination of tests is necessary to confirm the diagnosis.

For an effective management of glaucoma an understanding of the treatment effects is crucial. As glaucoma is a chronic disease the long-term effects should be taken into account. This is difficult as clinical trials mostly have a limited follow-up. However, recently several large clinical trials have become available in which patients were followed for a long period. Another major issue in the management of this chronic disease are the costs of treatment. In the last decades, these have substantially risen as a consequence of the introduction of new types of topical hypotensive drugs. These drugs are expensive but they have expanded the existing treatment options. There is a broad spectrum of drugs available now. There are several options for the initiation of therapy in case of contraindication to more classical drugs. When no or too little IOP reduction is achieved with the prescribed drug or if side-effects occur, other drugs are available. Finally, there are several different drugs which can be added to the prescribed medication when larger IOP reduction than the one achieved already is required. To define ideal treatment strategies for OH and POAG patients is a complex task requiring many factors to be taken into account.

One of the key questions is whether patients with ocular hypertension should be treated or not. After all, these patients do not have glaucoma yet, at least not detectable by current diagnostic techniques. Apart from costs, treatment is accompanied by discomfort and possibly by side-effects of medication. In favor of treatment are the results presented in this thesis which show that a therapeutic lowering of IOP in these patients reduces the risk of glaucoma. To assess the effects of treatment a long-term follow-up and a comparison of the conversion rates of patients with and without treatment is required. Although in the past many OH patients did receive treatment, there was little evidence on its efficacy until recently. In Chapter 2 all available scientific evidence on treatment effects in ocular hypertension is presented, based on a systematic literature review. The results of nine randomized clinical trials, in which OH patients with and without IOP lowering treatment were followed, are combined in a meta-analysis. This analysis shows that IOP lowering therapy in OH patients reduces the risk of conversion to glaucoma. The calculated pooled relative risk is 0.61 (95% confidence interval 0.45-0.83). In addition, it is shown that this relative risk decreases by 14% with each mm Hg of IOP reduction. At this moment, there is insufficient knowledge to identify OH patients who are at greater risk to develop glaucoma if untreated. Therapy for OH patients is generally recommended in case of high IOP values or if other risk factors are present. However, many patients included in the OH trials have IOP values below the recommended cut-off point when treatment is indicated and only some have additional risk factors. This implies that future research might be directed towards this topic.

The assumption behind strategies aimed at detecting and treating patients with ocular hypertension and early glaucoma is that this prevents blindness. In Chapter 3 a case-referent study is presented in which the effect of early detection of OH and POAG patients on the occurrence of glaucoma blindness is investigated. An exposure to screening tests for early detection of OH and POAG performed by an ophthalmologist, not based on the disease symptoms, is assessed for a group of cases and a group of referents. Cases are blind glaucoma patients. Referents represent the general population regarding the frequency of such testing. The underlying argumentation in this study is as follows. If patients undergo testing for OH and POAG detection while not having any disease symptoms, the disease is diagnosed and treated at an early stage. If treatment of OH and early glaucoma is effective in blindness prevention then one can assume that patients diagnosed at this stage will not progress to blindness. Conversely, the reason that blind patients did progress to blindness is that they were not detected (and treated) in time. The outcomes of the study confirm this supposition. Blind glaucoma patients underwent fewer screening examinations by which OH or POAG can be detected than the referents. The calculated relative risk is 0.57 (90% confidence interval 0.31-1.05). This study shows that detecting patients with OH and early glaucoma in the ophthalmic practice is effective in preventing glaucoma blindness.

At present there is no recommendation for a population screening program for glaucoma. The best alternative to detect patients early is case-finding among patients visiting an ophthalmologist. There are several alternatives as to how to address this issue. An interesting question concerning case-finding in the ophthalmic practice is whether IOP should be routinely measured in all initial patients, or only in selected groups of patients having risk factors for glaucoma. Ophthalmoscopy, by which the head of the optic nerve can be viewed, is mostly included in an ophthalmic examination. Tonometry on the other hand, has no other purpose than to detect an increased IOP. This test can easily be performed without much burden for a patient. A consequence of testing with tonometry is that more patients, mainly OH patients, will be detected and treated. Apart from the clinical effect this has an effect on costs. In Chapter 4 the long-term costs and effects of three different case-finding strategies are studied and evaluated by use of a decision model. Tonometry is routinely performed to: (1) all initial patients, (2) high-risk patients only, or (3) no one. These strategies are compared according to the methods of a cost-effectiveness analysis. It is concluded that it is most cost-effective to perform tonometry to all initial ophthalmic patients to prevent blindness due to glaucoma. Extra costs per year of vision saved are € 1 707 compared to strategy where tonometry is performed to no one. It is likely that costs a patient spends per year due to blindness, e.g. associated with the use of disability facilities, already exceed this amount.

The main costs in glaucoma treatment are the medication costs. The introduction of new IOP lowering drugs in the last decades has contributed to a change of the drug prescription pattern, accompanied by a considerable rise of treatment costs. For many years, non-selective beta-blockers such as timolol have been the first choice

in treatment. Nowadays, hypotensive lipids such as latanoprost are commonly used as first-line therapy. Latanoprost gives only a slightly better IOP lowering effect than timolol. Its cost price on the other hand, is much higher. The costs and clinical effects of the drugs should both be considered when choosing the type of medication. Especially in case of a drug used for the initiation of therapy, as many patients will use it for a long period. When sufficient IOP reduction is achieved in absence of side-effects, a patient will continue on this medication. Only if necessary, a drug substitution or a drug addition will follow. For patients with ocular hypertension it is not necessary to lower the IOP to the same extent as for glaucoma patients. Therefore, given the higher price of hypotensive lipids, one could question if initiation of therapy in OH patients with these agents is justified.

In Chapter 5 an analysis is presented in which the long-term clinical effects of initiating OH therapy with timolol and with latanoprost are studied and compared. In Chapter 6 a cost-effectiveness analysis of these two strategies is given. A simulation model is used for this purpose. In this model not only therapy initiation but also the adjustments of therapy are taken into account. The difference in the achieved IOP reduction between the two strategies is small. As conversion to glaucoma depends on IOP, the difference in glaucoma blindness between the strategies is small too. On average, this is about 1 month per person in both strategies, with a mean difference between the two strategies of 2 days spent in blindness per patient. On the other hand, the difference in costs spent on therapy between the two strategies is large. This is why initiating treatment in OH patients with latanoprost brings along extremely high incremental costs to prevent blindness when compared to initiating therapy with timolol. Given the current cost price of latanoprost, extra costs per year of vision saved are € 537 000.

Chapter 7 concludes this thesis with a general discussion and an outlook on future research. Recommendations for future research are to develop more accurate guidelines for when to start OH treatment and to identify subgroups of patients to which treatment strategies can be tailored.

Samenvatting

In dit proefschrift worden de klinische effecten en de kosteneffectiviteit bestudeerd van strategieën voor de detectie en de behandeling van patiënten met oculaire hypertensie (ocular hypertension, OH) en primair open-kamerhoek glaucoom (primary open-angle glaucoma, POAG). Laatstgenoemde aandoening, kortweg aangeduid met glaucoom, is een progressieve chronische oogziekte die uiteindelijk kan leiden tot blindheid. Het belang voor de volksgezondheid is groot, aangezien het, na cataract, wereldwijd de tweede oorzaak van blindheid betreft. De etiologie van glaucoom is onbekend. De ziekte treft hoofdzakelijk ouderen. Patiënten met oculaire hypertensie lopen een verhoogd risico op glaucoom. Bij deze patiënten neemt de intraoculaire druk (intraocular pressure, IOP) waarden aan boven het niveau dat door klinici als veilig wordt beschouwd. Een chronisch verhoogde oogdruk kent als zodanig geen symptomen en kan alleen met tonometrie worden vastgesteld. De kans om glaucoom te ontwikkelen stijgt met de oogdruk. Andere bekende risicofactoren zijn etniciteit en leeftijd en er is een erfelijke component.

Glaucoom wordt gekarakteriseerd door beschadiging van de optische zenuw. Dit veroorzaakt vermindering van de visuele functie. Gewoonlijk manifesteert de ziekte zich initieel door uitval in het perifere gezichtsveld. Het kan lang duren voordat patiënten hier daadwerkelijk hinder van ondervinden en dit als symptoom herkennen. In een latere fase kan glaucoom zich ontwikkelen tot tunnelzien en ten slotte tot blindheid, een proces dat onomkeerbaar is. Hoewel glaucoom ongeneeslijk is, kan de progressie van glaucoom worden geremd door therapie. Aangezien de snelheid van progressie afhankelijk is van de oogdruk, is glaucoomtherapie gericht op het verlagen van de IOP. In klinische onderzoekstrials is aangetoond dat IOP verlagende therapie het risico vermindert dat OH patiënten glaucoom ontwikkelen (zie de Ocular Hypertension Treatment Study) en dat het bij POAG patiënten inderdaad een beschermd effect heeft t.a.v. de progressie (zie de Early Manifest Glaucoma Trial en de Advanced Glaucoma Intervention Study). Er is echter een grote spreiding in het vermogen van OH en POAG patiënten om een verhoogde oogdruk te verdragen. Niet alle OH patiënten ontwikkelen glaucoom zonder therapie, terwijl ondanks een IOP verlagende therapie sommige POAG patiënten wel

progressie van glaucoom vertonen. Dit maakt duidelijk dat een verhoogde oogdruk niet de enige factor is in de pathogenese en de progressie van glaucoom. Momenteel is echter oogdruk de enige bekende factor in de ontwikkeling van glaucoom waarop medische behandeling gericht kan worden. Therapieën betreffen oogdrukverlagende medicatie, laserbehandeling en chirurgie. Het hoofddoel van elk van deze therapieën is het behoud van de visuele functie en het voorkomen van verdere progressie naar de eindfasen van de ziekte. Voor een succesvolle aanpak van glaucoom is het belangrijk dat patiënten in een vroegtijdig stadium worden ontdekt. Er bestaan verschillende technieken die gebruikt kunnen worden bij de diagnostiek van glaucoom: oogdrukmeting (tonometrie), visualisatie van de papil van de optische zenuw (ophthalmoscopie) en bepaling van het gezichtsveld (perimetrie). Gewoonlijk is een combinatie van deze technieken benodigd om de diagnose glaucoom te bevestigen.

Voor een effectief management van glaucoom is een gedetailleerd inzicht in de effecten van de behandelmethoden cruciaal. Aangezien glaucoom een chronische ziekte is, dient men de langetermijneffecten in ogenschouw te nemen. Dit is lastig, omdat de meeste klinische trials slechts een beperkte follow-up kennen. Recent zijn echter de resultaten van enkele grote klinische trials beschikbaar gekomen waarin patiënten over een lange periode werden gevolgd. Een ander hoofdthema voor het management van deze chronische ziekte wordt gevormd door de behandelkosten. In de laatste decennia zijn deze substantieel gestegen ten gevolge van de introductie van nieuwe types oogdrukverlagende middelen. Deze middelen zijn duur, maar ze hebben de bestaande behandel mogelijkheden verruimd. Tegenwoordig heeft men de beschikking over een breed spectrum aan middelen. Er zijn nu verschillende opties voor het starten van een therapie wanneer er contraindicaties zijn voor klassieke oogdrukverlagende middelen. Ook wanneer er geen of te weinig verlaging van de IOP wordt bereikt met een voorgeschreven middel, of wanneer bijwerkingen optreden, is alternatieve medicatie voorhanden. Ten slotte zijn er verschillende medicijnen die aan een reeds voorgeschreven medicatie kunnen worden toegevoegd wanneer een verdere verlaging van de IOP wenselijk is. Het is derhalve een gecompliceerde kwestie om tot ideale behandelstrategieën te komen voor OH en POAG patiënten, waarbij veel factoren in beschouwing dienen te worden genomen.

Een van de kernvragen is of patiënten met oculaire hypertensie wel of niet behandeld dienen te worden. Per slot van rekening hebben deze patiënten nog geen glaucoom, althans niet in een mate die met de huidige diagnostische technieken is vast te stellen. Behandeling gaat niet alleen gepaard met kosten, maar ook met ongemak en mogelijk ook met bijwerkingen van de medicatie. De resultaten van dit proefschrift wijzen op een gunstig effect van behandeling van OH patiënten: medicamenteuze oogdrukverlaging leidt tot een kleinere kans op het ontwikkelen van glaucoom. Om het effect van behandeling te bepalen is een langdurige follow-up nodig en dienen de incidenties van glaucoom bij patiënten met en zonder behandeling te worden vergeleken. Hoewel in het verleden OH patiënten vaak wel behandeld werden, had dit tot voor kort geen bewezen nut. In hoofdstuk 2 is alle beschikbare wetenschappelijk bewijs m.b.t. het effect van de behandeling van oculaire hypertensie samengebracht in een systematische literatuurstudie. De uitkomsten van

negen gerandomiseerde klinische trials, waarbij OH patiënten met en zonder IOP verlagende behandeling werden gevolgd, zijn gecombineerd in een meta-analyse. Deze analyse toont aan dat een IOP verlagende therapie bij OH patiënten de kans op het ontwikkelen van glaucoom vermindert. Het gepoolde relatieve risico bedraagt 0,61 (met een 95% betrouwbaarheidsinterval van 0,45-0,83). Tevens is gevonden dat het relatieve risico afneemt met 14% met iedere mm Hg oogdrukverlaging. Momenteel is er onvoldoende kennis beschikbaar om OH patiënten te identificeren die een verhoogd risico lopen op het ontwikkelen van glaucoom als behandeling uitblijft. Therapie voor OH patiënten wordt algemeen geadviseerd bij hoge IOP waarden of in aanwezigheid van andere risicofactoren. Veel OH patiënten in de trials hebben echter IOP waarden onder het niveau waarboven behandeling geadviseerd wordt, en bij lang niet iedereen is er sprake van andere risicofactoren. Verder onderzoek in deze richting is daarom gewenst.

De gedachte achter de verschillende strategieën voor het detecteren en behandelen van patiënten met oculaire hypertensie en beginnend glaucoom, is dat het uiteindelijk blindheid voorkomt. Hoofdstuk 3 beschrijft een case-referent studie waarin het effect van vroege opsporing van OH en POAG patiënten op het optreden van blindheid ten gevolge van glaucoom wordt onderzocht. Voor een groep ‘cases’ en voor een groep ‘referents’ wordt nagegaan in welke mate men in het verleden te maken kreeg bij de oogarts met screening tests voor de vroege opsporing van OH en POAG, zonder dat er directe aanleiding toe was vanwege symptomen. De groep ‘cases’ wordt gevormd door blinde glaucoompatiënten. De groep ‘referents’ representeert de algehele populatie t.a.v. de frequentie waarmee dergelijke tests worden uitgevoerd. De grondredenering in deze studie is als volgt. Als patiënten zonder symptomen tests ondergaan voor het opsporen van OH en POAG, dan kan de ziekte in een vroeg stadium worden opgespoord en behandeld. Als de behandeling van OH en beginnende POAG effectief is ter voorkoming van blindheid, dan is te verwachten dat dergelijke patiënten gewoonlijk geen blindheid zullen ontwikkelen. Omgekeerd kan worden gepostuleerd dat de reden dat blinde glaucoompatiënten blind zijn geworden, is dat zij niet bijtijds opgespoord (en behandeld) werden. De uitkomsten van deze studie bevestigen deze veronderstelling. Blinde glaucoompatiënten ondergingen minder vaak de screening tests waarmee OH en POAG kunnen worden opgespoord dan de ‘referents’. Het berekende relatieve risico is 0,57 (met een 90% betrouwbaarheidsinterval van 0,31-1,05). Deze studie laat zien dat vroege opsporing van patiënten met OH en POAG in de oogartsenpraktijk effectief is ter voorkoming van blindheid.

Momenteel bestaat er geen aanbeveling voor een screeningsprogramma voor glaucoom onder de gehele bevolking. Het beste alternatief voor een vroege opsporing van zulke patiënten is case-finding onder de patiënten die een oogarts bezoeken. Er zijn verschillende manieren om dit onderwerp te benaderen. Een interessante vraag m.b.t. case-finding in de oogartsenpraktijk is of de IOP routinematig gemeten zou dienen te worden bij alle nieuw binnenkomende patiënten, of alleen bij een selecte groep van patiënten met risicofactoren voor glaucoom. Ophthalmoscopie, waarmee de papil van de optische zenuw kan worden bekeken, maakt normaliter deel uit van

een ophthalmologisch onderzoek. Tonometrie dient echter alleen ter bepaling van een verhoogde oogdruk. Deze test kan eenvoudig worden uitgevoerd zonder veel ongemak voor de patiënt. Een gevolg van het routinematig testen met tonometrie is dat meer patiënten, hoofdzakelijk OH patiënten, zullen worden opgespoord en behandeld. Behalve een klinisch effect heeft dit ook een effect op de kosten. In hoofdstuk 4 worden de langetermijncosten en -effecten van drie verschillende case-finding strategieën bestudeerd en geëvalueerd met behulp van een beslismodel. Hierbij wordt tonometrie routinematig uitgevoerd: (1) bij alle nieuw binnenkomende patiënten, (2) alleen bij hoogrisico patiënten, (3) bij niemand. Deze strategieën worden vergeleken met methoden uit de kosteneffectiviteitanalyse. De conclusie luidt dat het het meest kosteneffectief is ter voorkoming van blindheid t.g.v. glaucoom, om tonometrie uit te voeren bij alle nieuw binnenkomende patiënten. De extra kosten per gered jaar met zicht bedragen € 1.707 in vergelijking tot de strategie waarbij tonometrie bij niemand wordt uitgevoerd. Het is aannemelijk dat de kosten die in geval van blindheid door een patiënt per jaar worden gemaakt als gevolg van deze handicap, dit bedrag ruim overstijgen.

De belangrijkste kosten bij de behandeling van glaucoom zijn de kosten van de medicatie. De introductie van de nieuwe types glaucoommiddelen heeft bijgedragen aan veranderingen in het prescriptiepatroon, en is hand in hand gegaan met een aanzienlijke toename van de behandelkosten. Lange tijd waren niet-selectieve bètablokkers zoals timolol de eerste medicijnkeuze bij behandeling. Tegenwoordig worden hypotensieve lipiden zoals latanoprost vaak gebruikt als eerstelijns therapie. De oogdrukverlagende werking van latanoprost is slechts een weinig sterker dan die van timolol. Anderzijds ligt de kostprijs van latanoprost een stuk hoger. De kosten en de klinische effecten van medicijnen dienen beide in beschouwing te worden genomen bij de keuze van een type medicatie. Dit geldt in het bijzonder voor medicijnen waarmee de behandeling geïnitieerd wordt, aangezien veel patiënten het voor lange tijd zullen gaan gebruiken. Als voldoende IOP verlaging wordt bereikt zonder het optreden van bijwerkingen, dan zal een patiënt op de betreffende medicatie worden gehouden. Een vervanging of toevoeging van een medicijn vindt alleen plaats wanneer daartoe een noodzaak bestaat. Voor patiënten met oculaire hypertensie is het niet nodig om de IOP evenveel te verlagen als bij glaucoompatiënten. Men kan zich daarom afvragen, in het licht van de hogere prijs voor hypotensieve lipiden, of het gerechtvaardigd is om de behandeling van OH patiënten met dergelijke middelen te initiëren.

In hoofdstuk 5 wordt een onderzoek beschreven, waarin de klinische langetermijneffecten van het initiëren van OH therapie met timolol en met latanoprost worden bestudeerd en vergeleken. In hoofdstuk 6 wordt een kosteneffectiviteitanalyse van deze twee strategieën gegeven. Hiertoe wordt een simulatiemodel gebruikt. In dit model wordt niet alleen met de initiatie van de therapie rekening gehouden, maar ook met de eventueel daaropvolgende aanpassingen. Het uiteindelijke verschil tussen de twee strategieën voor wat betreft de bereikte IOP verlaging is klein. Aangezien de kans op het ontwikkelen van glaucoom afhangt van de IOP, is ook het verschil in optredende blindheid t.g.v. glaucoom klein. Gemiddeld is dit ongeveer 1

maand per persoon voor beide strategieën, met een gemiddeld verschil tussen de strategieën van 2 dagen blindheid per patiënt. Daar staat tegenover dat het verschil in behandelkosten tussen de twee strategieën groot is. Dit maakt duidelijk waarom het initiëren van de behandeling van OH patiënten met latanoprost extreem hoge incrementele kosten met zich meebrengt in vergelijking tot het initiëren van de behandeling met timolol. Bij de huidige kostprijs van latanoprost bedragen deze extra kosten per gered jaar met zicht € 537.000.

Hoofdstuk 7 sluit dit proefschrift af met een algemene discussie en een vooruitblik op toekomstig onderzoek. Aanbevelingen voor zulk onderzoek zijn het ontwikkelen van preciezere richtlijnen die aangeven wanneer de behandeling van OH patiënten gestart dient te worden, evenals het identificeren van deelgroepen van patiënten waarop behandelstrategieën kunnen worden toegesneden.

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Andrea Peeters
Maastricht, november 2007

Curriculum vitae

Andrea Peeters-Karovičová was born in Bratislava, Slovakia, in 1962. In 1986 she graduated in General Medicine at the Medical Faculty of the Comenius University in Bratislava. She then worked as a doctor for five years at the Radiodiagnostic Clinic of the Dérerova hospital. In 1991 she moved to Amsterdam, where in 1994 she graduated in Epidemiology at the EMGO Institute of the Free University. Currently she lives in Maastricht, where she is employed by the Maastricht University Hospital since 2001. The research in this thesis was carried out at the Department of Epidemiology of Maastricht University and at the Department of Ophthalmology of the Maastricht University Hospital. She is now working at Maastro Clinic Maastricht, studying the cost-effectiveness of particle therapy.