Glaucoma management

Economic evaluations based on a patient level simulation model

Aukje van Gestel

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Chapter 1

Introduction

The topic of the research presented in this doctoral thesis is the economic evaluation of lifetime treatment strategies for ocular hypertension and primary open-angle glaucoma. This introduction aims to provide a concise context for the subsequent chapters by outlining the background of the research questions that led to this thesis, and by sketching the basic principles of glaucoma and health economic modeling in order to familiarize readers with these topics.

Primary open-angle glaucoma

Glaucoma is the name for a group of eye conditions characterized by damage to the optic nerve and permanent loss of visual function.¹ It has been defined in medical literature as 'a group of progressive optic neuropathies that have in common a slow progressive degeneration of retinal ganglion cells and their axons, resulting in a distinct appearance of the optic disc and a concomitant pattern of visual loss'.² Different types of glaucoma are distinguished, that are generally classified into open-angle or angle-closure glaucoma, based on the width of the angle between the cornea and iris in the anterior chamber of the eye.³ Also a reference to the aetiology is often added: secondary glaucomas are the result of known ocular or systemic diseases, drugs or treatment, while primary glaucomas are not associated with such underlying disorders. In most Western countries, including the Netherlands, the most common form of glaucoma is primary open-angle glaucoma (POAG).⁴ This thesis focuses on the latter type of glaucoma; angle-closure glaucoma and secondary glaucomas are beyond its scope.

The structural changes to the optic nerve in POAG and the degeneration of retinal ganglion cells causes irreversible damage to the visual field. The normal human visual field covers approximately 100 degrees on the temporal side to 60 degrees on the nasal side relative to the vertical meridian, and 60 degrees above and 75 degrees below the horizontal meridian in each eye.⁵ Nerve fibre bundles serving specific areas in the retina deteriorate as a result of glaucomatous damage at the optic nerve head. This causes the visual field to become affected by areas of partial or complete blindness (scotomas), which occur in patterns characteristic for glaucoma and predominantly affect the central 30 degrees of the visual field.^{1, 6} As the disease worsens, the scotomas deepen and spread across the central 30 degrees and into the more peripheral areas of the visual field. Typically a central island of vision is retained into advanced stages of glaucoma, but ultimately a patient can progress to complete blindness.¹ Maps of visual field examinations from automated perimeters like e.g. the Humphrey Field Analyzer, often indicate the light sensitivity of each area in the visual field by grey tones, with darker colors indicating

less sensitivity (i.e. more damage) and black indicating complete loss of light perception. Examples of such maps are included in figure 1. Patients with early or moderate glaucoma do not necessarily perceive scotomas as black areas in their visual field though. The missing parts can, to a certain extent, be filled in by the brain with information from the surrounding area or from the fellow eye.⁷ Patients with early POAG may therefore not notice anything wrong, except perhaps for a delayed awareness of e.g. traffic coming from the side or a curb in front of their feet (figure 1). This is a reason why glaucoma is sometimes referred to as a 'silent blinder'.⁸ POAG does not necessarily affect both eyes of a patient to the same extent, but POAG in one eye puts patients at a higher risk of developing it in the other, too and often both eyes are affected.⁹

Figure 1 The impact of glaucoma on vision, reprinted with permission from Hoste, 2003.⁷ Images and corresponding visual field examinations of a normal eye (A), and an eye affected by an early (B) or later stage (C) of glaucoma. The symbol in Figures B and C represent the patient's fixation point. Objects (and in this case children) located completely in the affected areas are not seen. These areas are filled-in with the colors and patterns of the surround.

The pathogenetic processes that lead to POAG are not yet fully understood, but studies have shown that the intraocular pressure plays an important role.¹⁰⁻¹⁴ A higher intraocular pressure is associated with a higher risk of developing POAG, and also with a higher risk of progression once conversion to POAG has occurred. The intraocular pressure, with a normal value around 15 mmHg, is regulated through the production of aqueous humour and its outflow through a natural filtration system consisting of the trabecular meshwork and Schlemm's canal.^{15, 16}

In open-angle glaucoma, the outflow of aqueous humour through the trabecular meshwork is restricted, resulting in a build-up of pressure. People with only a high intraocular pressure (i.e. higher than 21 mmHg) but no signs of damage to the retinal nerve fiber layer do not have glaucoma, but are at increased risk to develop it. Their condition is referred to as ocular hypertension (OHT).¹⁷ Ophthalmologist diagnose open-angle glaucoma and monitor its progression by comprehensive eye examinations, which include, but are not limited to, intraocular pressure measurement, assessment of the anterior chamber and angle, assessment of the optic nerve head and nerve fiber layer, and visual field measurements.

Prevalence and disease burden

POAG predominantly affects elderly people: the total number of patients with POAG in the Netherlands is estimated at 100,000, which represents approximately 0.6% of the total population.¹⁸ Of these patients, 80% are older than 60 years, and the prevalence of glaucoma among the population over 65 years approaches 3%.¹⁸ Based on age-specific incidence numbers and the distribution of age in the Dutch population, the number of new patients with POAG is estimated to be 14,000 per year.^{18, 19} The true number of prevalent and incident cases could be twice as large though, as large screening studies in general populations found that more than half of the identified patients with glaucoma were unaware that they had the condition.^{16, 20-23} The main reason for this is likely that the early stages of the disease pass without noticeable symptoms for the patients.^{7, 9, 24}

The number of patients with visual impairment or blindness due to glaucoma in The Netherlands cannot be established exactly, as no national registries are in place. The Dutch chapter of Vision2020 has made an inventory of available data in 2005, in which it reports that 6% to 18% of blindness not caused by refractive errors can be attributed to glaucoma.²⁵ Overall, the total number of patients with visual impairment or blindness from any cause in the Netherlands in 2005 was estimated at 300,000, among whom 12,657 (4%) were visually impaired or blind due to glaucoma.²⁶ Global burden of disease analyses of the World Health Organization have shown that the burden of glaucoma, expressed in terms of disability-adjusted

life-years (daly's), is typically around 40 per 100,000 inhabitants in most Western European countries.²⁷ For comparison, the daly rates of cataract and refractive errors were 12 and 284 respectively. The daly rate of glaucoma in the Netherlands was comparable to that of hypertensive heart disease (32) and multiple sclerosis (40).²⁷

The total treatment costs of glaucoma have been estimated at € 5 million per million inhabitants in Finland, Australia and the USA.^{28, 29} The costs of care and production losses as a result of glaucomatous visual impairment were not included in that estimate, but they might represent 50% of the total costs of glaucoma.³⁰ Therefore, the total cost-of-illness of glaucoma could be € 10 million per million inhabitants. In the Netherlands this would sum up to a total of € 160 million, which would represent 8% of the total expenditures on eye diseases in 2005.³¹

Treatment and treatment guidelines

There is currently no medical intervention that can repair damaged retinal nerve fibers in a glaucomatous eye, so there is no cure for glaucoma. Instead, treatment of glaucoma is directed at lowering the intraocular pressure in order to slow down the neurodegenerative process. Likewise, pressure-lowering treatment is used in patients with ocular hypertension to prevent development of POAG. Methods to reduce the intraocular pressure are classifiable into three groups: medication, laser treatment and surgery. Medication almost exclusively consists of eye-drops that patients need to self-administer once or several times daily. Laser treatment is used to open up the trabecular meshwork to improve the outflow of aqueous humor and thus reduce intra-ocular pressure. Eye surgery also aims to improve the outflow of aqueous humour, but involves a more invasive construction of alternative drainage routes like the creation of a filtering bleb by a guarded filtration procedure or implantation of a drainage device. Both laser treatment and surgery are usually performed on an outpatient basis.

Ophthalmologists in the Netherlands can refer to the treatment guidelines that have been issued by the European Glaucoma Society and amended by the Dutch Glaucoma Group to guide treatment decisions for patients with ocular hypertension or primary open-angle glaucoma.^{17, 32, 33} The treatment guidelines recommend setting a target pressure for each individual patient and to bring the intraocular pressure below that target. The target is described as the "highest intraocular pressure level that is expected to prevent further glaucomatous damage or that can slow disease progression to a minimum", but there is no guidance on how to establish this threshold value prospectively in an individual patient.¹⁷ A common approach in clinical practice is to set a conservative target pressure, start with

minimal treatment and monitor the patient closely to watch for signs of progression. When the latter inadvertently do occur, the target pressure is set to a lower level. This way, the patient is titrated towards the intraocular pressure that appears to have stabilized disease progression. Patients need to visit their ophthalmologist regularly for check-ups of intraocular pressure, occurrence of progression, and to consider alternative treatment options when the current treatment is insufficient or bothersome. Treatment usually starts with medication. Laser treatment and surgery are reserved for the instances where medication alone is not enough to get the intraocular pressure below the target, or when further visual field damage occurs despite maximally tolerable medical treatment. In advanced stages of the disease, when a patient has become visually impaired or blind, the focus of treatment shifts from the prevention of further visual field loss towards supportive care such as rehabilitation and nursing to cope with the impairment.

Research in this thesis

Rationale

Over the past twenty years, the possibilities to diagnose and treat glaucoma have increased substantially. In the second half of the 1990's and the early 2000's, several new glaucoma medications containing active ingredients with a different mode of action than the existing eye-drops, such as carbonic anhydrase inhibitors, prostaglandin analogues and α_2 -adrenergic sympathomimetics, became available.³⁴ The introduction of these medications did not only increase the therapeutic arsenal for single drug medication (monotherapy), but opened a whole range of options to treat patients with two or three medications simultaneously (combination therapy). Reimbursement of the first new medications was delayed until 1999 when a new protocol for glaucoma management was issued in the Netherlands.³⁵

The availability of new glaucoma medications provide the opportunity to treat glaucoma earlier and more effectively, and therefore ensure better protection against future visual impairment and blindness, but there are two potential objections to such an intensification of treatment. First, it may come at the cost of increased patient burden. Glaucoma eye drops can lead to local and systemic side-effects such as dry mouth, shortness of breath, stinging and redness of the eye, blurred vision, and some patients are simply bothered by the necessity of daily instillation of the drops.³⁶ Second, more intensive treatment might put a larger demand on the health care facilities and resources. A more intensive treatment regime requires a larger monetary investment for medication, laser and surgery, whereas many patients with ocular hypertension ultimately do not develop

glaucoma (even when untreated), and many glaucoma patients progress only slowly and do not live long enough to develop impairing visual field loss.^{37,38} It might therefore be better to allocate resources to the treatment of patients with advanced disease rather than prevention. In addition, the population of ocular hypertension and glaucoma patients is expected to increase rapidly due to the ageing population, increased screening and public awareness, whereas most glaucoma clinics are already struggling to manage the current workload.^{25, 29, 39} New management schemes for glaucoma care, including e.g. shared care schemes and multi-disciplinary hospital teams, are currently devised in order to diminish waiting lists, reduce costs and be prepared for the expected increase in patients.^{40, 41} An intensification of treatment might further add to this capacity problem. How we might apply the current treatment options for ocular hypertension and glaucoma to achieve an optimal level of effectiveness and efficiency, was the topic of this thesis.

Aim of the research

The aim of the research in this thesis was to investigate whether more intensive treatment would be better for the management of ocular hypertension and primary open-angle glaucoma than current care. What constitutes 'better' depends on the interests of the decision maker. In this respect we can discern three levels of decision making:⁴²

- The micro level, which represents decision making by healthcare professionals, and concerning individual patients. In glaucoma management it represents the treatment decisions that ophthalmologists make for (or with) individual OHT and POAG patients.
- The meso level, which represents decision making on a higher organizational level, like healthcare organizations or the medical profession. In glaucoma management this level would apply to the organizational board of ophthalmology clinics and to committees involved in the formulation of clinical treatment guidelines.
- The macro level, which represents decision making on a national or international policy level concerning e.g. the allocation of healthcare budgets and the reimbursement of medication/medical technologies.

The main interest for decision makers at the micro level is to provide each patient with the treatment that is expected to lead to the best overall health outcomes for that particular individual. The most important criteria at this level are therapeutic effects, side effects and compliance.⁴³ In addition, decision makers at the micro level will include their knowledge of the characteristics, personality and treatment history of the individual patient in their decision. The 'better' treatment option is therefore the one that is expected to generate the most benefit in that individual

patient at that moment in time. In contrast, decision makers at the meso and macro level aim to provide effective and affordable healthcare programs for the whole population. This means that they need to consider not only how a treatment is expected to affect health, but also how it will affect healthcare spending and how much value for money a treatment represents. In other words, economic criteria are added to the decision.^{42, 44}

In view of the different information needs of decision makers at the micro, meso and macro level, the methodological approach to most of the research described in this thesis was based on economic evaluations, as this approach entails both an assessment of clinical outcomes and an assessment of cost consequences. It should therefore be able to provide relevant information to decision makers in all three levels.

Economic evaluations and modeling

Cost-effectiveness analysis

The term economic evaluation refers to an evaluation of two or more alternative courses of action in terms of both their costs and consequences.⁴⁵ A cost-effectiveness analysis is a specific form of economic evaluation in which consequences (effects) are measured in natural units, such as life-years gained, or cases of blindness prevented. The difference in effects between an alternative treatment and a reference treatment (comparator) indicate how much extra health outcome can be expected from this alternative, which is referred to as the incremental effect or ΔE . Similarly, the difference in costs between an alternative treatment and the comparator, referred to as the incremental costs or ΔC , indicate how much extra money needs to be spent in order to achieve those extra effects. Combining information on both incremental effects and costs can lead to four distinct directions of the outcomes. These four directions are represented by the four quadrants in the cost-effectiveness plane visualized in Figure 2.

The north-west quadrant (A) represents the situation where the alternative is more costly and less effective than the comparator. In this case the comparator is clearly the most preferable strategy, and the alternative is dominated. The south-east quadrant (D) represents the situation where the alternative is less costly and more effective than the comparator, in which case it is clearly more preferable (i.e. dominant) than the comparator. Finally, the quadrants B and C represent the situation where the alternative is more effective but also more costly, and the situation where the alternative is less costly but also less effective respectively. In

Figure 2 Cost-effectiveness plane

the latter two situations, the balance between the incremental costs and effects can be quantified with the incremental cost-effectiveness ratio (ICER), which is calculated as the quotient of the incremental costs and effects ($\Delta C/\Delta E$). The incremental cost-effectiveness ratio quantifies either the price of each unit of health that is gained (B) or the monetary compensation for each unit of health that is lost (C). This outcome must then be compared to some benchmark value to decide whether the balance between effects and costs is acceptable or not.

A drawback of cost-effectiveness analyses is that the effectiveness term can capture only one specific outcome of a treatment strategy, and may therefore not reflect all consequences of the evaluated treatments that are relevant. Efforts to overcome this problem have led to the development of cost-utility analyses, in which the effectiveness of treatment is expressed in terms of quality-adjusted life-years (QALY). In this outcome measure, patients' life-years are adjusted for the quality-of-life they experience during that life-year. This quality-of-life needs to be quantified in a decimal number on a scale anchored by full health (1.0) and death (0.0). A number on this scale, also referred to as the 'utility', quantifies the value of a health state relative to full health and death.

Using QALYs as an outcomes measure rather than any other health effect relevant for glaucoma, like the occurrence of blindness or the height of the intraocular pressure, has several advantages. First, utility is an outcomes measure that captures all aspects of health-related quality-of-life, so all consequences of treatment, no matter their nature, ultimately translate into an impact on utility. This means that both the impact of adverse events (e.g. stinging eyes) and the effect of treatment (e.g. prevention of visual field loss) can be measured on the same scale. Second, the generic nature of the QALY enables comparisons of cost-utility analyses across diseases and health care sectors. In theory therefore, cost-utility analysis could be employed in a situation of limited resources to devise a health care system that generates the maximum amount of health within a fixed budget. Most Western countries do not actually use cost-utility outcomes in this manner, because it would imply the impractical reconsideration of the whole system with each change in clinical practice, and healthcare budgets are not usually fixed to a degree that they cannot be stretched.⁴⁶ However, the quantification of the incremental cost-effectiveness ratio in terms of costs per QALY allows for some degree of reference framing in the interpretation of the figure. The incremental cost-per-QALY ratio can be used to assess whether the investments necessary to obtain the extra health represent good value for money.

Simulation modeling

Cost-effectiveness analyses of glaucoma treatment strategies require data about resource use and health effects in each of the strategies over the patients' entire lifetime. Such data are not readily available from observational or experimental studies, among others because studies in glaucoma never have a lifelong follow-up, compare only two or three isolated treatment options rather than treatment strategies, do not withhold treatment to patients and hardly ever collect information on resource use. The cost-effectiveness analyses presented in this thesis were therefore conducted with data that were generated in a computer simulation model. Modeling is common in health economic research, because it provides a tool to aggregate different pieces of scientific and clinical information. The scope of economic research often goes beyond the scope of clinical research and modeling allows for the synthesis and extrapolation of scientific evidence.⁴⁷

The concept of simulation modeling is depicted in Figure 3. Suppose there is a real world system, like glaucoma and its treatment (the problem, Figure 3), and we need information on the consequences of changing the system, for example by introducing a new treatment strategy. When it is not feasible to perform experiments in the real world, as is the case in our research questions, the real world can be abstracted into a mathematical model (the model, Figure 3).

Figure 3 The abstraction of the real world into a model, analysis of a problem (simulation) and mapping the solution back into the real world. Reprinted with permission from Borshchev and Filippov, 2004.⁴⁸

The model is a simplified representation of reality and contains all elements that are important to the problem. The consequences of changes in the system can be evaluated with simulations (the optimized model, Figure 3), and the results of the simulation can be used to make decisions in the real world (the solution, Figure 3). The simulation model itself is basically a set of calculation instructions programmed in computer software, and it is executed by letting the computer perform the calculations.

Relevance of the research

The number of patients with glaucoma is expected to rise considerably in the next decades, and it can be expected that resources and capacity to treat these patients will become tighter.^{29, 39} There is therefore an urgent need for optimal targeting and efficient management of glaucoma patients.⁴⁰ The outcomes of the research described in this thesis contribute to that goal as it informs decision makers at the micro, meso and macro level about the consequences of altering treatment patterns in ocular hypertension and primary open-angle glaucoma both in the heterogeneous patient population and in individual patients. The former is important to establish which treatment strategy constitutes the best overall option, whereas the latter is important for decisions regarding the implementation of personalized or individualized medicine. In addition, doing the modeling exercises and thoroughly analyzing the

model outcomes (in the base case situation and in various alternative scenarios) gives direction to discussions about the criteria that may be important for the decisions. Moreover, because of the explicit nature of the model (i.e. there are no subjective decisions within the model structure) it has the capacity to reveal gaps in knowledge, and enables value of information analysis to inform us whether it is worthwhile to address these gaps in future research.⁴⁹

Research questions

The aim of the research as described in the previous paragraphs has been translated into the following research questions:

- I. What is the clinical effectiveness and cost-effectiveness of intensifying treatment for primary open-angle glaucoma compared to usual care, by:
 - a. Starting treatment with a more effective medication, or
 - b. Setting a lower target intraocular pressure, or
 - c. Monitoring for progression more frequently?
- II. What is the clinical effectiveness and cost-effectiveness of direct pressure lowering treatment in ocular hypertension compared to active surveillance without treatment?
- III. Is there value in individualized care?
- IV. Is there value in additional research to reduce parameter uncertainty?

Outline of the thesis

The research conducted to address the research questions listed above, is described in the next six chapters of this thesis. The first three of those are concerned with the construction of the mathematical simulation model, the last three are concerned with the outcomes of that model. Most input for the model was retrieved from existing scientific literature, but there was a critical lack of information regarding the impact of treatment and disease severity on the quality-of-life of patients with ocular hypertension and primary open-angle glaucoma. Therefore, *chapter two* describes the observational research that was conducted in Dutch patients to collect the missing data. *Chapter three* presents the results of a literature review and a very basic model to explore the effect of treatment on reducing the risk of blindness in patients with ocular hypertension. Avoiding the occurrence of blindness is the main clinical goal of ocular hypertension and glaucoma treatment, and therefore a crucial aspect in the evaluation of long term outcomes in any treatment strategy for these conditions.

Chapter four describes the design and validation of the cost-effectiveness model. The disease mechanisms of ocular hypertension and primary open-angle glaucoma were abstracted into a mathematical model based on scientific literature and expert opinion. The appendix to chapter 4 provides details on the sources and derivation of all parameter estimates that were used.

Chapter five presents the long term effectiveness and cost-effectiveness outcomes of four alternative strategies to usual care in primary open-angle glaucoma in the Netherlands. The alternatives are different in terms of the type of initial medication, the target pressure at treatment initiation and the frequency of visual field measurements to monitor progression.

Chapter six presents the long term effectiveness and cost-effectiveness of pressure lowering treatment in a heterogeneous population of patients with ocular hypertension, and in subpopulations of those patients defined by the initial intraocular pressure and the presence of other risk factors for glaucoma development.

Chapter seven is concerned with the impact of patient heterogeneity on the outcomes of effectiveness and cost-effectiveness analyses. This chapter presents the results of an exploration of the expected value of individualized care framework in general, and the possible value of subgroup care for patients with primary open-angle glaucoma in particular.

The results of the research presented in chapters two through seven and their implications for health care practice and future research endeavors are summarized and discussed in *chapter eight*.

References

1. American Academy of Ophthalmology. Basic and clinical science course 2010-2011 section 10: Glaucoma. American Academy of Ophthalmology: San Francisco; 2010.
2. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet* 2004; 363:1711-1720.
3. Webers C, Beckers H, Nuijts R, Schouten J. Pharmacological management of primary open-angle glaucoma: second line options and beyond. *Drugs Aging* 2008; 25:729-759.
4. Quigley HA. Number of people with glaucoma worldwide. *Br J Ophthalmol* 1996; 80:389-393.
5. Spector R. Visual Fields. In: Walker H, Hall W, Hurst J (eds), *Clinical Methods: The history, physical and laboratory examinations*. Boston: Butterworth Publishers; 1990.
6. Johnson C. Chapter 13: Perimetry. In: Morrison JC, Pollack I (eds), *Glaucoma: science and practice*. Hong Kong: Thieme Medical Publishers; 2003.
7. Hoste AM. New insights into the subjective perception of visual field defects. *Bull Soc Belge Ophthalmol* 2003; 65-71.
8. Coleman AL. Glaucoma. *Lancet* 1999; 354:1803-1810.
9. de Voogd S, Ikram MK, Wolfs RC, Jansonijs NM, Hofman A, de Jong PT. Incidence of open-angle glaucoma in a general elderly population: the Rotterdam Study. *Ophthalmology* 2005; 112:1487-1493.
10. Ray K, Mookherjee S. Molecular complexity of primary open angle glaucoma: current concepts. *J Genet* 2009; 88:451-467.
11. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Surv Ophthalmol* 2008; 53 Suppl1:S3-10.
12. Rivera JL, Bell NP, Feldman RM. Risk factors for primary open angle glaucoma progression: what we know and what we need to know. *Curr Opin Ophthalmol* 2008; 19:102-106.
13. Morrison J, Johnson E, Cepurna W, Jia L. Understanding mechanisms of pressure-induced optic nerve damage. *Prog Retin Eye Res* 2005; 24:217-240.
14. Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. *N Engl J Med* 2009; 360:1113-1124.
15. Klein BE, Klein R, Linton KL. Intraocular pressure in an American community. The Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci* 1992; 33:2224-2228.
16. Bonomi L, Marchini G, Marraffa M, Bernardi P, De Franco I, Perfetti S, Varotto A, Tenna V. Prevalence of glaucoma and intraocular pressure distribution in a defined population. The Egna-Neumarkt Study. *Ophthalmology* 1998; 105:209-215.
17. European Glaucoma Society. Terminology and guidelines for glaucoma (third edition). Dogma: Savona, Italy; 2008.
18. Poos M, Gijsen R. Visual disorders by age and sex [Gezichtsstoornissen naar leeftijd en geslacht]. National Compass of Public Health; Explorations of the future [Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid]. Bilthoven, The Netherlands: RIVM, 2010.
19. Statistics Netherlands (CBS). Statline. Available at: <http://statline.cbs.nl/StatWeb/>. Accessed: 2010
20. Dielemans I, Vingerling JR, Wolfs RC, Hofman A, Grobbee DE, de Jong PT. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology* 1994; 101:1851-1855.
21. Leske MC, Wu SY, Honkanen R, Nemesure B, Schachat A, Hyman L, Hennis A. Nine-year incidence of open-angle glaucoma in the Barbados Eye Studies. *Ophthalmology* 2007; 114:1058-1064.
22. McKean Cowdin R, Wang Y, Wu J, Azen SP, Varma R. Impact of visual field loss on health-related quality of life in glaucoma: the Los Angeles Latino Eye Study. *Ophthalmology* 2008; 115:941-948.
23. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J, Singh K. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol* 1991; 109:1090-1095.
24. Weinreb RN, Friedman DS, Fechtner RD, Cioffi GA, Coleman AL, Girkin CA, Liebmann JM, Singh K, Wilson MR, Wilson R, Kannel WB. Risk assessment in the management of patients with ocular hypertension. *Am J Ophthalmol* 2004; 138:458-467.

25. Vision 2020 Netherlands. Avoidable blindness and visual impairment in the Netherlands (Vermijdbare blindheid en slechtziendheid in Nederland). Leiden, the Netherlands: Vision 2020 Netherlands, 2005.
26. Netherlands V. Causes of blindness and visual impairment: the situation in the Netherlands. Available at: <http://www.vision2020.nl/sitNL.html>. Accessed: September 2011
27. World Health Organization. Death and DALY estimates for 2004 by cause for WHO Member States. Available at: http://www.who.int/healthinfo/global_burden_disease/gbddeathdalycountryestimates2004.xls. Accessed: September 2011
28. Tuulonen A. Economic considerations of the diagnosis and management for glaucoma in the developed world. *Curr Opin Ophthalmol* 2011; 22:102-109.
29. Tuulonen A, Salminen H, Linna M, Perkola M. The need and total cost of Finnish eyecare services: a simulation model for 2005-2040. *Acta Ophthalmol* 2009; 87:820-829.
30. Rouland J, Berdeaux G, Lafuma A. The economic burden of glaucoma and ocular hypertension; Implications for patient management: a review. *Drugs Aging* 2005; 22:315-321.
31. Van Wieren S, Poos M. Resource use and costs of eye diseases (Gezichtsstoornissen; welke zorg gebruiken patiënten en wat zijn de kosten?). In: RIVM, ed. National Public Health Compass (Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid). Bilthoven, 2011.
32. European Glaucoma Society. Terminology and guidelines for glaucoma (second edition). Dogma: Savona, Italy; 2003.
33. Dutch Glaucoma Group (Nederlandse Glaucoom Groep). Addendum EGS guidelines 2009. Available at: <http://www.oogheelkunde.org/uploads/9r/qz/9rqzc2g7praqHfQCMraSFg/addendum-EGSguidelines-2009.pdf>. Accessed: August 2011
34. Medicines Evaluation Board (CBG/MEB). Human medicines data bank. Available at: www.cbg-meb.nl. Accessed: 2010
35. Ziekenfondsraad. Protocol for the use of glaucoma medication (Protocol gebruik glaucoommiddelen). Amstelveen: Health Care Insurance Board (College voor Zorgverzekeringen), 1999.
36. Beckers HJ, Schouten JS, Webers CA, van der Valk R, Hendrikse F. Side effects of commonly used glaucoma medications: comparison of tolerability, chance of discontinuation, and patient satisfaction. *Graefes Arch Clin Exp Ophthalmol* 2008; 246:1485-1490.
37. Maier P, Funk J, Schwarzer G, Antes G, Falck-Ytter Y. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ* 2005; 331:134.
38. Peeters A, Webers C, Prins M, Zeegers M, Hendrikse F, Schouten J. Quantifying the effect of intra-ocular pressure reduction on the occurrence of glaucoma. *Acta Ophthalmol* 2010; 88:5-11.
39. Quigley H, Broman A. The number of people with glaucoma worldwide in 2010 and 2020. *BMJ* 2006; 90:262-267.
40. Morley AM, Murdoch I. The future of glaucoma clinics. *Br J Ophthalmol* 2006; 90:640-645.
41. van der Horst F, Webers C, Bours S. Transmural eye care model: development, implementation and evaluation of a regional collaboration (Transmuraal Model Oogzorg: ontwikkeling, implementatie en evaluatie van een regionaal samenwerkingsverband). Research Institute CAPHRI, Maastricht University: Maastricht, The Netherlands; 2003.
42. van Velden M, Severens J, Novak A. Economic evaluations of healthcare programmes and decision making; The influence of economic evaluations on different healthcare decision-making levels. *Pharmacoeconomics* 2005; 23:1075-1082.
43. Jansson S, Anell A. The impact of decentralised drug-budgets in Sweden - a survey of physicians' attitudes towards costs and cost-effectiveness. *Health Policy* 2006; 76:299-311.
44. Erntoft S. Pharmaceutical priority setting and the use of health economic evaluations: a systematic literature review. *Value Health* 2011; 14:587-599.
45. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes, Third ed. Oxford University Press: Oxford; 2005.
46. McKenna C, Chalabi Z, Epstein D, Claxton K. Budgetary policies and available actions: a generalisation of decision rules for allocation and research decisions. *J Health Econ* 2010; 29:170-181.
47. Brennan A, Akehurst R. Modelling in health economic evaluation. What is its place? What is its value? *Pharmacoeconomics* 2000; 17:445-459.
48. Borshchev A, Filippov A. From system dynamics and discrete event to practical agent based modeling: reasons, techniques, tools., *International Conference of the System Dynamics Society*. Oxford, UK; 2004.
49. Felli JC, Hazen GB. Sensitivity analysis and the expected value of perfect information. *Med Decis Making* 1998; 18:95-109.

Chapter 2

The relationship between visual field loss in glaucoma and health-related quality-of-life

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Abstract

Purpose: To investigate the relationship between visual field loss and health-related quality-of-life (HRQOL) in patients with ocular hypertension (OHT) or primary open-angle glaucoma (POAG).

Methods: We conducted a cross-sectional study among 537 OHT and POAG patients from seven hospitals in The Netherlands. Clinical information was obtained from medical files. Patients completed a questionnaire, containing generic health-related quality-of-life instruments (EQ-5D and Health Utilities Index mark 3), vision-specific National Eye Institute Visual Functioning Questionnaire (VFQ-25), and glaucoma-specific Glaucoma Quality-of-Life questionnaire (GQL-15). The impact of visual field loss on HRQOL scores was analysed with multiple linear regression analyses.

Results: A relationship between Mean Deviation (MD) and HRQOL was found after adjusting for age, gender, visual acuity, medication side-effects, laser trabeculoplasty and glaucoma surgery. We found interaction between MD in both eyes for GQL and VFQ-25 scores. The relationship between MD and utility was non-linear, with utility only affected at MD-values below -25 dB in the better eye. Visual acuity, side-effects and glaucoma surgery independently affected HRQOL. Binocular MD and MD in the better eye had similar impacts on HRQOL, whereas MD in the worse eye had an independent effect. HRQOL was affected more by binocular defects in the inferior than in the superior hemifield.

Conclusion: Visual field loss in progressing glaucoma is independently associated with a loss in both disease-specific and generic quality-of-life. It is important to prevent progression both in early and in advanced glaucoma, especially in patients with inferior hemifield defects and severe defects in either eye.

Introduction

Decisions to start or change therapy in glaucoma are mainly based on the intra-ocular pressure, structural changes to the optic nerve and progression of visual field defects. The use of the intraocular pressure is based on its causal relationship with glaucoma progression, whereas the use of visual field loss is based on the knowledge that it reflects defects in the retinal nerve fiber layer. More relevant, however, is the fact that visual field loss is related to vision and health-related quality-of-life (HRQOL), which directly reflect patients' experiences.¹⁻⁵ Ultimately the aim of glaucoma treatment is to prevent HRQOL loss, and knowledge about the relationship between visual field loss and HRQOL should play a role in treatment decisions. Several aspects of this relationship are clinically relevant. First, insight in the strength and causality of the association can help us understand the relative importance of visual field preservation in all severity stages of glaucoma. Second, it is likely that visual field loss is not the only factor relevant for HRQOL in glaucoma patients, and treatment benefits must be weighed against the potential HRQOL impact of treatment side-effects. Third, HRQOL may be affected by visual field loss in each eye independently, rather than via the integrated binocular visual field. The location of visual field defects within one eye may also play a role. Insight in these aspects can elucidate the need to focus treatment on either the better or worse eye, or on the eye with a specific location of visual field loss. Finally, it is of clinical interest to identify patients in whom HRQOL is more profoundly affected by visual field loss, for example as a result of concurrent impaired visual acuity. In this study we have investigated these four aspects of the relationship between visual field loss and HRQOL in a patient population representing all severity stages of glaucoma.

Methods

We held a cross-sectional survey among patients with ocular hypertension (OHT) or primary open-angle glaucoma (POAG) from the ophthalmology departments in seven Dutch hospitals. This survey was held in the context of a larger research project aiming to investigate the cost-effectiveness of alternative treatment strategies for OHT and POAG. In order to enable good interpolation within the data, all stages of disease severity needed to be represented in the study population. Ideally we had stratified patient sampling according to visual field defects, but the data required to do so were not readily available in the patient administration of the participating hospitals. Therefore we defined the following seven sampling strata based on diagnosis and treatment as a proxy for disease severity: 1) OHT without treatment, 2) OHT treated with medication only, 3) OHT with laser trabeculoplasty (LT) in the

treatment history, 4) POAG treated with medication only, 5) POAG with LT in the treatment history, 6) POAG with glaucoma surgery in the treatment history, and 7) end stage POAG, which was defined as a visual field limited to the central ten degrees in at least one eye as a result of glaucoma progression. The latter was independently assessed by two ophthalmologists (CW, HB) based on the patient's medical files. An overview of in- and exclusion criteria for each of the categories is provided in Table 1 of the appendix. For each category a sample list of potentially eligible patients was drawn up. Based on sample size calculations we aimed to include 70 patients in each group. When the sample list in a stratum was small, all patients were selected. In the other strata a random sample of 200 patients was drawn to compensate for the smaller number of patients in the other groups, aiming to include a total of 500 patients. The medical files of the selected patients were manually inspected to verify the in- and exclusion criteria and eligible patients were invited by mail to participate. They received written study information, an informed consent form, a questionnaire and a stamped and addressed envelope. Patients were encouraged to consult the researchers by mail or telephone for information or assistance in completing the questionnaire. If the patient did not return the questionnaire after two weeks, we sent a reminder by mail. After another two weeks without a response we called the patient to inquire whether there were any difficulties and to encourage him to return the questionnaire.

Data collection

The questionnaire contained questions on demographics, current glaucoma medication, and co-morbidities. Side effects of current medications were explored with two lists of 16 typical side effects from pressure lowering eye-drops.⁶ One list asked how often side effect occurred, ranging from never (0) to every day (5). The other asked how bothered the patient was by the side-effect, ranging from 'not bothered' (0) to 'extremely bothered' (4). The scores for frequency and severity were multiplied and summed to obtain a total side-effect score between 0 and 320. An additional question asked whether side effects from glaucoma medication had affected quality-of-life (6 levels, 'not at all' to 'very much'). Glaucoma-specific HRQOL was measured with the Glaucoma Quality-of-Life questionnaire (GQL-15), consisting of 15 items regarding daily activities.^{7,8} The GQL score ranges between 15 (best) and 75 (worst). Vision-specific HRQOL was measured with the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), containing 25 items in 12 domains: general health, general vision, ocular pain, near-vision, distant-vision, social functioning, mental health, role functioning, dependency, driving, colour vision, and peripheral vision.^{9,10} An overall weighted average between 0 (worst) and 100 (best) was calculated with the VFQ-25 algorithm.¹¹ Generic HRQOL was measured with the EQ-5D and the Health Utility Index mark 3 (HUI3). The EQ-5D

has 5 items in 5 domains: mobility, self-care, daily activities, pain/discomfort and anxiety/depression.¹² A Dutch value set was used to translate the EQ-5D profiles into utility values reflecting the value of a health-state relative to death (0) and perfect health (1).¹³ The HUI3 has 15 items in 8 domains: vision, hearing, speech, mobility, dexterity, cognition, emotion, and pain/discomfort.¹⁴ A value set has been generated from a Canadian general population sample.¹⁵ In the regression analyses all utilities were rescaled from 0-1 to 0-100.

The Mean Deviation (MD) from the 30-2 threshold program of the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Jena, Germany) closest to the date of participation was the primary variable to quantify visual field loss. All available visual field information was collected from automated perimeters or from printouts in the medical files. Not all patients in our sample had a recent 30-2 HFA measurement available. Since the availability of a 30-2 HFA measurement is related to disease severity, visual field data cannot be expected to be 'missing completely at random'.¹⁶ Because analyses based on complete cases only would lead to biased results, we have imputed missing MD values based on all available other visual field information (see Table 2 in the appendix).¹⁶ If visual field data were only available for one eye (n=31), this was presumed to be the worse eye. Visual acuity data closest to the date of participation in the study were retrieved from the medical files. We used the visual acuity measurement with the patients' own correction, or without correction if the former was not available (8 % of the cases). Decimal and Snellen fraction notations were converted to logMAR values using conversion tables.¹⁷

Data analysis

Data were analysed in SPSS 14.0 (SPSS Inc, Chicago, IL). Patient characteristics and outcomes are reported as median with 25th- and 75th-quartiles if their distribution deviated from normal. The statistical significance of differences between characteristics of participating versus non-participating patients was tested with a Mann-Whitney test. Differences between selection categories were tested with a Kruskal-Wallis test. Univariate relationships were tested for statistical significance with Spearmans' rho in bivariate correlations. The impact of visual field loss on each of the HRQOL outcomes was assessed in multiple linear regression analyses that adjusted for the potentially confounding effect of age, sex, visual acuity in both the better and the worse eye, and side-effects from medication, LT or glaucoma surgery. Each of these factors was also entered in a single regression model. Assumptions for linear regression analysis were checked. Non-linearity in the multiple linear regression model was tested with Ramsey's reset test, and explored with dummy variables for six categories of MD in the better eye relative to the reference category of MD > 0: -5≤MD<0, -10≤MD<-5, -15≤MD<-10, -20≤MD<-15,

-25≤MD<-20, and MD<-25. Estimates of binocular MD were calculated from the total deviation plots of both eyes according to the best-location algorithm described by Nelson-Quigg *et al.*¹⁸ Regression coefficients are reported with 95% confidence intervals (CI). A significance level of 0.05 was used throughout all statistical analyses. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Results

Between April 2006 and January 2007, 654 eligible patients were invited to participate in the study; 531 patients consented (81%) and completed the questionnaire. We explored the differences between participating and non-participating patients in terms of age, visual acuity and visual field (table 3, appendix). Formal statistical testing indicated significantly lower age and better visual acuity in participating patients, but the absolute differences were small from a clinical point of view (5 years, 0.05 logMAR in the better and 0.08 logMAR in the worse eye respectively) and did not compromise the representativeness of the sample nor raise concerns for selection bias. The characteristics of participating patients are listed in table 1. For most patients (95%) visual field information was available. The median interval from the last visual field test to completion of the questionnaire was nine months. The interval was longer in OHT patients and end stage POAG patients and shorter in medically treated POAG patients, reflecting variation in the frequency of visual field testing between these groups. Visual field data from a HFA 30-2 program within two years of study participation was available for 74% of the eyes. An additional 22% could be imputed based on all available visual field data from other sources. The majority of HFA 30-2 measurements were performed with the sita-fast (73%) or the sita-standard (25%) strategy. The median reliability indices of the HFA 30-2 measurements (10%-90% percentiles) were as follows. Better eye: fixation loss 15% (0-40%), false negative 5% (0-14%), false positive 4% (0-11%). Worse eye: fixation loss 13% (0-33%), false negative 8% (0-21%), false positive 4% (0-10%). The reliability indices did not worsen with increasing disease severity, except for the percentage of false negatives which increased from 2% to 9% in the better eye and from 3% to 8% in the worse eye between untreated OH patients and end stage POAG patients. The majority of patients with glaucoma surgery in their treatment history had had no more than one surgery in each eye (82%). The remaining 18% had undergone glaucoma surgery more than once in either or both eyes. Descriptive statistics of HRQOL scores in each selection category are listed in table 2.

Strength and causality of the relationship

We found statistically significant coefficients for MD in both the better and worse eye in the single regression analyses of GQL, the VFQ-25, the EQ-5D utility and the HUI3 utility (table 3, EQ-5D results are in the supplemental information). The coefficients for MD were smaller after adjusting for confounding factors. There was no indication for non-linearity in the relationship between visual field loss and glaucoma- and vision-specific HRQOL. However, the relationship was not linear for EQ-5D and the HUI3, where utility seemed only significantly affected when MD was below -25 dB (Figure 1). The number of patients in this latter category was small (n=8), but additional analyses did not indicate that outliers or influential cases had undue impact on these results. We varied the dummy variable cut-off point from -22 to -27 dB, but that did not result in a better fitting model.

Contribution of other factors

Some of the factors included in the multiple linear regression model showed a significant relationship with HRQOL, notably visual acuity and side effects of medication. In GQL and VFQ-25 scores also previous glaucoma surgery had a significant impact. The total amount of variance explained by the included factors was 0.54 for the GQL and VFQ-25 scores, 0.18 for EQ-5D utility and 0.26 for HUI3 utility (table 3).

Contribution of either eye and type of visual field loss

The impact of visual field loss in the better eye was stronger than visual field loss in the worse eye (table 3). We repeated the multiple regression analyses with an estimate of the binocular MD rather than MD in both eyes separately. In GQL scores the coefficient of binocular MD was -0.83/dB (95% CI: -0.99; -0.66). The model significantly improved by adding MD in the worse eye, but not by adding MD in the better eye. The coefficients for binocular MD (-0.61/dB) and MD in the worse eye (-0.28/dB) were similar to the coefficients for respectively MD in the better and MD in the worse eye in the original regression model. GQL was predominantly affected by binocular visual field loss in the inferior hemifield (-0.71/dB, 95% CI: -1.02; -0.41), and to a lesser extent by loss in the superior hemifield (-0.15/dB, 95% CI: -0.42; 0.13). We saw the same pattern in the regression analyses of VFQ-25, with a coefficient of 1.02/dB (95% CI: 0.80; 1.24) for binocular MD. The latter could be separated into 0.70/dB (95% CI: 0.30; 1.11) for loss in the inferior hemifield and 0.35/dB (95% CI: -0.22; 0.71) for loss in the superior hemifield. The coefficient for binocular MD did not reach statistical significance in the multiple regression model for EQ-5D utility, but it did in the model for HUI utility (0.68/dB, 95% CI: 0.28; 1.08). The coefficient for loss in the inferior hemifield was 0.79/dB (95% CI: 0.05; 1.53), and for loss in the superior hemifield -0.06/dB (95% CI: -0.73; 0.61).

Table 1 Demographic and clinical characteristics of the total population and stratified in each sample category, median (25th;75th percentile)

Selectiongroup	All	Untreated OHT	OHT medication	OHT LT	POAG medication	POAG LT	POAG surgery	End stage POAG	p-value ¹
Invited	654	80	133	16	160	40	142	83	
Participated (n)	531	61	114	14	133	37	105	64	
Age	71 (63; 78)	67 (62; 73)	72 (64; 76)	70 (62; 74)	72 (64; 80)	67 (58; 77)	73 (62; 80)	71 (63; 79)	0.023
Male	52 %	53%	50%	29%	51%	57%	54%	59%	0.508
Number of medications, n (%)									
0	131 (25%)	61 (100%)	0	10 (71%)	3 (2%)	7 (19%)	36 (34%)	15 (23%)	<0.001
1	207 (39%)	0	78 (68%)	2 (14%)	69 (51%)	15 (41%)	27 (26%)	17 (27%)	
2	123 (23%)	0	31 (27%)	1 (7%)	39 (29%)	8 (22%)	25 (24%)	19 (30%)	
>2	68 (13%)	0	5 (4%)	1 (7%)	25 (18%)	7 (19%)	17 (16%)	13 (20%)	
Side-effect score	4 (0; 16)	0	4 (0; 12.5)	0 (0; 2)	2 (0; 12)	2 (0; 16.5)	1 (0; 15)	1 (0; 20.5)	<0.001
Visual acuity									
VA in better eye (logMAR)	0.05 (0.00; 0.15)	0.00 (-0.08; 0.05)	0.00 (0.00; 0.10)	0.02 (0.00; 0.10)	0.10 (0.00; 0.22)	0.00 (0.00; 0.10)	0.10 (0.00; 0.22)	0.10 (0.01; 0.30)	<0.001
VA in worse eye (logMAR)	0.22 (0.05; 0.40)	0.05 (0.00; 0.11)	0.10 (0.00; 0.30)	0.07 (0.00; 0.19)	0.22 (0.10; 0.40)	0.10 (0.05; 0.37)	0.30 (0.10; 0.92)	0.70 (0.22; 1.5)	<0.001
Visual field									
Time since last test (years)	0.8 (0.1; 2.5)	1.4 (0.5; 2.1)	1.6 (0.0; 3.4)	1.0 (0.2; 3.1)	0.3 (-0.2; 1.9)	0.7 (0.3; 2.1)	0.8 (0.2; 2.1)	1.2 (0.4; 3.0)	<0.001
MD in better eye, with imputed data	-1.7 (-5.0; -0.1)	0.0 (-0.9; 0.4)	-0.4 (-1.6; 0.2)	0.0 (-1.4; 0.6)	-1.8 (-3.9; 0.4)	-1.8 (-6.7; 0.5)	-4.9 (-12.0; -1.5)	-13.8 (-22.9; -3.7)	<0.001
MD in better eye, without imputed data	-1.6 (-4.7; 0.0)	-0.2 (-1.3; 0.8)	-0.4 (-1.7; 0.4)	-0.1 (-1.6; 0.7)	-1.7 (-3.4; -0.4)	-2.5 (-7.8; 0.5)	-4.4 (-10.1; -1.8)	-9.9 (-16.9; -3.5)	<0.001
MD in worse eye, with imputed data	-5.6 (-18.0; -1.4)	-0.4 (-1.8; 0.0)	-1.4 (-3.2; -0.1)	-1.7 (-4.3; 0.0)	-5.5 (-11.9; -1.6)	-8.5 (-16.3; -1.6)	-15.7 (-20.5; -9.3)	-28.4 (-30.5; -26.0)	<0.001
MD in worse eye, without imputed data	-3.8 (-12.8; -1.1)	-0.7 (-2.5; 0.2)	-1.5 (-3.0; -0.3)	-2.3 (-4.2; -0.3)	-4.8 (-11.6; -1.4)	-7.7 (-14.9; -1.3)	-13.9 (-20.4; -8.7)	-28.2 (-30.5; -26.0)	<0.001
Intraocular pressure									
IOP in better eye (mmHg)	16 (14; 19)	22 (20; 24)	18 (15; 20)	18 (16; 20)	16 (14; 18)	16 (13; 19)	14 (11; 18)	13 (11; 16)	<0.001
IOP in worse eye (mmHg)	16 (14; 19)	22 (20; 24)	18 (15; 20)	18 (17; 20)	16 (14; 18)	16 (13; 19)	14 (10; 16)	14 (11; 17)	<0.001

¹Kruskal-Wallis test, Chi-square test. LT= laser trabeculoplasty; VA= visual acuity; MD= Mean Deviation; IOP= intraocular pressure.

Table 2 Quality-of-life and utility scores in sampling categories. Mean, median (25th;75th percentile)

Instrument (worst-best score)	Total population	Untreated OHT	OHT medication	OHT LT	POAG medication	POAG LT	POAG surgery	End stage POAG	p-value ¹⁾
GQL score (75-15)	28, 23 (17; 34)	20, 18 (16; 23)	22, 18 (16; 25)	24, 20 (15; 27)	24, 20 (17; 27)	28, 24 (17; 34)	34, 31 (23; 43) ²⁾	48, 49 (29; 65) ²⁾	<0.001
VFQ-25 composite score (0-100)	78, 85 (70; 93)	88, 90 (84; 95)	87, 91 (84; 95)	85, 89 (80; 94)	83, 87 (77; 93) ²⁾	78, 84 (72; 92)	71, 77 (60; 86) ²⁾	53, 49 (31; 75) ²⁾	<0.001
EQ-5D VAS (0-100)	76, 80 (70; 85)	77, 80 (70; 83)	79, 80 (70; 90)	79, 80 (70; 90)	76, 80 (70; 85)	75, 80 (70; 80)	75, 80 (70; 85)	70, 70 (60; 80) ²⁾	0.014
EQ-5D utility (0-1)	0.87, 0.90 (0.81; 1.00)	0.89, 0.89 (0.81; 1.00)	0.90, 1.00 (0.81; 1.00)	0.92, 1.00 (0.81; 1.00)	0.88, 1.00 (0.81; 1.00)	0.89, 0.90 (0.81; 1.00)	0.84, 0.90 (0.77; 1.00)	0.79, 0.87 ²⁾ (0.69; 1.00)	0.050
HUI 3 utility (0-1)	0.70, 0.79 (0.54; 0.92)	0.78, 0.85 (0.68; 0.92)	0.77, 0.85 (0.70; 0.97)	0.77, 0.81 (0.63; 0.92)	0.68, 0.79 ²⁾ (0.54; 0.91)	0.74, 0.79 (0.63; 0.92)	0.66, 0.71 (0.47; 0.92)	0.54, 0.57 ²⁾ (0.33; 0.85)	<0.001

¹⁾ Kruskal-Wallis test, ²⁾ p<0.008 in Mann-Whitney test, compared to all previous groups.

GQL= Glaucoma Quality of Life questionnaire; VFQ= Visual Functioning Questionnaire;

EQ-5D= EuroQol questionnaire; VAS= Visual Analogue Scale; HUI3= Health Utilities Index mark 3;

OHT= ocular hypertension; LT= laser trabeculoplasty; POAG= primary open-angle glaucoma.

Figure 1 Regression coefficients for dummy variables representing categories of MD in the better eye relative to MD ≥ 0 (n=136), adjusted for age, sex, visual acuity, medication side-effects, LT, glaucoma surgery and MD in the worse eye. The grey error bars indicate the 95% confidence

intervals of the coefficients. The light grey line represents the expected value of the coefficient according to the original multiple linear regression model with MD in the better eye as a continuous variable.

Table 3 Coefficients from single and multiple regression analysis with GQL-15 score, VFQ-25 score, and HUI3 utility (scale 0 – 100)

	Single		Multiple	
	Adjusted R ²	Coefficient (95% CI)	Adjusted R ²	Coefficient (95% CI)
GQL				
Constant			0.543	20.3 (14.0; 25.6)
Age (per year)	0.016	0.19 (0.07; 0.30)		-0.03 (-0.12; -0.06)
Male (versus female)	0.000	-1.2 (-3.8; 1.4)		-2.0 (-3.9; -0.2)
VA better eye (per 0.1 logMAR unit)	0.216	3.5 (2.9; 4.0)		1.6 (1.0; 2.1)
VA worse eye (per 0.1 logMAR unit)	0.128	1.1 (0.86; 1.4)		0.35 (0.20; 0.51)
Side effects (per point)	0.076	0.20 (0.14; 0.26)		0.14 (0.09; 0.18)
LT in treatment history	0.044	7.4 (4.5; 10.3)		0.81 (-1.5; 3.1)
Glaucoma surgery in treatment history	0.172	14.1 (11.4; 16.7)		3.2 (0.7; 5.7)
MD in better eye (per dB)	0.370	-1.4 (-1.6; -1.2)		-0.55 (-0.77; -0.33)
MD in worse eye (per dB)	0.128	-0.90 (-1.0; -0.80)		-0.32 (-0.47; -0.17)
VFQ-25				
Constant			0.543	91.2 (82.7; 99.7)
Age (per year)	0.021	-0.28 (-0.44; -0.12)		0.01 (-0.11; 0.13)
Male (versus female)	0.000	0.21 (-3.3; 3.7)		0.78 (-1.7; 3.3)
VA better eye (per 0.1 logMAR unit)	0.256	-5.1 (-5.8; -4.3)		-2.7 (-3.4; -1.9)
VA worse eye (per 0.1 logMAR unit)	0.222	-1.3 (-1.5; -1.1)		-0.46 (-0.67; -0.26)
Side effects (per point)	0.092	-0.30 (-0.38; -0.22)		-0.22 (-0.28; -0.16)
LT in treatment history	0.034	-8.9 (-12.9; -5.0)		-0.8 (-3.8; 2.3)
Glaucoma surgery in treatment history	0.152	-17.8 (-21.3; -14.2)		-4.4 (-7.8; -1.0)
MD in better eye (per dB)	0.351	1.9 (1.6; 2.1)		0.77 (0.48; 1.07)
MD in worse eye (per dB)	0.317	1.1 (1.0; 1.3)		0.28 (0.08; 0.48)
HUI3				
Constant			0.263	113.8 (98.5; 129.1)
Age (per year)	0.079	-0.75 (-0.97; -0.53)		-0.47 (-0.69; -0.26)
Male (versus female)	0.000	2.5 (-2.5; 7.4)		1.3 (-3.2; 5.8)
VA better eye (per 0.1 logMAR unit)	0.138	-5.3 (-6.4; -4.1)		-2.7 (-4.1; -1.3)
VA worse eye (per 0.1 logMAR unit)	0.095	-1.2 (-1.6; -0.9)		-0.47 (-0.84; -0.09)
Side effects (per point)	0.064	-0.36 (-0.47; -0.24)		-0.30 (-0.41; -0.20)

Table 3 Continued

	Single		Multiple	
	Adjusted R ²	Coefficient (95% CI)	Adjusted R ²	Coefficient (95% CI)
HUI3				
LT in treatment history	0.000	-2.0 (-7.6; 3.7)		3.5 (-2.0; 9.0)
Glaucoma surgery in treatment history	0.029	-11.2 (-16.6; -5.8)		-0.7 (-6.8; 5.4)
MD in better eye (per dB)	0.100	1.4 (1.0; 1.8)		0.40 (-0.13; 0.93)
MD in worse eye (per dB)	0.099	0.90 (0.67; 1.13)		0.28 (-0.08; 0.65)

GQL= Glaucoma Quality of Life questionnaire; VA= visual acuity; LT= argon laser trabeculoplasty; MD= Mean Deviation; CI= Confidence interval.

Patients at risk for quality-of-life loss due to visual field loss

We assessed the existence of patient characteristics that predicted a greater impact of visual field loss on HRQOL by introducing interaction terms in the multiple analysis. The interaction terms were constructed from MD in the better eye on the one hand, and each of the other factors in the multiple regression model on the other hand. Only one significant interaction was found, between the visual field loss in the better and the worse eye (only for GQL and VFQ-25 scores). The coefficients for MD in the better eye were no longer statistically significant in the models containing the interaction term. For GQL scores the coefficient for MD in the worse eye became -0.27/dB (95% CI: -0.42; -0.12) and the coefficient for the interaction term ($MD_{\text{better}} \times MD_{\text{worse}}$) was 0.04/dB² (95% CI: 0.02; 0.05). For VFQ-25 scores these coefficients were 0.22/dB (95% CI: 0.02; 0.43) and -0.04/dB² (95% CI: -0.07; -0.02) respectively.

Discussion

This observational study assessing the relationship between visual field loss and health-related quality-of-life has several merits. Our patient population was large and heterogeneous, and we have measured glaucoma-specific, vision-specific and generic HRQOL (utility). The multiple regression analyses showed that visual field loss was associated with loss of glaucoma-specific and vision-specific

HRQOL, but utility did not seem to be affected until the visual field defect in the better eye was below -25 dB. However, the sample size (specifically in the worst group) was small in the context of the large variance observed in utility. Additionally, the multiple regression model may have over-adjusted for some covariance. Visual acuity was entered to correct for the presence of non-glaucomatous eye diseases, notably cataract, which affects both HRQOL and MD. This assures that any loss of HRQOL that is not glaucoma related is not represented in the regression coefficient for MD. However, visual acuity contains a glaucoma-related component when central vision is affected by visual field loss. Indeed we saw a moderate association between visual acuity and MD within the same eye (better eye $r = -0.35$ ($p < 0.01$), worse eye $r = -0.46$ ($p < 0.01$)). By adjusting for visual acuity, we have also adjusted for the glaucomatous loss of visual acuity, which may have lead to an underestimation of the regression coefficient for MD.

The multiple regression coefficients of MD in the better eye were higher than those for MD in the worse eye, indicating that a worsening of visual field in the better eye has a larger HRQOL impact than visual field loss in the worse eye. We saw that the binocular visual field was almost completely determined by the visual field in the better eye (Spearman's $r = 0.96$, $p < 0.001$), which probably explains the relatively large impact of the better eye in vision-related activities and visual functioning. In order to maintain HRQOL in glaucoma patients it is therefore important to monitor the better eye with an equal amount of vigilance as the worse eye, even when it is not (yet) affected. This is even more so when the worse eye has suffered considerable visual field loss, since the regression analyses with interaction terms showed that the impact of visual field loss in the better eye grows with increasing visual field loss in the worse eye. Since there is such a strong correlation of defects in the binocular visual field and in the better eye, there is no need to integrate both eyes' visual fields for better monitoring. Defects in the inferior hemifield call for closer monitoring as they affect HRQOL more strongly than defects in the superior hemifield.

We explored non-linearity in the relationship between HRQOL and MD. There was no indication for non-linearity in the multiple regression models for GQL and VFQ-25 when the interaction term for visual field loss in the better and the worse eye was included, signifying that glaucoma- and vision-specific HRQOL is equally impacted by early loss and advanced loss of visual field. However, we did find indications for non-linearity in the utility models, which was obviated in the regression analyses with dummy variables for categories of MD loss (Figure 1). Only the coefficient for 'MD in the better eye below -25 dB' was significantly different from zero, suggesting that utility is only affected by severe visual field loss in both

eyes. Comparable observations have been made by Kobelt *et al* and Burr *et al*. for EQ-5D utilities in glaucoma patients, but their sample sizes were smaller and the utilities were not adjusted for visual acuity.^{19, 20}

The visual field tests that provided the MD values of the participating patients were more recent in some patients than in others (table 1). However, since a low frequency of visual field testing is likely to reflect a low probability of progression (either from disease stability or an end-stage plateau), the impact of bias in MD values based on visual field tests that were longer ago will probably be small. Moreover, when we added 'time since the last visual field test' to the regression models, the coefficients for MD in the better and worse eye were not affected.

Visual acuity of both eyes should explicitly be addressed in POAG patient management because prevention of any visual acuity loss can preserve HRQOL. Side effects from medication had an independent impact on all HRQOL scores. To enable interpretation of the coefficients, we have calculated the difference in the average side-effect score from patients who indicated that glaucoma medication had "none" or "hardly any" impact on their quality-of-life (9 ± 16 , $n = 324$) and patients that indicated that the impact was "quite a bit" or "much" (52 ± 39 , $n = 20$). Multiplying the difference of 43 units with the regression coefficient for the HRQOL instruments yields a loss of 6 units in GQL score, 9 units in VFQ-25 score, 9% EQ-5D utility and 13% HUI utility as a result of severe side effects. For comparison, based on the regression coefficients found in the multiple regression models, the expected loss in HRQOL as a result of an MD decrease of 10 dB in both eyes would be 9, 11, 2% and 7% respectively. Apparently, utility loss from side effects can be larger than utility loss from glaucoma progression, although the relationship between side effects and HRQOL may represent a certain degree of concurrent validity rather than an impact of side effects alone, because the side effect score may have captured components of quality-of-life. Discrete choice experiments have shown that patients value preservation of central and near vision, mobility and daily activities much higher than the absence of eye discomfort.^{20, 21} The burden of side effects is usually temporary since treatment can be adjusted when side-effects occur, but the impact of side effects on all HRQOL levels in this study emphasizes the need to address this issue in patient management. We also found an independent impact of glaucoma surgery on glaucoma- and vision-specific HRQOL (but not generic HRQOL) which suggests that surgery may cause a reduction in quality-of-life, potentially as a result of post-surgical symptoms. Based on the coefficients for VFQ-25 (table 3), the impact of surgery in terms of HRQOL would correspond to an MD decrease of 5 dB in the better eye, implying that the expected preservation of visual field must exceed 5 dB in order for the long term benefits of surgery to

outweigh the short term hindrance. These results are not in accordance with the Collaborative Initial Glaucoma treatment Study (CIGTS), where the investigators indeed found surgery to be associated with more frequent and more bothersome symptoms, but not with worse vision-specific or generic HRQOL, nor in worse patient satisfaction.²² Despite the fact that the multiple regression models in our study corrected for the potential confounding effect of disease severity, the 'surgery' variable may have come up as an intermediate for aspects of disease severity not reflected by MD or visual acuity but associated with both quality-of-life and the likelihood of surgery. The causality of the relationship between surgery and quality of life can therefore not be inferred from these data.

The variables in the multiple regression models explained only part of all observed variance, and HRQOL in glaucoma patients is affected by additional factors than those that were included in our regression model. For example, when we included the presence of sixteen types of comorbidities, education level and employment status, the amount of variance explained in GQL, VFQ, EQ-5D and HUI3 scores increased to 60%, 60%, 34% and 35% respectively. These additional factors did not confound or modify the primary relationship between visual field and HRQOL, so they were excluded from the main analyses reported here.

Part of our patient population consisted of OH patients without visual field damage, who were nevertheless included in the analyses. They represent one end of the glaucoma severity scale are therefore a reference point. Additionally, their experience with treatment in terms of HRQOL was very relevant in our analyses. There may be concern though that the HRQOL scores in this group have unduly affected the regression lines, so we have repeated the analyses with data from POAG patients only. The conclusions remained unaltered. The coefficients for MD in the better and worse eye changed only slightly, and we still found non-linearity in the utility models and an interaction between MD in the better and worse eye for VFQ-25 and GQL outcomes.

The results from this study indicate that increasing visual field loss in progressing glaucoma is independently associated with a loss in both disease-specific and generic quality-of-life. In terms of glaucoma- and vision-specific HRQOL it is equally important to prevent progression in early stages as it is in advanced stages of glaucoma, especially in the better eye of the patient. Moreover, monitoring visual acuity, side-effects, visual field defects in the inferior hemifield and patients with severe visual field impairment in one eye are of clinical importance.

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References

1. Maier P, Funk J, Schwarzer G, Antes G, Falck-Ytter Y. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ* 2005; 331:134.
2. Peeters A, Webers C, Prins M, Zeegers M, Hendrikse F, Schouten J. Quantifying the effect of intra-ocular pressure reduction on the occurrence of glaucoma. *Acta Ophthalmol* 2010; 88:5-11.
3. Gutierrez P, Wilson M, Johnson C, Gordon M, Cioffi G, Ritch R, Sherwood M, Meng K, Mangione C. Influence of glaucomatous visual field loss on health-related quality of life. *Arch Ophthalmol* 1997; 115:777-784.
4. Parrish R, Gedde S, Scott I, Feuer W, Schiffman J, Mangione C, Montenegro-Piniella A. Visual function and quality of life among patients with glaucoma. *Arch Ophthalmol* 1997; 115:1447-1455.
5. McKean Cowdin R, Wang Y, Wu J, Azen SP, Varma R. Impact of visual field loss on health-related quality of life in glaucoma: the Los Angeles Latino Eye Study. *Ophthalmology* 2008; 115:941-948.
6. Beckers HJ, Schouten JS, Webers CA, van der Valk R, Hendrikse F. Side effects of commonly used glaucoma medications: comparison of tolerability, chance of discontinuation, and patient satisfaction. *Graefes Arch Clin Exp Ophthalmol* 2008; 246:1485-1490.
7. Nelson P, Aspinall P, Papasouliotis O, Worton B, O'Brien C. Quality of life in glaucoma and its relationship with visual function. *J Glaucoma* 2003; 12:139-150.
8. Nelson P, Aspinall P, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. *Br J Ophthalmol* 1999; 83:546-552.
9. Van der Sterre G, Van de Graaf E, Verezen C, Meulendijks C, Schouten J, Saxena R, Polling J, Van Rijn L, Hoyng C, Essink-Bot M, Simonsz H. National Eye Institute Visual Functioning Questionnaire-25: Dutch consensus translation (VFQ-25/NL). Rotterdam: Erasmus Medical Center Rotterdam, department of Ophthalmology, 2001.
10. Mangione C, Lee P, Pitts J, Gutierrez P, Berry S, Hays R, for the NEI-VFQ Field Test Investigators. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). *Arch Ophthalmol* 1998; 116:1496-1504.
11. NEI VFQ-25 scoring algorithm. Available at: http://www.nei.nih.gov/resources/visionfunction/manual_cm2000.pdf. Accessed: 23 June 2008
12. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001; 33:337-343.
13. Lamers L, Stalmeier P, McDonnell J, Krabbe P, van Busschbach J. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. *Ned Tijdschr Geneesk* 2005; 149:1574-1578.
14. Torrance GW, Furlong W, Feeny D, Boyle M. Multi-attribute preference functions. *Health Utilities Index. Pharmacoeconomics* 1995; 7:503-520.
15. Furlong W, Feeney D, Torrance G, Goldsmith C, DePauw S, Boyle M, Denton M, Zhu Z. Multiplicative multi-attribute utility function for the Health Utilities Index Mark 3 (HUI3) System: A Technical Report. Working Paper No 98-11 McMaster University Centre for Health Economics and Policy Analysis.
16. Donders A, Van der Heijden G, Stijnen T, Moons K. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006; 59:1087-1091.
17. Ferris 3rd FL, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol* 1982; 94:91-96.
18. Nelson-Quigg J, Cello K, Johnson C. Predicting binocular visual field sensitivity from monocular visual field results. *Invest Ophthalmol Vis Sci* 2000; 41:2212-2221.
19. Kobelt G, Jonsson B, Bergstrom A, Chen E, Linden C, Alm A. Cost-effectiveness analysis in glaucoma: what drives utility? Results from a pilot study in Sweden. *Acta Ophthalmol Scand* 2006; 84:363-371.
20. Burr J, Kilonzo M, Vale L, Ryan M. Developing a preference-based glaucoma utility index using a discrete choice experiment. *Optom Vis Sci* 2007; 84:797-808.
21. Aspinall P, Johnson Z, Azuara-Blanco A, Montarzino A, Brice R, Vickers A. Evaluation of quality of life and priorities of patients with glaucoma. *Invest Ophthalmol Vis Sci* 2008; 49:1907-1915.
22. Janz N, Wren P, Lichter P, Musch D, Gillespie B, Guire K, Mills R, and the CIGTS Study Group. The Collaborative Initial Glaucoma Treatment Study; Interim quality of life findings after initial medical or surgical treatment of glaucoma. *Ophthalmology* 2001; 108:1954-1965.

**The relationship between
visual field loss in glaucoma and
health-related quality-of-life**

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This document contains supplementary information to the paper “The relationship between visual field loss and health-related quality-of-life” in Eye. The information pertains to the in-and exclusion criteria we used in the observational survey, the method used to impute missing MD values, the average HRQOL scores, and the results of single and multiple regression analysis of EQ-5D utilities.

Table 1 In- and exclusion criteria for the seven sampling categories.

Sampling category	Diagnosis OHT by ophthalmologist (either eye)	Diagnosis POAG by ophthalmologist (either eye)	Currently using glaucoma medication	Previously using glaucoma medication	Laser trabeculoplasty in treatment history	Glaucoma surgery in treatment history	Glaucoma or ocular hypertension treatment history	Visual field limited to central 10 degrees (either eye)	Comorbidities that may cause elevated IOP	Comorbidities that may cause visual field limitation to central 10 degrees
1 OHT untreated	i	e	e	e	e	e	e		e	
2 OHT, medication	i	e	i		e	e				
3 OHT, LT	i	e			i	e				
4 POAG, medication		i	i		e	e				
5 POAG, LT		i			i	e				
6 POAG, surgery		i				i				
7 POAG, blind		i						i		e

OHT= ocular hypertension; POAG= primary open-angle glaucoma; LT= laser trabeculoplasty; IOP= intraocular pressure; i= inclusion criterion; e= exclusion criterion. If more than one category applied to a particular patient, the highest number was assigned. All patients read the written patient information and signed the informed consent form before being included in the study.

Table 2 Methods to impute an MD value from the available visual field measurements.

Situation	Method to estimate current MD	Applied to
1. The most recent VF measurement was performed with a 30-2 or 24-2 HFA full threshold program.	Use the Mean Deviation from the last VF measurement (i.e. no imputation).	71.8% of eyes
2. The most recent VF measurement was from an Octopus G1 program.	$MD_{HFA} = (MD_O \cdot -1.170) - 0.874$. ²³ Use the most recent MD _O value.	6.0% of eyes
3. None of the above, but there is a VF measurement with HFA (30-2 or 24-2) / Octopus (G1) within the last two years.	Use the MD from the most recent HFA measurement / calculate from the most recent octopus measurement with $MD_{HFA} = (MD_O \cdot -1.170) - 0.874$. ¹⁾	2.2% of eyes
4. There are HFA 30-2 or 24-2 measurements in the past, but for the last two years (or more) only HFA 10-2 measurements.	Plot 30-2 MD against time, and 10-2 MD against time for each patient. Estimate current 30-2 MD from the historic 30-2 MD values and observed progression rate in 10-2 MD.	2.6% of eyes
5. There are only HFA 10-2 measurements.	Estimate 30-2 MD from 10-2 MD with the formula $MD_{30-2} = -1.2 + 0.88 \cdot MD_{10-2}$. ²⁾	4.6% of eyes
6. None of the above, but there are HFA 76- or 120 point screening VF tests, type 'quantify defects'.	Estimate 30-2 MD by averaging the defect depth of all points in the central 30°.	1.9% of eyes
7. None of the above, but there is a HFA 30-2 measurement in the past.	Use the Mean Deviation from the last HFA 30-2 measurement.	0.8% of eyes
8. None of the above, but there are HFA 76- or 120 point screening VF tests, type '2 zone' or '3 zone'.	Estimate 30-2 MD from absolute and relative defects in the central 30°. ³⁾	1.8% of eyes
9. None of the above, but the patient was recruited as an 'ocular hypertension' patient.	Assume that MD = 0	4.1% of eyes
10. None of the above, but there was a peritest in the patient file.	Defects > 2, MD = 25 dB Defects 1.4 – 1.8, MD = 16 dB Defects 0.8 – 1.2, MD = 10 dB Defects > 0.6, MD = 7 dB	0.6% of eyes
11. None of the above.	MD = missing.	3.6% of eyes

HFA= Humphrey Field Analyzer (Carl Zeiss Meditec, Jena, Germany); VF= visual field;
MD (or MD_{HFA})= Mean Deviation from HFA; MD_O= Mean Defect from Octopus (Haag-Streit AG, Koeniz, Switzerland) visual field measurement.

¹⁾ Zeyen T, Roche M, Brigatti L, Caprioli J. Formulas for conversion between Octopus and Humphrey threshold values and indices. Graefes Arch Clin Exp Ophthalmol 1995; 233:627-634.

²⁾ This equation was derived from regression analysis with data from 188 combinations of 30-2 and 10-2 visual field measurements performed on the same day in the study participants.

³⁾ The MD was estimated by assuming a deviation of 0 dB in normal points, -20 dB in relative defect points and -30 dB in absolute defect points, and averaging across all points in the central 30°.

Table 3 Participating versus non-participating patients, median (25th to 75th percentile).

Selectiongroup	All	Untreated OHT	OHT medication	OHT LT	POAG medication	POAG LT	POAG surgery	End stage POAG
Number (n)								
Selected	704	82	141	17	175	43	158	88
Died	50	2	8	1	15	3	16	5
Invited	654	80	133	16	160	40	142	83
Refused	123	19	19	2	24	3	37	19
Participated	531	61	114	14	136	37	105	64
Participation rate	81%	76%	86%	88%	85%	93%	74%	77%
Age								
Not participated	76 (63; 83)	67 (63; 76)	59 (47; 82)	62 (58; 66)	77 (68; 86)	72 (42; 82)	79 (69; 83)	76 (64; 83)
Participated	71 (62; 77) ^b	67 (61; 72)	72 (63; 76)	70 (61; 73)	71 (64; 80)	67 (57; 76)	72 (62; 80)	70 (62; 79)
VA better eye (LogMAR)								
Not participated	.10 (.00; .22)	.10 (.00; .13)	.10 (.00; .11)	.04 (-.08; .16)	.10 (.00; .22)	.10 (.00; .70)	.19 (.06; .30)	.30 (.10; .52)
Participated	.05 (.00; .16) ^b	.00 (-.08; .05) ^b	.00 (.00; .10)	.02 (.00; .10)	.10 (.00; .22)	.00 (.00; .10)	.10 (.00; .22) ^b	.10 (.01; .30)
VA worse eye (LogMAR)								
Not participated	.30 (.10; .75)	.10 (.00; .22)	.22 (.10; .40)	.85 (-.08; 1.77)	.26 (.10; .47)	.40 (-.00; .70)	.52 (.30; 1.82)	1.00 (.30; 2.5)
Participated	.22 (.05; .40) ^b	.05 (.00; .11)	.10 (.00; .30)	.07 (.00; .19)	.22 (.10; .40)	.10 (.05; .37)	.30 (.10; .93) ^b	.70 (.22; 1.51)
MD better eye								
Not participated	n=68 -2.5 (-7.0; 0.1)	n=13 -0.2 (1.8; 0.8)	n=6 0.1 (-3.6; 1.5)	n=2 -6.2 (-13.4; 1.0)	n=19 -2.0 (-6.0; -0.0)	n=3 -5.3 (-15.3; 0.9)	n=16 -9.4 (-17.3; -4.0)	n=7 -15.7 (-28.4; -4.5)
Participated	-1.6 (-4.9; -0.0)	-0.0 (-0.9; 0.4)	-0.4 (-1.6; 0.2)	-0.0 (-1.4; 0.6)	-1.8 (-3.9; -0.4)	-3.5 (-6.7; 0.5)	-4.9 (-12.0; -1.5)	-13.8 (-22.9; -3.7)
MD worse eye								
Not participated	n=78 -7.5 (-22.7; -1.5)	n=13 -1.4 (-2.5; 0.3)	n=7 0.0 (-5.0; 1.0)	n=2 -11.4 (-23.3; 0.6)	n=19 -4.1 (-15.0; -1.0)	n=3 -7.9 (-26.6; -1.6)	n=20 -21.2 (-27.3; -10.6)	n=13 -21.5 (-29.0; -14.2)
Participated	-5.1 (-17.6; -1.1)	-0.4 (-1.8; 0.0)	-1.4 (-3.2; -0.1)	-1.7 (-4.3; -0.0)	-5.5 (-11.9; -1.6)	-8.5 (-16.3; -1.6)	-15.7 (-20.5; -9.3) ^b	-28.4 (-30.5; -26.0) ^b

^a Data on visual acuity and visual field were not available for all non-participating patients.

The numbers given for n in each cell of non-participating patients indicates the number of patients for whom the information was available. ^b p<0.05 for the difference between participating and non-participating patients in a Mann-Whitney test

Table 4 Coefficients from single and multiple regression analysis with EQ-5D utility (scale 0 – 100)

	Single		Multiple	
	Adjusted R ²	Coefficient (95% CI)	Adjusted R ²	Coefficient (95% CI)
Constant			0.176	98.5 (88.2; 108.8)
Age (per year)	0.026	-0.28 (-0.42; -0.14)		-0.12 (-0.26; 0.03)
Male (versus female)	0.017	5.1 (2.0; 8.2)		4.6 (1.5; 7.6)
VA better eye (per 0.1 logMAR unit)	0.076	-2.5 (-3.3; -1.8)		-1.4 (-2.3; -0.5)
VA worse eye (per 0.1 logMAR unit)	0.057	-0.61 (-0.82; -0.40)		-0.31 (-0.56; -0.05)
Side effects (per point)	0.067	-0.23 (-0.31; -0.16)		-0.21 (-0.28; -0.13)
LT in treatment history	0.000	0.63 (-3.0; 4.3)		3.7 (-0.0; 7.4)
Glaucoma surgery in treatment history	0.021	-6.3 (-9.7; -2.8)		-2.6 (-6.7; 1.5)
MD in better eye (per dB)	0.045	0.61 (0.37; 0.85)		0.07 (-0.29; 0.43)
MD in worse eye (per dB)	0.045	0.39 (0.24; 0.55)		0.11 (-0.13; 0.36)

EQ-5D= EuroQoL questionnaire; VA= visual acuity; LT= argon laser trabeculoplasty;
MD= Mean Deviation; CI= Confidence interval.

Chapter 3

Ocular hypertension and the risk of blindness

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Submitted

Abstract

Purpose: To estimate the risk of blindness in patients with ocular hypertension (OHT) using an appropriate model and current empirical data.

Design: A Markov-model with data from a systematic literature review.

Methods: A Markov-model with three health-states was built: OHT, primary open-angle glaucoma (POAG) and unilateral blindness. Literature was searched for reports on conversion from OHT to POAG, and progression from POAG to blindness to estimate a range of annual conversion and progression probabilities. The model had a cycle length of one year.

Results: The 15-years risk estimates ranged from 3.1% to 9.4% in untreated, and from 0.9% to 8.6% in treated OHT patients. The ranges were the result of differences in patient populations, treatments and outcome definitions in currently available empirical data.

Conclusions: The best estimates of the 15-year risk of unilateral blindness in OHT patients, based on currently available empirical data and an appropriate model, show that the risk is lower than 10%.

Introduction

Primary open-angle glaucoma (POAG) is one of the major causes of blindness, and ocular hypertension (OHT) is a well known risk factor for the development of primary open-angle glaucoma.¹ Not all patients with OHT develop POAG though, and not all patients with POAG develop blindness, which raises the question whether OHT should be treated or not. The aim of this brief report was to quantify the risk of blindness in treated and untreated patients with OHT, using an adaption to a previously reported calculation of the 15-year risk of unilateral blindness in OHT patients that was based on available data from population-based studies.² The authors of the original article point out that their calculation method systematically underestimated the blindness risk. This brief report therefore uses a more appropriate calculation model and an update of available data.

Methods

A Markov chain model with the following three health states was built: ocular hypertension, primary open-angle glaucoma and unilateral blindness (figure 1).³ The cycle length was one year. The Markov-model simulated the distribution of a population of OHT patients over the health states using the probability to move between the states after one cycle (transition probabilities A to E). For example, if the model starts with 100 patients with OHT and the chance to go from OHT to POAG (B) is 2% per year, then the number of patients with OHT after one year will be $100 - (0.02 \cdot 100) = 98$ and after two years it will be $98 - (0.02 \cdot 98) \approx 96$. Simultaneously, patients with POAG can move to 'blindness' by transition D. By running this model for 15 cycles, the expected proportion of patients in 'blindness' after 15 years can be calculated.

Figure 1 Markov model for progression to blindness in OHT and POAG patients

Transition probabilities B and D in figure 1 represent the risk of POAG in OHT patients (conversion) and the risk of blindness in POAG patients (progression) respectively. E equals 1 because the risk to remain blind is 100%; A equals 1-B and C equals 1-D. Annual transition probabilities were calculated from cumulative incidences with a hazard function (table 1). If the rate of conversion/progression is assumed to be constant, the cumulative incidence is equal to $1 - e^{-rt}$, in which r is the annual rate and t is the time measured in years. For example, a cumulative incidence of conversion of 9.5% in five years leads to $r = 0.019964$ and a transition probability of 1.98% per year.

The estimate of the transition probability B was based on the randomized controlled trials identified in a recently published meta-analysis on the effect of IOP lowering therapy on the incidence of conversion.⁴ An update of the literature search conducted in the meta-analyses identified one more report.⁵ Only studies with a high quality score (≥ 9 out of 16) were included here, and only conversion incidences based on visual field defects or a glaucomatous disc were considered.⁶⁻¹¹

To estimate transition probability D we performed a systematic literature search in Medline searching for the keywords 'open-angle glaucoma', 'blind(ness)', 'incidence', and 'risk' or 'rate' in the abstracts. All observational and intervention studies in POAG populations with unilateral (legal) blindness as one of the outcomes and a follow-up of at least 5 years were selected.¹²⁻¹⁸ Because death was not considered in our model, we used censored survival data from Kaplan-Meier curves. The outcomes of the model therefore represent the estimated risk of blindness in OHT patients in the next 15 years given they survive that period.

Results

The outcomes of the model are presented in figure 2. This figure shows how the 15-years risk of blindness in OHT patients varies depending on the conversion and progression rates. This graph also presents the point estimates of the 15-year blindness risk in OHT patients based on the lowest, highest and weighted transition rates listed in table 1. Overall, the risk of blindness in untreated OHT patients was 4.1% (range 3.1%-9.4%). The risk of blindness in treated OHT patients was 3.5% (range 0.9%-8.6%). The definition of treatment, disease status and study endpoints varied widely across studies, which compromised the generalizability and comparability of study results. This resulted in the wide range of risk estimates. However, these estimates are the best estimates of the risk of blindness in OHT patients that can be made, given that they are based on currently available empirical data and an appropriate calculation model.

Table 1 Kaplan-Meier estimates of cumulative incidences found in the literature for conversion from OHT to POAG and progression from POAG to blindness in untreated and treated patients

Study	Year	N	Cumulative incidence OHT→POAG ^c	Annual risk (transition B)	Marker in figure 2
Untreated					
<i>Weighted average^a</i>				2.8%	○
Kass et al. ⁶	2002	819	9.5% in 5 years	2.0 %	◇
Kass et al. ⁸	1989	62	12% in 5 years	2.5%	
EGPS ⁷	2005	541	14.1% in 5 years	3.0 %	
Kamal et al. ⁹	2003	174	12.2% in 4 years	3.2%	
Epstein et al. ¹⁰	1989	54	19.5 % in 4 years	5.3 %	
Heijl et al. ¹¹	2000	44	22% in 5 years 55% in 10 years	4.9% 7.7%	△
Treated					
<i>Weighted average^a</i>				1.7%	●
Kass et al. ^{5,6}	2002 2010	817 694	4.4% in 5 years 16% in 13 years	0.9% 1.3%	◆
Kamal et al. ⁹	2003	182	5.4% in 4 years	1.4%	
Epstein et al. ¹⁰	1989	53	7.4% in 4 years	1.9%	
Kass et al. ⁸	1989	62	10% in 5 years	2.1%	
EGPS ⁷	2005	536	13.4% in 5 years	2.8%	
Heijl et al. ¹¹	2000	46	15% in 5 years 26% in 10 years	3.2% 3.0%	▲
Study	Year	N	Cumulative risk POAG→ blindness ^{c,d}	Annual risk (transition D)	Marker in figure 2
Untreated					
Wilson et al. ¹²	2002	151	15.7% in 10 years ^b	1.7%	◇△○
Treated					
<i>Weighted average^a</i>				2.0%	●
Ang et al. ¹⁸	2007	121	0% in 7.4 years	0%	◆
Kwon et al. ¹⁴	2001	40	19% in 22 years	1.0%	
Chen ¹⁵	2003	186	14.6% in 15 years	1.1%	
Forsman et al. ¹⁷	2007	106	21% in 15 years	1.6%	
AGIS, low ¹³	2004	167	14.5% in 10 years	1.6%	
AGIS, high ¹³	2004	211	23.3% in 10 years	2.6%	
Hattenhauer et al. ¹⁶	1998	295	50% in 20 years ^b	3.4%	▲

^a Weighting was based on sample size N.

^b (legal) blindness based on visual field only (not visual acuity).

^c based on censored survival data.

^d legally blind in one or both eyes.

Figure 2 Outcomes of the Markov model. **A:** The estimated 15-year risk of unilateral blindness in OHT patients depending on conversion and progression rates. Triangles and diamonds represent the point estimates based on the highest and lowest rates found in literature (table 1). Circles represent the estimates based on the weighted averages in treated and untreated patients. Graph **B** shows the range in risk estimates from lowest to highest in treated and untreated patients, and the point estimates (X) based on the weighted averages for conversion and progression

References

1. Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. *N Engl J Med* 2009; 360:1113-1124.
2. Weinreb RN, Friedman DS, Fechtner RD, Cioffi GA, Coleman AL, Girkin CA, Liebmann JM, Singh K, Wilson MR, Wilson R, Kannel WB. Risk assessment in the management of patients with ocular hypertension. *Am J Ophthalmol* 2004; 138:458-467.
3. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993; 13:322-338.
4. Peeters A, Webers C, Prins M, Zeegers M, Hendrikse F, Schouten J. Quantifying the effect of intra-ocular pressure reduction on the occurrence of glaucoma. *Acta Ophthalmol* 2010; 88:5-11.
5. Kass MA, Gordon MO, Gao F, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JK, Miller JP, Parrish RK, Wilson MR. Delaying treatment of ocular hypertension: the ocular hypertension treatment study. *Arch Ophthalmol* 2010; 128:276-287.
6. Kass M, Heuer D, Higginbotham E, Johnson C, Keltner J, Miller J, Parrish R, Wilson R, Gordon M, the Ocular Hypertension Treatment Study Group. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002; 120:701-713.
7. Miglior S, Zeyen T, Pfeiffer N, Cunha-Vaz J, Torri V, Adamsons I, The European Glaucoma Prevention Study (EGPS) Group. Results of the European Glaucoma Prevention Study. *Ophthalmology* 2005; 112:366-375.
8. Kass M, Gordon M, Hoff M, Parkinson J, Kolker A, Hart WJ, Becker B. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals. A randomized, double-masked, long-term clinical trial. *Arch Ophthalmol* 1989; 107:1590-1598.
9. Kamal D, Garway-Heath D, Ruben S, O'Sullivan F, Bunce C, Viswanathan A, Franks W, Hitchings R. Results of the betaxolol versus placebo treatment trial in ocular hypertension. *Graefes Arch Clin Exp Ophthalmol* 2003; 241:196-203.
10. Epstein D, Krug J, Hertzmark E, Remis L, Edelstein D. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. *Ophthalmology* 1989; 96:1460-1467.
11. Heijl A, Bengtsson B. Long-term effects of timolol therapy in ocular hypertension: a double-masked randomised trial. *Graefes Arch Clin Exp Ophthalmol* 2000; 238:877-883.
12. Wilson M, Kosoko O, Cowan C, Sample P, Johnson C, Haynatzki G, Enger C, Crandall D. Progression of visual field loss in untreated glaucoma patients and glaucoma suspects in St. Lucia, West Indies. *Am J Ophthalmol* 2002; 134:399-405.
13. Ederer F, Gaasterland D, Dally L, Kim J, VanVeldhuisen P, Blackwell B, Prum B, Shafranov G, Allen R, Beck A, AGIS investigators. The Advanced Glaucoma Intervention Study (AGIS): 13. Comparison of treatment outcomes within race: 10-year results. *Ophthalmology* 2004; 111:651-664.
14. Kwon Y, Kim C, Zimmerman B, Alward W, Hayreh S. Rate of visual field loss and long-term visual outcome in primary open-angle glaucoma. *Am J Ophthalmol* 2001; 132:47-56.
15. Chen P. Blindness in patients with treated open-angle glaucoma. *Ophthalmology* 2003; 110:726-733.
16. Hattenhauer MG, Johnson DH, Ing HH, Herman DC, Hodge DO, Yawn BP, Butterfield LC, Gray DT. The probability of blindness from open-angle glaucoma. *Ophthalmology* 1998; 105:2099-2104.
17. Forsman E, Kivela T, Vesti E. Lifetime visual disability in open-angle glaucoma and ocular hypertension. *J Glaucoma* 2007; 16:313-319.
18. Ang GS, Eke T. Lifetime visual prognosis for patients with primary open-angle glaucoma. *Eye* 2007; 21:604-608.

Chapter 4

Modeling complex treatment strategies: construction and validation of a discrete event simulation model for glaucoma

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Abstract

Objective: Discrete event simulation modeling (DES) has several advantages over simpler modeling techniques in health economics, such as increased flexibility and the ability to model complex systems. However, these benefits may come at the cost of reduced transparency, which may compromise the model's face validity and credibility. We aimed to produce a transparent report on the construction and validation of a DES model using a recently developed model of ocular hypertension and glaucoma.

Methods: Current evidence of associations between prognostic factors and disease progression in ocular hypertension and glaucoma was translated into DES model elements. The model was extended to simulate treatment decisions and effects. Utility and costs were linked to disease status and treatment, and clinical and health economic outcomes were defined. The model was validated at several levels. The soundness of design and the plausibility of input estimates were evaluated in interdisciplinary meetings (face validity). Individual patients were traced throughout the simulation under a multitude of model settings to debug the model, and the model was run with a variety of extreme scenarios to compare the outcomes with prior expectations (internal validity). Finally, several intermediate (clinical) outcomes of the model were compared with those observed in experimental or observational studies (external validity) and the feasibility of evaluating hypothetical treatment strategies was tested.

Results: The model performed well in all validity tests. Analyses of hypothetical treatment strategies took about 30 minutes per cohort and lead to plausible health-economic outcomes.

Conclusion: There is added value of DES models in complex treatment strategies such as glaucoma. Achieving transparency in model structure and outcomes may require some effort in reporting and validating the model, but it is feasible.

Introduction

The application of discrete event simulation (DES) modeling in health economic decision analyses has been growing steadily in recent years.¹ This may be partly ascribable to the advances in computing technology, which enables faster Monte Carlo simulations, but undoubtedly also to some of the appealing advantages of DES in terms of flexibility and the ability to model complex systems.¹⁻⁴ Such increased complexity of a model can enhance the accuracy of the outcomes, but may come at the cost of a loss in transparency and therewith face validity and credibility.^{1,2} This is a problem since a lack of understanding of a model and trust in its outcomes may limit the degree to which information generated by the model is considered by the target audience. It is therefore important to not only maximize transparency, but also to convincingly validate a model and its outcomes.⁵ With this article we aim to contribute to the literature regarding the construction, validation and reporting of DES models in complex treatment strategies, drawing from our experience with a recently developed health economic DES model to simulate disease progression in glaucoma patients.

Glaucoma is an ocular condition involving the slow but gradual and irreversible loss of retinal nerve fibers, leading to visual field loss and possibly blindness. The etiology of glaucoma is unknown, but the most important known risk factor for its occurrence is an elevated intra-ocular pressure (IOP). As long as the IOP is elevated without signs of retinal nerve fiber loss, the condition is termed ocular hypertension (OHT). However, when nerve fiber loss occurs to a level that causes optic nerve cupping and/or visual field loss, the condition is termed primary open-angle glaucoma (POAG). The transition from OHT to POAG is termed 'conversion'. If nerve fiber loss continues (progression), the visual field deteriorates and a patient may progress to blindness. Treatment of glaucoma is directed at lowering the intra-ocular pressure (IOP) to slow down the neurodegenerative process.^{6,7} Since glaucoma is a chronic condition, patients are usually monitored and treated lifelong from the moment of diagnosis. Treatment guidelines for glaucoma have been formulated based on evidence from clinical trials, but several issues in these guidelines remain unspecified due to a lack of evidence.^{8,9} For example, it is unclear how often patients need to be evaluated for progression, and how low the target pressure should be to prevent further progression.

The information necessary to resolve these issues cannot be generated by clinical trials, because the follow-up period needed to establish differences in relevant outcomes (i.e. vision impairment or blindness) is long, and by the time the results are available they may no longer be relevant. Moreover, until the results of clinical

trials are available, treatment decisions still need to be made today. A large number of trials would be necessary to investigate all relevant combinations of treatment strategy characteristics (initiation, monitoring frequency, type of intervention, target pressure, etc) yielding a massive need for study subjects, and for obvious ethical reasons it is not possible to investigate the effect of withholding treatment. Finally, the study protocols would be inflexible to future treatment options and insights from scientific research in the pathogenesis of glaucoma. Therefore, rather than obtaining new evidence, we have used a modeling approach to synthesize all currently available evidence regarding glaucoma disease progression and the effects of treatment. The resulting health economic disease progression model will be employed to generate predictions of the (cost) effectiveness of a wide range of treatment strategies for ocular hypertension (OHT) and primary open-angle glaucoma (POAG) patients. We have used the DES model structure because it was expected to provide important advantages over other modeling techniques in the context of glaucoma and our research objectives. In this article we intend to: 1) justify the choice for a DES model, 2) describe how disease progression and treatment effects in glaucoma were translated into the structure of a DES model, and 3) present the results of the model validation.

Methods

Justifying the chosen model structure

One of the first steps in decision analytic modeling is to choose the most appropriate model structure. The choice for any particular model type must be based on the decision problem(s), the theory of the health condition being modeled, and on additional desired features such as flexibility or user-friendliness.¹⁰⁻¹² Various model types represent various levels of complexity, and the chosen model structure should only be complex enough to meet its intended purpose.⁵ Modeling glaucoma and its treatment calls for a relatively complex model structure because of (among others) the following reasons.¹³ Glaucoma is a chronic condition that requires lifetime monitoring and treatment, so a decision analytic model should facilitate a lifetime horizon of disease progression and treatment. Within this lifetime a number of treatment options are available, such as watchful waiting, medication, laser treatment or surgery, and a concurrent or sequential combination thereof. Even within medicinal treatment over 56,000 combinations of agents and dosages are possible.¹⁴ A decision analytic model of glaucoma therefore needs to compare treatment *strategies* rather than single treatment options. In addition, a treatment strategy is not only defined by the way treatments are ordered or combined, but also by the circumstances that call for a treatment change. After all, in clinical

practice a great number of factors may be considered in the decision to alter the existing glaucoma treatment, such as age, disease history, treatment history, current clinical status, the efficacy and tolerability of previous therapies, and the outcomes of diagnostic tests. Therefore, in order to evaluate different treatment strategies in the glaucoma decision analytic model, the model must be able to discern all the factors that are deemed relevant for the treatment strategy. In addition, the model must take account of all factors that are relevant for the costs and outcomes. Lastly, glaucoma disease progression is not characterized by clearly discernable disease states, but rather represents a sliding scale of anatomical and functional disease manifestations.¹⁵

The most common model types used in decision analytic modeling are (in increasing order of complexity) decision trees, Markov models and discrete event simulation (DES) models.²⁻⁴ Several authors have recently reviewed model structures and offered a guide on choosing the most appropriate method.¹⁶⁻¹⁹ Given the requirements described in the previous paragraph, we needed an individual sampling model based on either a Markov or a DES model structure. The main limitations of Markov models precluded its applicability in our research. First, in view of the multifaceted nature of glaucoma treatment and the fact that Markov health states are mutually exclusive (i.e. a patient can only be in one health state at the time), the necessary amount of health states and transition probabilities would be enormous. For example, simplifying the disease status to four levels (OHT, mild POAG, severe POAG, and blind) and the number of treatments to ten (no treatment, seven types of (combinations of) medications, and two invasive procedures) would already yield forty health states and up to sixteen hundred transition probabilities. Second, the cycle time in a Markov model is fixed whereas we wanted to explicitly evaluate the effects of altering the frequency of ophthalmologist consultations on cost-effectiveness outcomes. Third, a Markov model has no memory with regard to the treatment history of a patient, whereas the treatment options of a glaucoma patient depend on his exposure to and experience with previous treatments. Also the effectiveness of some treatments may vary depending on past exposure to other treatments. The structure of a DES model enabled us to overcome these issues, and has the additional advantage that a 'finished' model allows for relatively easy adjustments to future research questions, new treatment options or new scientific evidence.

Building blocks of discrete event model

The typical elements of a discrete event simulation (DES) model are: entities, attributes, events, relationships and outcomes. In order to simulate glaucoma and its treatment with a DES model, we have 'conceptualized' our knowledge of the

underlying pathogenetic and therapeutic processes in terms of these DES model elements. In order to facilitate the identification of model elements in the remainder of this paper we have used the notation described in Table 1. The entity in the model is a patient (further referred to in the masculine form). Attributes are characteristics that refer to the patient or his better eye. Attributes can either be fixed throughout the simulation (e.g. sex), or change in time (e.g. age). Events represent relevant moments in time. At an event the attributes of the entity are reevaluated and adjusted. In our model time-progression is event-based, which means that the model 'jumps' from one event to the next (Figure 2 in the appendix). The timing of future events may be conditional upon the new values of the attributes. This issue will be discussed more elaborately when we explain how the attributes managing future events ($\langle \text{time-to-xxx} \rangle_A$) was calculated in the model. Relationships are the model elements that link entities, attributes, events and outcomes together with mathematical and/or logical terms. Outcomes are the model element that aggregate information needed to draw conclusions from the simulations. An outcome is expressed by a relationship involving any of the model elements or a combination of elements. Examples of outcomes are 1) $\langle \text{average IOP} \rangle_O$, which is an outcome based on an attribute, 2) $\langle \text{occurrence of conversion} \rangle_O$, which is an outcome based on an event, 3) $\langle \text{age at conversion} \rangle_O$, which is an outcome based on both an attribute and an event, and 4) $\langle \text{discounted lifetime costs} \rangle_O$, which is an outcome based on attributes (e.g. $\langle \text{medication} \rangle_A$), events (e.g. $\langle \text{visit} \rangle_E$), discount rates and time.

Table 1 Notation of model elements

Specific model elements are referred to with their name in angle brackets $\langle \rangle$.
The subscript indicates the type of model element:
A for an attribute $\langle \rangle_A$
E for an event $\langle \rangle_E$
O for an outcome $\langle \rangle_O$

For example: $\langle \text{Age} \rangle_A$ signifies that the referred model element is an attribute with the name "Age" and $\langle \text{Visit} \rangle_E$ signifies that the referred model element is an event called "Visit".

Various methods exist to transfer a DES model concept into a running model, ranging from pure programming languages to dedicated software packages.²⁰ We have used Microsoft Excel spreadsheets to simulate the individual patient, and added Visual Basic macro's to create a heterogeneous population of simulated patients.

Conceptualizing glaucoma and its treatment

We have conceptualized glaucoma and its treatment from a clinical perspective. This means that we have not necessarily simulated the actual pathogenetic processes themselves, but rather how they manifest themselves in clinical practice. In the model, OHT and POAG represent two distinct disease states (Figure 1 in the appendix). Conversion is modeled as an event upon which the disease state changes from OHT to POAG. Visual field damage is a proxy for glaucoma severity and is expressed as Mean Deviation ranging from 0 (no damage) to -35 (severe damage) decibel (dB).²¹ Below a certain MD threshold patients are considered blind. Progression is modeled by means of an intrinsic rate at which the visual field decreases annually. The effect of treatment is that it lowers IOP, which in turn affects the conversion risk and the progression rate in the model.

The set of attributes, events and relationships that simulate this natural disease progression of an individual patient is discussed in the next paragraph. Additional model elements were added to the disease progression model to simulate treatment decisions and –effects. These are discussed in subsequent paragraphs. An overview of the most important events, attributes and relationships in the model is presented in Table 2. Details on model elements and parameter estimates are provided in the appendix.

Simulation of natural disease progression

At the start of a simulation (T_0) a set of baseline attributes is determined for the patient and his better eye, including $\langle \text{age} \rangle_A$, $\langle \text{gender} \rangle_A$, $\langle \text{IOP} \rangle_A$, and $\langle \text{risk profile} \rangle_A$. The $\langle \text{Risk profile} \rangle_A$ represents a set of factors (other than age and gender) quantifying the relative risk of conversion in the patient relative to the average patient.²² The baseline $\langle \text{disease status} \rangle_A$ is set by the user to either OHT or POAG. The values of the other baseline attributes are randomly drawn from distributions. The specifications of these distributions can be adjusted to generate specific patient populations, like a high risk OHT population or a young POAG population. To establish which event occurs next, the model uses special attributes (time-to-xxx) that set the time interval to each possible future event. The intervals are compared, and the smallest value determines which event occurs next and when. The model then jumps to that event and recalculates all attributes, including all time-to-xxx attributes.

If the baseline $\langle \text{disease state} \rangle_A$ of the simulated patient is OHT, two events may occur in the future: $\langle \text{conversion} \rangle_E$ and $\langle \text{death} \rangle_E$. Time-to-death is calculated by subtracting the current $\langle \text{age} \rangle_A$ from $\langle \text{age at death} \rangle_A$. The latter is determined at baseline by a random draw from a distribution of life-expectancies.²³ Time-to-conversion is based on $\langle \text{risk profile} \rangle_A$, $\langle \text{age} \rangle_A$ and $\langle \text{IOP} \rangle_A$ at the time of the event. The determination of $\langle \text{time-to-conversion} \rangle_A$ occurs via a new random draw from a

Table 2 Overview of the most important attributes and relationships in the model

Attributes	Relationships	Updated at all events?
Age	$\text{Age} = F(\text{Age}_0, \text{time})$	Yes
Gender		No
IOP	$\text{IOP}_u = F(\text{IOP}_0, \text{surgery}, \text{time})$ $\text{IOP}_i = F(\text{IOP}_u, \text{effect}(\%))$	Yes
Disease status		Only at 'conversion'
MD	$\text{MD} = F(\text{MD}_0, \text{MDR}, \text{time})$	Yes
MDR	$\text{MDR} = F(\text{MDR}_0, \text{IOP})$	Yes
Treatment type		Only at 'visit'
Medication		Only at 'visit'
Effect (%)	$\text{Effect} = F(\text{medication}, E_0)$	Yes
Side-effects	$\text{Side-effect} = F(\text{medication}, \text{SE}_0)$	Yes
Time-to-next-event	$\text{Time-to-death} = F(\text{Age}, \text{gender})$ $\text{Time-to-conversion} = F(\text{IOP}, \text{Age}, \text{Risk}_0)$ $\text{Time-to-visit} = F(\text{treatment type}, \text{visit number})$	Yes
	$\text{IOP}_{\text{target}} = F(\text{disease status}, \text{progression})$	

$_0$ = baseline; IOP_u = IOP without medication or LT effect; IOP_i = current intraocular pressure;
 $F(x)$ = function of x ; MD = Mean Deviation; MDR = Mean Deviation Rate; E = effect; SE = side-effect.

distribution at each event (Figure 14 in the appendix). The distribution itself is redefined at each event to adjust it to the current values of $\langle \text{age} \rangle_A$ and $\langle \text{IOP} \rangle_A$. At higher values for age and IOP, the chance to draw a small value for time-to-conversion is higher, the chance that this value is the smallest time-to-event value is higher, and so the likelihood of conversion occurring is higher.

The distribution of time-to-conversion is based on a survival function (Equation 1) that is customized to the individual patient at the specific event. The latter is established by calculating the individual's current hazard (h_i) from the average hazard of conversion observed in OHT-populations, hazard ratios for age and IOP as reported in literature, and the hazard ratio of other risk factors given by $\langle \text{Risk profile} \rangle_A$ (Equation 2). With the resulting hazard h_i , Equation 1 can be completed to generate an updated cumulative distribution of time-to-conversion for individual i .

A random draw from the thus created distribution provides the value for $\langle \text{time-to-conversion} \rangle_A$ at the current event. Incidentally, as the time-to-conversion distribution is only updated during events, large time intervals between events would induce flawed risk estimations because the risk from increasing age between events would not be accounted for. A separate event ($\langle \text{update} \rangle_E$) was introduced in the model to solve this problem. The interval between updates was fixed to ensure a regular update of the patient attributes, regardless of the frequency of the other events.

Equation 1 cumulative risk of conversion (constant hazard)

$$P = 1 - S = 1 - e^{-h_i \cdot t}$$

Equation 2 Calculation of current hazard rate for conversion from OHT to POAG of individual i

$$h_i = HR_i \cdot h = e^{\ln(HR_{\text{Age}}) \cdot \left(\frac{\langle \text{Age} \rangle_A - \text{Age}_{\text{av}}}{10} \right)} \cdot e^{\ln(HR_{\text{IOP}}) \cdot (\langle \text{IOP} \rangle_A - \text{IOP}_{\text{av}})} \cdot HR_{\text{other}_i} \cdot h$$

P = cumulative probability of conversion

S = Conversion free survival

h_i = current hazard rate of individual i at current event

t = time

h = hazard rate in reference OHT population

HR_i = Total hazard ratio of individual i at current event

HR_{Age} = Hazard ratio of age (per 10 years older)

HR_{IOP} = Hazard ratio of IOP (per mmHg higher)

$\langle \text{Age} \rangle_A$ = Age of individual i at current event

Age_{av} = Average age of reference OHT population

$\langle \text{IOP} \rangle_A$ = IOP of individual i at current event

IOP_{av} = average IOP in the reference OHT population (mmHg)

HR_{other} = Hazard ratio of other risk factors

When disease state changes to POAG, two additional attributes become relevant: Mean Deviation ($\langle \text{MD} \rangle_A$) and Mean Deviation Rate ($\langle \text{MDR} \rangle_A$). MD (dB) represents the disease severity of the POAG patient, and MDR (dB/year) represents the speed of progression. As mentioned previously, a higher IOP is a risk factor for progression, so we needed to define another relationship in the model to create the link between these two factors. For each patient a fixed value for $\langle \text{MDR}_{\text{ref}} \rangle_A$ is drawn from a distribution based on the average MDR in a POAG population.²⁴ This attribute represents the MDR if the patient had a risk profile and IOP similar to the average in

the referent POAG population. During the simulation, the actual value of $\langle \text{MDR} \rangle_A$ is calculated according to Equation 3, using the fixed $\langle \text{MDR} \rangle_{\text{ref}}$, the current $\langle \text{IOP} \rangle_A$ and an additional attribute ($\langle \text{progression risk} \rangle_A$) that represents an aggregation of other risk factors for progression.

Equation 3 Calculation of current MDR of individual i

*When $\text{IOP} \geq \text{IOP}_{\text{no progression}}$

$$\text{MDR} = \text{MDR}_{\text{ref}} \cdot \text{HR}_i = \text{MDR}_{\text{ref}} \cdot e^{\ln(\text{HR}_{\text{IOP}}) \cdot (\langle \text{IOP} \rangle_A - \text{IOP}_{\text{av}})} \cdot \text{HR}_{\text{other}}$$

*When $\text{IOP} < \text{IOP}_{\text{no progression}}$

$$\text{MDR} = 0$$

MDR = Mean Deviation Rate of individual i at current event

MDR_{ref} = Mean Deviation Rate of individual i if IOP and HR_{other} were as the average in the reference POAG population.

HR_i = Total hazard ratio of individual i at current event

HR_{IOP} = Hazard ratio of IOP (per 1 mmHg higher than average IOP in the reference POAG population)

HR_{other} = Hazard ratio of other risk factors ($\langle \text{progression risk} \rangle_A$)

$\langle \text{IOP} \rangle_A$ = IOP at current event (mmHg)

IOP_{av} = average IOP (mmHg) in the reference POAG population (15.5 mmHg)

$\text{IOP}_{\text{no progression}}$ = IOP threshold for disease progression.

Simulation of treated disease progression

The previous paragraphs have described how the *natural* disease progression of glaucoma was translated into a DES model structure. With an additional set of events, attributes and relationships, this model was extended to simulate the *treated* course of disease. Before elaborating on these additional model elements, we will briefly discuss what typically constitutes ‘treatment’ in OHT and POAG management. Watchful waiting is the least intensive form of treatment, and consists of regular consultations with the ophthalmologist to monitor IOP, optic disc and visual field but without active intervention. In terms of active interventions there are three different methods to reduce IOP: medication (eye drops), laser treatment (LT) and surgery. The pressure reducing effect of medication and LT is proportional to the IOP before treatment, whereas the IOP level after surgery is independent on the pre-surgical IOP. Treatment guidelines advice to start treatment for OHT and POAG with medication(s) and to proceed to laser and/or surgery if maximally tolerated medication is not sufficiently effective.^{8,9} A scheme of this treatment flow is provided in Figure 3 and 4 in the appendix.

The only new event that was added to the model to simulate treatment was $\langle \text{visit} \rangle_E$. The associated attribute $\langle \text{time-to-visit} \rangle_A$ was defined by means of a look-up table

specifying the interval to the next $\langle \text{visit} \rangle_E$, depending on treatment type and the number of visits since the last treatment change (Table 4 in the appendix).

Attributes

A considerable amount of attributes was added to the model to simulate treatment and its effects. Some attributes do not represent any physical characteristic of the patient but rather aid the model to keep track of treatment history. Other new attributes represent the information an ophthalmologist has available to inform his/her treatment decisions. For example, the model always uses the real MD value to simulate disease progression and calculate utilities, but it uses a second MD attribute (representing the MD as measured) to inform treatment decisions. The latter can be influenced by settings in the treatment strategy such as the frequency or the sensitivity of visual field testing (which enables the evaluation of such aspects of treatment), whereas the progression of the real MD is not affected by such treatment settings.

The effect of medication and laser treatment (LT) are simulated as a relative pressure lowering (%) of the IOP. The effect of surgery is simulated by resetting the IOP. Two sets of attributes were therefore created in the model. The first calculates an IOP ($\langle \text{IOP} \rangle_{u,A}$), that indicates how high the IOP would be in the absence of medication or LT treatment. If a patient has not undergone surgery, the IOP_u is similar to the baseline IOP with a small annual increase. When surgery occurs, IOP_u is reset. The second set of attributes calculates the total pressure lowering effect (in %) of all currently prescribed medications and previously performed LT treatment that act upon the IOP_u . The combination of IOP_u and the total pressure lowering effect yields the actual IOP of the patient ($\langle \text{IOP} \rangle_A$). Four different types of medication are used: β -blockers, prostaglandin analogues, carbonic-anhydrase inhibitors and α_2 -adrenergic agonists. There are two types of surgery: trabeculectomy and a tube implantation. The effect of all types of medication and LT, and the specific value of the new IOP_u after surgery in the simulated patient are randomly drawn for each individual patient and are determined at baseline. In addition, randomly drawn attributes define whether the patient has contraindications or will experience side-effects with each type of medication.

The simulation of treatment decisions and effects was more elaborate in the model than described above (see appendix). Briefly, the model allowed for the combination of medications, LT and surgery and used additional sets of effect estimates to calculate the aggregate effect of the combination therapies. Also, the model accounted for a gradual loss of effect after LT treatment, and for three different types of response to surgery: no response, a temporary response and a lifelong response.

Relationships

One of the most appealing features of DES modeling is its ability to mimic complex and individual treatment decisions, and what is more, to enable adjustments in the complete treatment strategy from one analysis to the next through minor alterations in the model. In the glaucoma model this was achieved by defining a specific set of relationships that represent the 'decision rules'. The decision rules are logical relationships, and are composed for the most part of 'if-then' statements based on the treatment flowcharts. An example is presented in Figure 1, which shows how a series of if-then relationships leads to a new value of $\langle \text{treatment} \rangle_A$. Within the decision rules, the values of patient attributes are compared with benchmark values such as the target IOP or the minimal effectiveness required to continue a single medication. The benchmark values of a treatment strategy are specified before a cohort of patients is simulated, and so is the order of the medication types. Adjustments in a treatment strategy can be made by simply changing the value of these benchmarks.

Figure 1 Examples of logical relationships that collectively create a decision regarding the simulated patient's future treatment

Outcomes

The flexibility of a DES model allows for the collection of basically all types of outcomes that may be of interest to the targeted audience. In the glaucoma model for example, the main outcomes that were collected from the simulation of an individual's disease progression were 1) whether conversion occurred, 2) whether the eye progressed to blindness, 3) the number of life-years adjusted for the VFQ-25 score (see below), 4) the number of life-years adjusted for utility, and 5) the total costs associated with the disease and its treatment. The outcomes had a societal perspective and took a discounting factor into account.²⁵ Future effects were discounted with 1.5% per year, and future costs were discounted with 4% per year according to Dutch guidelines for pharmacoeconomic research.²⁶ Blindness was defined as an MD lower than -25 dB in the simulated eye. VFQ-25 is a vision specific health-related quality of life questionnaire.²⁷ The life-years adjusted for VFQ-25 score were calculated by multiplying the length of the time-intervals between events with the VFQ-25 score during those time-intervals. The VFQ-score was calculated based on the MD, the presence of side-effects and the presence of cataract, and was transformed from the original 0-100 scale to a 0-1 scale (Equation 4).²⁸ The life-years adjusted for utility (QALY's) were calculated in a similar fashion, multiplying the time-intervals between events with utility based on the Health Utilities Index (Equation 5). The costs associated with treatment and impaired vision were calculated by linking the occurrence of treatment and the patient's MD respectively to resource costs. The derivation of all utility and cost estimates is described in the appendix.

Equation 4 Calculation of VFQ-score

$$\text{Score}_{\text{VFQ-25}} = 0.94 + 0.016 \cdot \text{MD} - 0.1 \cdot \text{SE} - 0.092 \cdot \text{Cataract}$$

Equation 5 Calculation of utility

$$\text{Utility}_{\text{HUI3}} = 0.88 + 0.01 \cdot \text{MD} - 0.1 \cdot \text{SE} - 0.059 \cdot \text{Cataract}$$

MD = Mean Deviation

SE = presence of side-effects, 0=no, 1=yes

Cataract = presence of cataract, 0=no, 1=yes

Validation

The disease progression model for OHT and POAG was developed with a high level of attention for quality, validity and transparency. Guidelines for model development

must remain quite general due to the large variety in models, and there is not a specific checklist to assess the quality of a DES model.^{11, 12, 29, 30} However, we have regarded the good practice guidelines for decision analytic modeling by Philips *et al.* as a minimal set of requirements during the development of the model.¹¹ In these guidelines three dimensions of quality are distinguished: structure, data and consistency. The dimension of structure refers to the definition of the decision problem, the objective and scope of the model, justification of the model type, structural assumptions and the translation of the disease to the model structure. These issues are important for 'face validity', which is discussed in more detail below. The dimension of data refers to the transparency and justification of all activities involving the identification, analysis and incorporation of data. Transparency in this dimension requires more text space than a journal article can provide, so issues regarding data have been included in the appendix. Another aspect within the dimension of data is the assessment of four types of uncertainty (methodological, parameter, structural, and heterogeneity). The assessment of all four types of uncertainty is feasible with a DES model, but uncertainty analyses must be made in the context of a specific decision analysis and cannot be reported here for the model as a whole. The dimension of consistency refers to the internal- and external consistency of the model, and is described in more detail below.

The face validity of a model refers to the soundness of the design and the plausibility of the input estimates as perceived by experts in the field. There should be a general feeling that all relevant events and attributes are considered in the model, and that the defined relationships are correct. Face validity was guarded throughout the development process by continuous consultation with glaucoma experts, epidemiologists, and health technology assessment experts. The development of the model concept and the establishment of the quantitative parameter estimates were discussed in frequent multidisciplinary meetings with the abovementioned experts. During these meetings no information was provided on the outcomes of the simulations to prevent bias towards desirable outcomes. The model design was presented to an independent panel of Dutch glaucoma experts in November 2007 to seek feedback. An extensive report about the model design and outcomes was evaluated by independent reviewers for The Netherlands organization for health research and development (ZonMW), and has been approved in February 2009.

The internal validity of the model refers to the consistency between the theoretic model design and the product that is eventually used to run the simulations. The internal validity of the model was evaluated in several ways. The model was programmed in Microsoft Excel spreadsheets, enabling the programmer (AvG) to review all attributes during all events in the complete disease- and treatment history of an individual patient. A visual excerpt of such an overview, showing the most

important attributes, is presented in Figure 2. A detailed review of events and attributes was conducted for a large number of patients with specific characteristics and treatment strategy settings, to check whether the attributes in the model changed according to expectation and whether the model 'made' the right treatment decisions. Furthermore, the model was run in a series of simulations with test scenarios in order to check whether the outcomes of the patient populations were as expected. For example, a scenario in which none of the treatments have any effect must give the same health outcomes as a scenario in which none of the patients is ever treated at all, increasing the efficacy of treatments should lead to better health outcomes and increasing cost-prices should lead to higher costs.

Figure 1 Examples of simulated disease and treatment histories of two individual OHT patients. Patient A does not develop POAG and receives lifelong monotherapy. Patient B develops POAG and receives multiple medications, LT, and surgery to reach the (downward adjusted) target pressure, and progresses to an MD of -15 dB. MD = Mean Deviation (dB), POAG = primary open-angle glaucoma, IOP = intraocular pressure (mmHg), TE = trabeculectomy, ReTE = second trabeculectomy, VFQ-25 = visual functioning questionnaire score.

The external validity of the model refers to the similarities between outcomes observed in patient populations and the outcomes of the model in comparable circumstances. The external validity of the model was evaluated in terms of two clinical endpoints: conversion to POAG in an OHT population and progression to blindness in a POAG population.

A cohort of ocular hypertension patients was simulated in the model in order to compare the incidence of conversion in five years with that observed in a recent systematic review.⁶ The baseline age and IOP of the simulated patients was drawn from distributions based on the Ocular Hypertension Treatment Study population.³¹ The treatment strategies specified in the model were 1) No treatment unless conversion is observed, and 2) Treatment with a target pressure at 80% of the initial IOP. The results produced by the model are presented in Table 3. The incidence of conversion in the simulated patients was comparable to a weighted average of what was found in literature, and well within the range of reported conversion incidences. The relative risk of treatment found with the model results was 0.56 (0.082/0.146) which is exactly similar to the outcome of the meta-analysis of the efficacy of pressure lowering treatment in ocular hypertension.⁶ The results also show that leaving treatment decisions to the model leads to very plausible IOP values for treated patients.

Table 3 Comparison of outcomes of the model simulating an ocular hypertension patient population and outcomes of a review of clinical studies

	Model		Review studies ⁶	
	Control	Treatment	Control	Treatment
Age	55.2 ± 9.8			
Baseline IOP (mmHg)	25.9 ± 2.4			
IOP during follow-up (mmHg)	25.7 ± 2.8	18.6 ± 2.3	23 - 26	19 - 22
Conversion in 5 years (95% CI)	14.6% (13.3%; 15.9%)	8.2% (7.2%; 9.2%)	13.0%* 9% - 37% [†]	7.0%* 4% - 25% [†]

* Incidence calculated as the total number of converting patients relative to the total number of included patients summed over all studies included in the meta-analysis. [†] Lowest and highest incidences reported in the studies included in the meta-analysis. IOP= Intraocular Pressure; CI= confidence interval.

Two observational studies reporting the cumulative risk of blindness in populations with open-angle glaucoma were imitated in order to compare the incidence of blindness after ten to fifteen years. In a retrospective study in 186 patients Chen *et al.* report the incidence of blindness in the better eye of a population treated for open-angle glaucoma.³² We mimicked this study by modeling an untreated POAG population with an average baseline intraocular pressure similar to the average follow-up IOP reported by Chen *et al.* The results are presented in Table 4. The incidence of blindness in the model was lower than that reported. A possible explanation for the difference is the fact that Chen *et al.* used a retrospective design and included patients based on the availability of visual field measurements. This may have resulted in some selection bias towards patients with faster progression. Alternatively, the patient population in the study may have been distributed towards a higher risk of progression, for example due to the genetic make-up of the hospital population. However, the difference may also be the result of some of the assumptions made in the model, particularly with respect to the linearity of MD loss in time. This issue is addressed in the discussion.

Table 4 Outcomes reported by Chen *et al.* and Wilson *et al.* and outcomes of the model simulating similar POAG populations

	Chen <i>et al.</i> 2003 ³²	Model
Age	61 ± 13	61 ± 13
IOP during follow-up	17 ± 3	17 ± 3
MD at baseline in better eye	-3.4 dB	-3.4 dB
Bilateral blindness after 15 years	6.4% (95% CI: 2.9%; 9.9%)	2.2% (95% CI: 1.3%; 3.1%)
	Wilson <i>et al.</i> 2002 ³³	Model
Age	42	42
IOP during follow-up	21 ± 4.3	21 ± 4.3
MD at baseline in better eye	-4 dB	-4 dB
Blindness after 10 years	15.7% (95% CI: 10.0%; 21.4%)	16.5% (95% CI: 14.2%; 18.8%)

IOP= Intraocular Pressure; MD= Mean Deviation; dB= decibel; CI= confidence interval.

The second study mimicked with the model was described by Wilson *et al.* and concerned an untreated population of glaucoma patients in the West-Indies.³³ At baseline patients were on average 42 years old, had a baseline AGIS score of 3.7

(which corresponds to an MD of approximately -4 dB)³⁴ and an IOP during follow-up of approximately 21 mmHg. After 10 years, 45 out of 287 eyes had progressed to endstage visual field, which was AGIS score 18. In this case, blindness in the model was defined as an MD lower than -18 dB. The results of the model simulation are presented in Table 4. The incidence of blindness found with the model was comparable to the reported study results.

Finally, in order to test the feasibility of the model, we have applied it to an average POAG population and compared the outcomes of three different treatment strategies to a reference scenario in which patients are never seen nor treated by the ophthalmologist. The three treatment strategies differed in terms of the target pressure and the frequency of visual field tests. A summary of results is presented in table 5. All three treatment strategies lead to better outcomes and lower costs than the referent strategy. A higher frequency of visual field measurements and a lower target pressure resulted in lower average IOP, higher incidence of surgery, better outcomes and lower total costs. Indeed, the costs associated with treatment

Table 5 Model results (mean $\pm$ SD) comparing three treatment strategies to 'no treatment' in an average POAG population

	No treatment	A. Target 24, 21, 18 mmHg. VF every 5 years	B. Target 24, 21, 18 mmHg. VF every year	C. Target 21, 18, 15 mmHg. VF every year
Life-years in the model	15.2 $\pm$ 8.0			
IOP during follow-up (mmHg)	29.3 $\pm$ 3.0	19.1 $\pm$ 2.1	18.5 $\pm$ 2.0	17.2 $\pm$ 2.1
Incidence of LT / TE / reTE / Implant (%)	0 / 0 / 0 / 0	20 / 11 / 1 / 1	25 / 17 / 3 / 2	45 / 33 / 7 / 4
Lowest MD (dB)	-24.5 $\pm$ 10.3	-14.1 $\pm$ 7.0	-13.4 $\pm$ 6.6	-12.0 $\pm$ 5.6
Incidence of blindness (%)	52.2	8.9	5.3	1.1
VFQ adjusted life-years (discounted)	8.5 $\pm$ 4.0	10.1 $\pm$ 4.8	10.2 $\pm$ 4.8	10.4 $\pm$ 4.9
Qaly's (discounted)	9.1 $\pm$ 4.2	10.1 $\pm$ 4.8	10.2 $\pm$ 4.9	10.3 $\pm$ 4.9
Total costs (discounted)	€ 41,618 $\pm$ € 31,007	€ 25,648 $\pm$ € 24,366	€ 25,465 $\pm$ € 24,097	€ 23,466 $\pm$ € 22,742

IOP= Intraocular Pressure; LT= laser trabeculoplasty; TE= trabeculectomy;
reTE= second trabeculectomy; MD= Mean Deviation; Qaly= quality-adjusted life-year;
VF= visual field measurement.

were higher (from € 1,118 without treatment to € 7,938 in strategy C), but the costs associated with low-vision were much lower (from € 40,500 without treatment to € 15,255 in strategy C), resulting in overall cost-savings.

Discussion

We have been able to build a model that simulates the disease progression of ocular hypertension and glaucoma patients and that mimics the treatment choices that are made in clinical practice. The DES model structure has enabled us to discern relevant characteristics of individual patients and of treatment strategies, that would have been impossible (or at the least impractical) within a decision tree or Markov structure. Still, a model remains a simplified version of reality and also in this model several relevant assumptions were made. First, we have simulated the disease progression in the better eye of the patient, assuming that the other eye is only slightly worse. In fact this comes down to modeling both eyes but assuming that they progress equally. In reality glaucoma may progress asymmetrically. For example, Heeg *et al.* found that half of their cohort of glaucoma patients had unilateral glaucoma.³⁵ The disease severity in the better eye has the highest impact on quality-of-life, but the disease progression in the worse eye may have the highest impact on treatment decisions, also those concerning the better eye.^{28, 36} It is possible to model both eyes separately in the DES structure, but we have chosen not to. It would have added considerably to the complexity of the model (e.g. in terms attributes and relationships) whereas it was unclear whether it would improve the suitability of the model outcomes to inform guideline decision making. The impact of the assumption that both eyes are symmetrically affected needs to be tested with univariate sensitivity analyses in presentations of the model results. The results of the current model in terms of the incremental cost-effectiveness of a certain treatment strategy can be regarded as valid for an OHT or POAG population with a symmetrically developing disease. Second, we have assumed that the natural progression of glaucoma can be described with a linear function of MD in time. An evaluation of the validity of this assumption is hampered by the fact that there are no records of long-term MD progression in untreated POAG patients, but the assumption is not contradicted by current evidence. The explicitness of the DES model structure allows for a univariate (structural) sensitivity analysis of this assumption, and the impact of a different disease progression pattern on the model outcomes can be evaluated quite readily. We have not included sensitivity analyses in this article because the conclusions from such analyses are only valid for the particular population and strategies that were analyzed, and no general conclusions regarding the model itself can be drawn from them. We have performed cost-

effectiveness analyses of three treatment strategies with the model as a way of demonstrating how changes in the treatment strategy setting affect the model outcomes. A full cost-effectiveness analysis to inform guideline decisions, including full sensitivity and probabilistic analyses, is outside the scope of this article and is the subject of future research. However, our preliminary results in table 5 show that treatment of POAG is expected to lead to a gain of 1.2 Qaly's with a cost-reduction of € 25,000 per patient compared to withholding treatment. Recently Rein *et al.* have reported an incremental cost-effectiveness ratio of \$20,000/QALY for POAG treatment compared to no treatment.³⁷ The fact that incremental costs rather than cost-savings were found in this study is most likely due the fact that almost no low-vision associated costs (i.e. home care, aids and services) were included in the calculations.

Despite the apparent advantages DES has within modeling complex treatment strategies, several disadvantages of the technique have previously been described.⁴ These pertain mainly to the added simulation time, building time, data collection and the degree of experience needed by the modeler. The increased simulation time is the result of the need to simulate individual patients rather than cohorts, and is inherent to micro-simulation. This can become particularly problematic in probabilistic analyses, and even more so in expected value of perfect parameter information (EVPI) analyses, which require the execution of large numbers of first-order simulations. Our model needed approximately 30 minutes to run a first order analysis of 3000 patients. However, more efficient programming with e.g. specialized software or pure programming language can sometimes reduce computation times dramatically. Building the model and collecting data to inform the model may seem more strenuous than with simpler model structures, but it can be argued that the combination of building the model and collecting the data require equal efforts in Markov and DES models. Markov models often require (behind the scene) data processing to adjust the literature data to the specific health states, transition probabilities and cycle length of the model, whereas in DES models the literature data can often be inserted in the model directly. Any extrapolation of the data occurs explicitly in the defined relationships that are part of the model. Therefore DES models generally take more time to build but hardly any time to adjust. Even structural alterations can be made in an instant. Finally, the lack of experience with DES among health economists is only a disadvantage if it would prevent the application of the method where it would be appropriate. The transparent dissemination of discrete event models in the scientific literature could positively contribute to the experience with this methodology. Achieving insight in the model's structure and trust in its outcomes may require some extra effort due to the high level of flexibility and therefore variability in DES model structures. Decision

trees and Markov models can be visualized with schematic drawings that are similar across all applications, i.e. the branching tree structures and the bubble diagrams respectively, but such a standard format to communicate model structure is not (yet) available for DES models. This article aimed to transparently report on the construction and validation of a DES model for the complex strategies involved in glaucoma treatment. In order to do so we have justified the choice for a DES model structure, explained how current knowledge regarding disease progression in glaucoma was synthesized within the structure of a DES model, and presented the results of the model validation. The resulting model was flexible and had good face validity. Also the internal and external consistencies were satisfying. We hope to have demonstrated the added value of DES in modeling complex treatment strategies, and to have made a contribution to the discussion on how to transparently report about model structure, assumptions, parameter estimates and validation steps.

References

- Weinstein MC. Recent developments in decision-analytic modelling for economic evaluation. *Pharmacoeconomics* 2006; 24:1043-1053.
- Karnon J, Brown J. Selecting a decision model for economic evaluation: a case study and review. *Health Care Man Sci* 1998; 1:133-140.
- Karnon J. Alternative decision modelling techniques for the evaluation of health care technologies: Markov processes versus discrete event simulation. *Health Econ* 2003; 12:837-848.
- Heeg BM, Damen J, Buskens E, Caleo S, de Charro F, van Hout BA. Modelling approaches: the case of schizophrenia. *Pharmacoeconomics* 2008; 26:633-648.
- Eddy DM. Accuracy versus transparency in pharmacoeconomic modelling: finding the right balance. *Pharmacoeconomics* 2006; 24:837-844.
- Maier P, Funk J, Schwarzer G, Antes G, Falck-Ytter Y. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ* 2005; 331:134.
- Peeters A, Webers C, Prins M, Zeegers M, Hendrikse F, Schouten J. Quantifying the effect of intra-ocular pressure reduction on the occurrence of glaucoma. *Acta Ophthalmol* 2010; 88:5-11.
- American Academy of Ophthalmology Glaucoma Panel. Primary open-angle glaucoma. Preferred practice pattern. San Francisco: American Academy of Ophthalmology, 2005.
- European Glaucoma Society. Terminology and guidelines for glaucoma (third edition). Dogma: Savona, Italy; 2008.
- Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation, First ed. Oxford University Press: Oxford, UK; 2006.
- Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Pharmacoeconomics* 2006; 24:355-371.
- Weinstein M, O'Brien B, Hornberger J, al. e. Principles of good practice of decision analytic modeling in health care evaluation: Report of the ISPOR Task Force on Good Research Practices-Modeling Studies. *Value Health* 2003; 6:9-17.
- Kobelt G. Health economics, economic evaluation, and glaucoma. *J Glaucoma* 2002; 11:531-539.
- Realini T, Fechtner R. 56,000 ways to treat glaucoma. *Ophthalmology* 2002; 109:1955-1956.
- Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet* 2004; 363:1711-1720.
- Stahl JE. Modelling methods for pharmacoeconomics and health technology assessment: an overview and guide. *Pharmacoeconomics* 2008; 26:131-148.
- Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. *J Health Serv Res Policy* 2004; 9:110-118.
- Cooper K, Brailsford S, Davies R. Choice of modelling technique for evaluating health care interventions. *J Oper Res Soc* 2007; 58:168-176.
- Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. *Health Econ* 2006; 15:1295-1310.
- Law A, Kelton W. Simulation modeling and analysis, Third ed. McGraw-Hill: New York, USA; 2000.
- Heijl A, Patella V. Essential perimetry; The field analyzer primer, Third ed. Carl Zeiss Meditec: Dublin, California, USA; 2002.
- Gordon MO, Torri V, Miglior S, Beiser JA, Floriani I, Miller JP, Gao F, Adamsons I, Poli D, D'Agostino RB, Kass MA. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. *Ophthalmology* 2007; 114:10-19.
- Mortality rates by age and gender. Available at: <http://statline.cbs.nl/StatWeb/>. Accessed: 12-07-2005
- Heijl A, Leske C, Bengtsson B, Hyman L, Bengtsson B, Hussein M, for the Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression; results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002; 120:1268-1279.
- Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes, Third ed. Oxford University Press: Oxford; 2005.
- Rodenburg-Van Dielen H. Guidelines for pharmacoeconomic research (version 2006). Diemen, The Netherlands: Health Insurance Board, 2005.
- Mangione C, Lee P, Gutierrez P, Spritzer K, Berry S, Hays R, for the National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* 2001; 119:1050-1058.
- Van Gestel A, Webers C, Beckers H, Van Dongen C, Severens J, Hendrikse F, Schouten J. The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye* 2010; 24:1759-1769.
- McCabe C, Dixon S. Testing the validity of cost-effectiveness models. *Pharmacoeconomics* 2000; 17:501-513.
- Sculpher M, Fenwick E, Claxton K. Assessing quality in decision analytic cost-effectiveness models. A suggested framework and example of application. *Pharmacoeconomics* 2000; 17:461-477.
- Kass M, Heuer D, Higginbotham E, Johnson C, Keltner J, Miller J, Parrish R, Wilson R, Gordon M, the Ocular Hypertension Treatment Study Group. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002; 120:701-713.
- Chen P. Blindness in patients with treated open-angle glaucoma. *Ophthalmology* 2003; 110:726-733.
- Wilson M, Kosoko O, Cowan C, Sample P, Johnson C, Haynatzki G, Enger C, Crandall D. Progression of visual field loss in untreated glaucoma patients and glaucoma suspects in St. Lucia, West Indies. *Am J Ophthalmol* 2002; 134:399-405.
- The AGIS investigators. The Advanced Glaucoma Intervention Study (AGIS): 14. Distinguishing progression of glaucoma from visual field fluctuations. *Ophthalmology* 2004; 111:2109-2116.
- Heeg G, Blanksma L, Hardus P, Jansonius N. The Groningen longitudinal glaucoma study. I. Baseline sensitivity and specificity of the frequency doubling perimeter and the GDx nerve fibre analyser. *Acta Ophthalmol Scand* 2005; 83:46-52.
- McKean Cowdin R, Varma R, Wu J, Hays RD, Azen SP. Severity of visual field loss and health-related quality of life. *Am J Ophthalmol* 2007; 143:1013-1023.
- Rein D, Wittenborn J, Lee P, Wirth K, Sorensen S, Hoerger T, Saaddine J. The cost-effectiveness of routine office-based identification and subsequent medical treatment of primary open-angle glaucoma in the United States. *Ophthalmology* 2009; 116:823-832.

Modeling complex treatment strategies: construction and validation of a discrete event simulation model for glaucoma

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Introduction

In the manuscript “Modeling complex treatment strategies: construction and validation of a discrete event simulation model for glaucoma” we have presented the basic structure of the health economic model for ocular hypertension and primary open-angle glaucoma. In this appendix we present the sources and methods of the derivations of the most important structural relationships and the sources, best estimates and distributions of the main parameter estimates in the base case model, as well as graphical presentations of several aspects of the model design. Only distributions pertaining to patient variability and heterogeneity are described here (first order uncertainty). The distributions that were created to represent uncertainty in the estimates of population means (second order uncertainty) are not discussed here. Future reports that present the outcomes of probabilistic sensitivity analyses will be accompanied by a description of the distributions used to represent second order uncertainty.

Discrete Event Simulation model for glaucoma

Conceptualization of glaucoma disease progression

We have conceptualized glaucoma and its treatment from a clinical perspective. This means that we have not necessarily simulated the actual pathogenetic processes themselves, but rather how they manifest themselves in clinical practice. An elevated intra-ocular pressure (IOP) is the most important known risk-factor for primary open-angle glaucoma. As long as the IOP is elevated without signs of retinal nerve fiber loss, the condition is termed ocular hypertension (OHT). However, when nerve fiber loss occurs to a level that causes optic nerve cupping and/or visual field loss, the condition is termed primary open-angle glaucoma (POAG). The transition from OHT to POAG is termed ‘conversion’. If nerve fiber loss continues (progression), the visual field deteriorates and a patient may progress to blindness. Lowering the IOP by treatment reduces both conversion and progression.^{1, 2} This information has been translated into the model as shown in Figure 1.

Figure 1 Conceptualization of disease progression for the DES model.
A) Natural course of disease. **B)** Disease progression under treatment: conversion is delayed, progression rate is reduced.

OHT and POAG represent two distinct disease states. Conversion is modeled as an event upon which the disease state changes from OHT to POAG. Visual field damage is a proxy for glaucoma severity and is expressed as Mean Deviation ranging from 0 (no damage) to -35 (severe damage) decibel (dB).³ Below a certain MD threshold, patients are considered blind. Progression is modeled by means of an intrinsic rate at which the visual field decreases annually. The effect of treatment is that it lowers IOP, which in turn affects the conversion risk and the intrinsic progression rate of the simulated patient.

Event-based time progression

Events in a discrete event simulation (DES) model represent relevant moments in time. At an event the attributes of the entity are reevaluated and (if needs be) adjusted (Figure 2). In our model, time-progression is event-based, which means that the model 'jumps' from one event to the next. The timing of future events may be conditional upon the new values of the attributes.

Figure 2 Event-based time progression in discrete event simulation model and updating of attributes at each event.

Summary of parameter estimates

In later paragraphs of this appendix, the derivation of the parameter estimates used in the base case setting of the model will be addressed. Here we present a summary of the parameter estimates.

Table 1 Parameter estimates.

Parameter	Best estimate	Distribution	Source
Hazard rate for conversion	0.02/year	n.a.	4
Hazard ratio age for conversion	1.26 per decade older than 55 years.	n.a.	5
Hazard ratio IOP for conversion	1.09 per mmHg higher than 24 mmHg.	n.a.	5
MDR	-0.34 dB/year	Gamma	6-10
Relative Risk IOP for MDR	1.13 per mmHg higher than 15.5 mmHg	n.a.	10
Medication Mean effect / Incidence side-effects ^{a)}			
β-blocker	26 % / 8%	Beta	11, 12
Prostaglandin analogue	29.5 % / 8%	Beta	11, 12
Carbonic-anhydrase inhibitor	19.5 % / 14%	Beta	11, 12
α ₂ -adrenergic agonist	21 % / 23%	Beta	11, 12
Mean effect LT	34 %	Beta	10, 13-17
Mean IOP after surgery (TE)	12.5 mmHg	Gamma	18-22
Mean IOP after surgery (tube)	15.0 mmHg	Gamma	19, 22, 23

IOP= Intraocular Pressure; MDR= Mean Deviation Rate; LT= Laser Trabeculoplasty; TE= Trabeculectomy.

^{a)} Side-effects that lead to a treatment switch.

Table 2 Costs associated with attributes and events in the simulation model.

Resource	Costs	Source
β-blocker	€ 6.00/month	24, 25
Prostaglandin analogue	€ 20.20/month	24, 25
Carbic-anhydrase inhibitor	€ 13.90/ month	24, 25
α ₂ -adrenergic agonist	€ 14.00/month	24, 25
Ophthalmologist consultation	€ 65	26, 27
Visual field measurement	€ 133 (€ 266 in case of progression)	26, 27
LT	€ 75	27, 28
Trabeculectomy	€ 1,214 (+ 1 ophthalmologist consultation)	26, 27
Implant surgery	€ 1,714 (+ 1 ophthalmologist consultation)	26, 27
Cataract surgery	€ 1,400	26, HA
Paid household help	€ 37 / month (if MD < -10 dB)	29, 30,26
Homecare nursing	€ 159 / month (if MD < -10 dB)	29,26, 30
Family help	€ 56 / month (if MD < -15 dB)	26, 29
Homecare grooming	€ 103 / month (if MD < -15 dB)	26, 29, 30
Retirement home	€ 80 / month (if MD < -20 dB)	26, 29, 30
Nursing home	€ 130 / month (if MD < -20 dB)	26, 29, 30
Informal care	€ 20 / month (if MD < -5dB)	26, 29, 30
Low-vision services	€ 1-5 /month	29-31
Transport to ophthalmologist	€ 4.90 / visit (if MD > -10 dB) € 8.90 / visit (if MD < -10 dB)	26, 29, 30
Transport to pharmacy	€ 1.50 / visit (if MD > -10 dB) € 2.60 / visit (if MD < -10 dB)	26, 29, 30
Low-vision aids	€ 325 (once) if MD moves below -15 dB	29, 30, 32
Productivity loss	€ 3,029 (once) if MD moves below -15 dB	26, 29, 30

Costs for LT (Laser Trabeculectomy) and surgery are doubled to account for the same procedure in the other (i.e. worse) eye. Transport costs to the pharmacy are incurred once in three months if the patient receives medication, and transport costs to the ophthalmologist/hospital are incurred for each visit and for each procedure (LT, surgery). HA= Hospital Administration.

Treatment schedule

The choice for the various treatment options in the model is made based on the two flow-charts presented in Figure 3 (between treatment types) and Figure 4 (within the medication blocks shown in Figure 3).

Figure 3 Intervention for OHT and POAG in the model; the order of treatment types. Reasons to change treatment are A) side-effects, B) insufficient effectiveness and C) IOP above the target IOP.

The main 'route' through the various treatment types are shown in Figure 3 by the black arrows, but there are several detours built into the schedule as well (grey arrows):

- ~ LT is skipped if a patient has received cataract surgery in the past (attribute).
- ~ Surgery (i.e. trabeculectomy and implant surgery) is skipped if a patient is too old.
- ~ A second trabeculectomy is not performed if there was immediate failure of the first trabeculectomy.

OHT patients are only treated with medication block 1 and/or laser treatment. They can never move to trabeculectomy or medication block 3.

Trabeculectomy is not performed if no visual field progression has been observed. If trabeculectomy is indicated due to an IOP that is higher than the target IOP, but progression has not been observed (either because no visual field measurement has been performed, or because the visual field measurement did not indicate progression), the medication the patient was previously taking is continued until progression is observed.

Detours are also possible in the medication flowchart (Figure 4). If a patient suffers from side-effects or low effectiveness on the current medication, the model finds

the next medication by moving one step downward in the flowchart. However, if that next medication is contraindicated (fixed attribute) or has given rise to side-effects in the past (attribute), the model makes another step downward. If the current medication has good effectiveness and does not give side-effects, but the resulting IOP is nonetheless higher than the target IOP, the model make one step rightward. In the default model the order of monotherapies is timolol (Mono 1), latanoprost (Mono 2), dorzolamide (Mono 3) and brimonidine (Mono 4).

Figure 4 Interventions for OHT and POAG in the model; the order of medications within the first medical treatment block. The specifications of MONO 1, MONO 2, MONO 3 and MONO 4 can be determined by the model user. Reasons to change treatment are A) side-effects, B) insufficient effectiveness and C) IOP above the target IOP.

If a patient moves to LT by a rightward step, all medication is continued. If a patient moves to LT by a downward step, all medication is stopped. However, if in the latter case the patient does not reach the target pressure three months after LT, medication is added again. The model chooses the last medication not causing side-effects the patient received before the LT.

The definition of the target IOP constitutes a part of the treatment strategy. Before the analyses, the target pressures used in the model can be defined by the model user. A target pressure can be entered for four different situations (Table 3).

Table 3 Example of a look-up table for target IOP depending on disease status and the occurrences of disease progression.

Disease status	IOP _{target}
OHT	24 mmHg
POAG, without observed progression	21 mmHg
POAG, and one observed progression	18 mmHg
POAG, and two or more observed progressions	15 mmHg

IOP_{target} = target Intraocular Pressure; OHT= Ocular Hypertension; POAG= primary open-angle glaucoma

Visit schedule

The frequency of visits to the ophthalmologist in the model is part of a treatment strategy and is therefore adjustable by the user. In the default model the schedule presented in Table 4 is used. The length of the time interval between two visits depends on two factors: 1) whether or not there has been a treatment change, and 2) the type of new treatment. The number of visits since that last treatment change is counted in the leftmost column of Table 4, while the new treatments are listed in the top row. For example, a patient that is not treated at all will visit the ophthalmologist every 36 months (3 years). The first visit after a change in medication will take place 3 months after the change, but the next visits will occur every 6 months as long as the treatment remains unaltered. After LT or surgery a series of short visit intervals follows to be able to monitor the patient closely. The visit frequency gradually returns back to the normal interval length.

Drug effectiveness

Pre-surgery medication

There is a wide variety of pressure-lowering eye-drops for the treatment of elevated intra-ocular pressure. Four classes of pharmaceuticals are commonly used nowadays: beta-adrenergic antagonists, prostaglandin analogues (or hypotensive

Table 4 Periods between visits in base case model (months).

Visit number	No treatment	Medication	LT	Surgery
1	36	3	0.23	0.1
2	36	6	1.15	0.1
3	36	6	6	0.1
4	36	6	6	0.1
5	36	6	6	0.23
6	36	6	6	0.23
7	36	6	6	0.23
8	36	6	6	0.5
9	36	6	6	0.5
10	36	6	6	1
> 10	36	6	6	6

lipids), carbonic anhydrase inhibitors and alpha-2 adrenergic agonists. In most cases several analogues exist within each of these classes. The pressure-lowering eye drops can be applied individually (as monotherapy) or in combination with each other (combination therapy). Oral pressure-lowering medication is also in use (e.g. acetazolamide), but since this medication is often only used temporarily, it was not included in the present model.

The model offers the possibility to define four monotherapies, one within each class, which will be used throughout the treatment strategy. In the default scenario the models uses a representative medication from each class. These are timolol, latanoprost, dorzolamide and brimonidine respectively. The effectiveness of each medication is expressed as the pressure lowering relative to the intra-ocular pressure before treatment was started. From literature it is known that the relative pressure-lowering effect of medication that is added to existing medication is lower than the effect if the same medication is applied as a monotherapy.

In order to account for this variation in effectiveness depending on the existing treatment, the effectiveness of medication is estimated for three separate situations:

- 1) medication is applied as a monotherapy
- 2) medication is added to one other medication
- 3) medication is added to two or more other medications.

7.1.1 Monotherapy

Default estimates for drug effectiveness as monotherapy were derived from a meta-analysis of 'all commonly used glaucoma drugs' in 2005.¹¹ This meta-analysis included studies that compared pressure-lowering eye-drops monotherapy to placebo in POAG and/or OHT patients, and that used IOP as the primary endpoint of the study.

An excerpt of the results of the meta-analysis is reported in Table 5.

Table 5 Meta-analysis of pressure lowering drug effects.¹¹

	Absolute change (mmHg) (95% confidence limits)	Relative change (%) (95% confidence limits)
Timolol, trough	-6.9 (-7.4; -6.5)	-26 (-28; -25)
Timolol peak	-6.9 (-7.5; -6.3)	-27 (-29; -25)
Latanoprost, trough	-6.8 (-7.6; -6.1)	-28 (-30; -26)
Latanoprost, peak	-7.9 (-8.3; -7.4)	-31 (-33; -29)
Dorzolamide, trough	-4.5 (-5.0; -4.0)	-17 (-19; -15)
Dorzolamide, peak	-5.9 (-6.5; -5.2)	-22 (-24; -20)
Brimonidine, trough	-4.5 (-5.2; -3.8)	-18 (-21; -14)
Brimonidine, peak	-6.1 (-6.7; -5.4)	-25 (-28; -22)

In the model, the average of the reported effectiveness for trough and peak was used as an estimate of the average drug effectiveness.

In order to estimate a distinct effectiveness of MONO1 through MONO4 in individual patients in the model, random distributions were used. However, there is no information in the literature regarding the distribution of medication effectiveness in OHT or POAG population samples. Only the mean (and sometimes the standard deviation or the standard error of the mean) is reported. A beta distribution was used to describe the medication effectiveness, because the beta distribution has the characteristics that it is limited to values between 0 and 1 (or in this case, 0 and 100% pressure lowering).

The beta distribution is defined by two parameters, alpha and beta. Using the method of moments, alpha and beta could be estimated from observed means and variances by the formulas in Table 6. Unfortunately, most articles reporting the results of RCT's for drug effects do not report the variances in relative pressure reductions.

From the reported variances, standard deviations and or standard errors of the mean surrounding IOP's and absolute pressure lowering in the individual studies used in the meta-analysis, the variance of the relative pressure lowering effect of monotherapies was estimated at around 1-1.7%.¹¹

Table 6 The relationship between mean, variance and the parameters (α and β) of the beta distribution.

$$\mu = \frac{\alpha}{\alpha + \beta}$$

$$s^2 = \frac{\alpha\beta}{(\alpha + \beta)^2(\alpha + \beta + 1)}$$

$$\alpha = \mu\left(\frac{\mu(1-\mu)}{s^2} - 1\right)$$

$$\beta = \frac{\alpha(1-\mu)}{\mu}$$

With a variance of 1% (s^2) and a mean effect of 27% (μ), the method of moments would lead to an estimate of $\alpha = 5$ and $\beta = 14$, and a distribution of the timolol effectiveness in the OHT/POAG population as visualized by the histogram in Figure 5. In this distribution, 26% of the population has a relative effectiveness lower than 20%, 11% has a relative effectiveness higher than 40% and 2% has a relative effectiveness higher than 50%.

According to clinical experts (CW, HB, JS), the probability of an effectiveness higher than 40% with timolol are smaller than the 11% that is the result of this theoretical beta distribution, which means that the proposed distribution is too wide. This may be due to the fact that the effectiveness in literature is reported with parameters assuming a normal distribution (μ and s^2), whereas the distribution of effectiveness may deviate from normal. In the absence of any other information, the theoretical distribution was fine-tuned to the experts' expectations. The estimates for alpha and beta values are presented in Table 7 and the distributions are drawn in Figure 6.

Figure 5 Histogram of pressure lowering effectiveness of timolol effectiveness in the simulated population based on a beta distribution with $\alpha = 5$, $\beta = 14$.

Table 7 Default estimates of medication effectiveness in the model (Beta distribution)

	Average	Standard deviation	Estimated Alpha	Estimated Beta	% below 20%	% above 40%
Timolol	27%	8%	8	22	20%	6%
Latanoprost	29.5%	8%	9	22	11%	10%
Dorzolamide	19.5%	8%	5	19	57%	1%
Brimonidine	21%	8%	5	20	49%	2%

Combination therapy: first addition

The relative pressure-lowering effectiveness of the medications when added as the second drug to previously initiated medication, was estimated based on empirical research in the University Eye Clinic Maastricht (DURING study).¹¹ This research prospectively included patients with ocular hypertension (OHT) and glaucoma that were treated with pressure lowering medication. The initiation of therapy and any change in therapy were registered either prospectively or retrospectively from the medical files. The resulting change in intra-ocular pressure was calculated from the intra-ocular pressure measurements before and after the adjustment in therapy. The results for the four representative medications are presented in Table 8.

Figure 6 Histograms of the pressure lowering effectiveness of four medications derived from beta distributions.

Figure 6 Continued.

Table 8 Additive effectiveness observed in the DURING study.

	N	Average IOP before addition (mmHg)	Pressure lowering (95% CI)	SE (derived)	SD (derived)
Timolol	32	25.5	14.1% (7.6; 20.6)	3.3%	19%
Latanoprost	127	23.2	17.7% (14.7; 20.7)	1.5%	17%
Dorzolamide	20	21.6	8.8% (2.0; 15.6)	3.5%	16%
Brimonidine	39	22.9	16.6% (12.2; 21.0)	2.2%	14%

In a recent large systematic review Webers et al. investigated the pressure-lowering effectiveness of second-line glaucoma medication.³³ The authors included studies that investigated the additional pressure lowering effectiveness of adding a medication to further lower intra-ocular pressure. They distinguished the additional effectiveness at peak, trough and on the day-curve. A summary of the results is presented in Table 9. This overview provided a large amount of information regarding the pressure lowering of added medication, but as the authors of the article state, the results from these studies may be biased towards higher effectiveness estimates. In the clinical trials included in the systematic review, the study designs included a run-in phase with the initial medication and no further selection of the patients based on their response to the run-in medication. In clinical

practice (and also in the disease progression model), a second medication is only added if the target pressure is not achieved despite a sufficient response to the initial medication (i.e. more than 20% pressure lowering). If a proportion of the patients in the studies included in the systematic review were in fact non-responders to the run-in medication, the treatment effect that was measured may have been a combination of both initial and additive effectiveness. And since initial effectiveness can be expected to be higher, the treatment effects in the systematic review may have been overestimated.

Table 9 Summarized results of a systematic literature review of the additional pressure lowering-effectiveness of second line glaucoma medications.³³

	Number of included studies	Minimal additional effectiveness found in included studies (%)	Maximal additional effectiveness found in included studies (%)
Timolol			
Trough	-	-	-
Peak	2	19.2 ± 14.1	20.2 ± 7.5
Day-curve	2	10.6 ± 7.6	15.0 ± 11.3
Latanoprost			
Trough	3	15.7 ± 10.5	26.0 ± 12.0
Peak	4	17.0 ± nr	24.6 ± 14.1
Day-curve	8	12.0 ± 14.7	29.9 ± 10.2
Dorzolamide			
Trough	17	11.3 ± 12.5	23.1 ± 8.3
Peak	18	10.2 ± nr	23.1 ± 12.6
Day-curve	8	11.6 ± 7.7	26.9 ± 12.3
Brimonidine			
Trough	7	7.3 ± 12.5	19.7 ± nr
Peak	11	13.4 ± 9.1	27.6 ± nr
Day-curve	1	12.5 ± 11.4	-

Non-responder bias was not an issue in the DURING study because the data were drawn from clinical practice. It is unlikely that a medication would have been added to an ineffective medication. For that reason the estimates of the additive effectiveness of medication in the model were based on the results in de DURING

study, and the hierarchy in effectiveness in the monotherapies was maintained (Table 7). The estimated effectiveness of brimonidine from the DURING study (16.6%) was slightly adjusted downward to the effectiveness of Timolol (14%), because as a monotherapy timolol is more efficacious than brimonidine.¹¹

The distributions of the effectiveness of added medication in a heterogeneous OHT/POAG population were simulated with a beta distribution. The distribution parameters alpha and beta were based on the means and variances. The standard deviation in second-line effectiveness was based on the results of the DURING study and the systematic review, and fine-tuned to 8% in order to obtain a distribution that met the experts' expectations. The resulting parameters and distributions are presented in Table 10 and Figure 7.

Table 10 Default estimates for the relative effectiveness of medication if added to one other medication (Beta distribution).

	Average	Standard deviation	Alpha	Beta	% below 20%	% above 40%
Timolol	14%	8%	2	15	79	1
Latanoprost	18%	8%	4	18	64	1
Dorzolamide	9%	8%	1	11	90	0
Brimonidine	14%	8%	2	15	79	1

Figure 7 Histograms of the pressure lowering effectiveness of four medications when added to a single other medication, derived from beta distributions.

Figure 7 Continued.

Combination therapy: second addition

If two medications still do not suffice to reach the target pressure, a third medication may be added to the therapy. This only applies to the monotherapies that are the third and the fourth option in the treatment strategy (Figure 4). In the default situation the order of monotherapy options is timolol, latanoprost, dorzolamide and brimonidine. Therefore, in the default situation only the effectiveness of dorzolamide and brimonidine as the third medication needs to be estimated. The literature on the effectiveness of the second added medication is very scarce and there are no formal clinical trials that have investigated it. To make estimates for the model the proportional effectiveness of the second-line medications was calculated relative to the monotherapies, and this factor was applied to the effectiveness of the second-line medications. For example, the estimated effectiveness of dorzolamide as a second line medication was 9%, and as monotherapy 20%. The factor $0.09/0.20$ was applied to 0.09, and the resulting estimate is 4%. Similarly the resulting estimate for the effectiveness of brimonidine if added to two other medications is 9%. The estimated standard deviation is 4%. These estimates are presented in Table 11.

Table 11 Default estimates for the relative effectiveness of medication if added to two or more other medications (Beta distribution).

	Average	Standard deviation	Alpha	Beta
Dorzolamide	4%	4%	1	22
Brimonidine	9%	4%	5	46

Post-surgery medication

If patients undergo surgery resulting in a functional filter or tube, the relative pressure lowering effectiveness of medications no longer applies. There is no quantitative information from literature about the effectiveness of medication after successful surgery, but expert opinion is that the effectiveness is much lower than in eyes without previous surgery. Also, the differences between drugs (compounds) are less pronounced. Based on expert opinion (CW, HB, JS) the average pressure lowering effectiveness of all medication in eyes with functional filters or tubes was estimated at 2 ± 0.5 mmHg. A normal distribution truncated at 0 mmHg was used for the OHT/POAG population distribution. The draw from the distribution however is based on the same random number as the draw from the beta distributions for the effectiveness before surgery. This ensures that the effectiveness of the medications before and after surgery are correlated ($r = 1$).

The truncated normal distribution of the post-surgery effectiveness of all medications is shown in Figure 8.

In combination therapy after surgery, the absolute pressure lowering effect of each added monotherapy to the combination is adjusted in order to prevent that the effectiveness of the combination therapy in the model becomes too high. The factor for adjustment is based on the relationship between the drugs' estimated effectiveness in monotherapy, first addition and second addition (Table 7, Table 10). The correction for the first added medication is 0.5, for the second added medication 0.25 and for the third added medication 0.1. For example, the average absolute pressure lowering effectiveness of timolol (2 mmHg) and latanoprost (2 mmHg) is $2 + 0.5 \times 2 = 3$ mmHg.

Figure 8 Histogram of the absolute pressure lowering effect of all medications after successful surgery, derived from a normal distribution with average 2.0 and standard deviation 0.5, truncated at zero.

If a simulated patient receives surgery, the effectiveness of all subsequent medication will be considered in terms of an absolute pressure lowering as long as the filter or tube is functioning. If the latter is no longer the case, e.g. after failed trabeculectomy, the effectiveness of any subsequent medication will be considered in terms of the relative pressure lowering effect again (as in the pre-surgery situation).

LT pressure lowering effect

The literature does not provide a systematic review of the pressure lowering effectiveness of laser trabeculoplasty in patients with OHT or primary open-angle

glaucoma (POAG). Since October 2007 there is a systematic review for 'Laser trabeculoplasty for open angle-glaucoma' in the Cochrane library³⁴, but this has not investigated the pressure lowering efficacy of laser treatment. The committee on Ophthalmic Procedure Assessments of the American Academy of Ophthalmology has issued an Ophthalmic Procedure Assessment regarding 'Laser trabeculoplasty for primary open-angle glaucoma' in 1996. In this report the committee states that "The ocular hypotensive effect of laser trabeculoplasty is usually apparent within 1 month after treatment. Most studies have shown an initial reduction in intraocular pressure of approximately 20% to 30% or 6 to 9 mmHg."³⁵

We have conducted a literature review for articles reporting the pressure lowering effect of laser trabeculoplasty in OHT of POAG patients. Many of the identified articles did not report the pressure lowering effect of the procedure, but rather used the success rate as the primary (and only) outcomes measure, defined as the proportion of patient with a pressure under a certain threshold value. These articles were excluded because they did not provide information that could be translated into model input. The included articles and their results are presented in Table 12.

In previously untreated patients a pressure reduction of 31-35% was seen, in medically treated patients the reduction was 13-19%. In the model, LTP is either applied as a 'monotherapy' or it can be added to the medication to further lower intra-ocular pressure. Based on the review results we have estimated an average effectiveness for LTP in monotherapy of 34%, and an average effectiveness for LTP when added to medications of 16%. As far as the distribution of LTP effectiveness in the OHT/POAG population is concerned, there is less information from literature. Only one of the reviewed studies gave a standard deviation of the effectiveness, but did not report the shape of the distribution.

For the model, the variance in the effectiveness of LTP was assumed to be similar to that of latanoprost, since the estimate of the average effectiveness of LTP is also very similar to that of latanoprost. The final estimated distributions and their parameters are presented in Figure 9 and Table 13.

Table 12 Included studies from the literature review for the pressure lowering effectiveness of laser trabeculoplasty.

Article	Year	Patients	N	IOP baseline (mmHg)	Pressure lowering	Follow-up
McIlraith I <i>et al.</i> ¹³	2005	Untreated OHT or open-angle glaucoma	74	26.0 ± 4.3	31%	1 month
Glaucoma Laser Trial Research Group. ¹⁴	1995	Untreated POAG.	271	27.2	35%	1 year
Heijl A <i>et al.</i> ¹⁰	2002	Untreated open-angle glaucoma	129	20.6 ± 4.1 17.9 after betaxolol treatment.	13% after initial betaxolol treatment. 25% in combination with betaxolol.	3 months
Chung PY <i>et al.</i> ¹⁵	1998	Uncontrolled open-angle glaucoma with maximally tolerated medication.	50	21.4 ± 1.0	18% (pre-LTP medication is continued)	1 month
Damji KF <i>et al.</i> ¹⁶	1999	Uncontrolled open-angle glaucoma with maximally tolerated medication.	36	22.8 ± 3.0 (1.8 – 2.3 co-medications)	12% (2.1 – 2.5 co-medications)	1 month
Juzych MS <i>et al.</i> ¹⁷	2003	Uncontrolled open-angle glaucoma with maximally tolerated medication.	154	24.3 ± 4.1 (2.5 co-medications)	19.4 ± 16.3 % (2.5 co-medications)	1 month

Table 13 Default estimates of LTP effectiveness in the model (Beta distribution).

	Average	Alpha	Beta	% below 20%	% above 40%
LTP monotherapy	34%	12	22	3	23
LTP added to concurrent medication	16%	3	17	72	1

Figure 9 Histograms of LTP effectiveness derived from beta distributions.

Prevalence of Timolol contraindications

Timolol contraindications are asthma and severe chronic obstructive pulmonary disease, sinusbradycardia, second- or third degree atrioventricular block, and latent or uncontrolled heart failure.²⁴ In the DURING study, the prevalence of respiratory contraindications (which is the most evident and directive contraindication in clinical practice) was 123/1273.³⁶ This was rounded up to a default estimate of 10%.

Side-effects with medication

The prevalence of side-effects with each of the medications in the model was based on the results of the DURING study.¹² In this study, previously untreated patients starting pressure lowering medication, and patients that switched medication, were followed for the next three visits. When the initiated treatment was stopped due to side-effects this was registered. The estimate of the incidence of side-effects was based on the proportion of patients on a certain treatment that stopped the medication due to side-effects (as judged by the ophthalmologist) within one or two follow-up visits.

In the model, the occurrence of side-effects indicates that the patient suffers from side-effects that are severe enough to warrant a switch to another therapy. There are a number of randomized controlled trials that have investigated pressure lowering monotherapies and reported on the occurrence of adverse events, but the occurrence of side-effects that warrant a treatment switch cannot be derived from these numbers. Therefore the estimates of the incidence of side-effects with the four base case medications were based solely on our own observational data. The original data from this research was used as input to the beta distributions. Alpha is the number of patients stopping treatment, and beta is the number of patients not stopping treatment.

Table 14 Point-estimate of the incidence of side-effects, and parameters for second-order distribution (beta distribution).

	Average	Alpha	Beta
Timolol	8%	10	109
Latanoprost	8%	22	258
Dorzolamide	14%	2	12
Brimonidine	23%	5	17

Surgery effectiveness

In the model, the effect of glaucoma surgery, i.e. trabeculectomy (with mitomycin C) and Baerveldt implantation, is expressed as a new intra-ocular pressure. The average intra-ocular pressure after trabeculectomy and after Baerveldt implantation was estimated from literature.

Intra-ocular pressure after trabeculectomy

A literature review was performed to estimate the average intra-ocular pressure after a successful trabeculectomy (i.e. the cases of immediate failure are not included). The included studies and their results are presented in Table 16.

The average intra-ocular pressure after trabeculectomy was estimated to be 12.5 mmHg based on this review and a weighted averaging of the outcomes according to sample size. In literature the average IOP's after surgery were reported with a standard deviation, but the distribution of IOP's after surgery cannot be normally distributed with e.g. 9.9 ± 5.0 , because that would mean that a vast amount of patients reached an intra-ocular pressure below the physiological limit (± 6 mmHg) and some patients reached a negative intra-ocular pressure. The distribution of post-operative IOP's in the model was simulated with a gamma distribution, because this distribution can take the shape of a normal distribution but always remains higher than 0.

The parameters of the gamma distribution (alpha and beta) are related to each other through the formulas in Table 15. However, completing these formulas with the values for means and standard deviations reported in literature would lead to very wide distributions of the postoperative IOP. Therefore we first set the boundaries of plausible values of a post-surgical IOP in discussions with clinical experts, which were approximately 6 mmHg at the lowest and approximately 20 mmHg at the highest. This latter (maximum) value is based on the fact that in the model it is assumed that a proportion of the patients does not respond to the trabeculectomy

Table 15 The relationship between mean (μ), variance (s^2) and the parameters (α and β) of the gamma distribution.

$$\mu = \alpha \cdot \beta \quad s^2 = \alpha \cdot \beta^2 \quad \beta = \frac{s^2}{\mu} \quad \alpha = \frac{\mu}{\beta}$$

Table 16 Literature review for trabeculectomy results.

Article	Year	Patients	N	IOP baseline (mmHg)	IOP after surgery (mmHg)	Follow-up
Becker's <i>et al.</i> ¹⁸	2003	Severe glaucoma	60	22.3 ± 9.3 (1.4 co-medications)	12.6 ± 3.5 (0.5 co-medications)	5.5 ± 0.9 years.
Wilson <i>et al.</i> ¹⁹	2003	POAG or PACG	64	26.9 ± 8.5	13.2	6 months
Singh <i>et al.</i> ²⁰	2000	Glaucoma	108	23.2	$58\% > 12$ mmHg $83\% > 15$ mmHg	11 ± 7 months
Wudunn <i>et al.</i> ²¹	2002	Glaucoma	58	21.9	9.9 ± 5.0	12 months
Gedde <i>et al.</i> ²²	2007	Glaucoma	105	25.6 ± 5.3	12.7 ± 5.8 (0.5 $\pm$ 0.9 co-medications)	12 months

and keeps his/her preoperative IOP. This proportion should not be represented by the distribution of IOP's after successful surgery.

The value of beta was varied while the expected value was kept at 12.5 mmHg. Alpha was adjusted such that the last formula in Table 15 was always valid. The value of beta was fine-tuned to reach the desired distribution. The result is presented in Figure 10.

Figure 10 Histogram of the intra-ocular pressure after trabeculectomy, derived from a gamma distribution with alpha 62.5 and beta 0.2.

Intra-ocular pressure after Baerveldt implantation

Literature about the post-operative IOP after Baerveldt implantations is scarce. The point estimate of the IOP after a Baerveldt implantation was based on expert opinion and two studies in literature.

The estimate of two ophthalmologists that frequently perform implantation surgery in glaucoma patients (HB, NJ) was that the post-operative intra-ocular pressure was 12 to 14 mmHg in the presence of some co-medication. Based on these estimates and the literature results (which were also in the presence of co-medication) a point-estimate of 15 mmHg without co-medication was made. In order to make an estimate of the distribution of IOP's after Baerveldt implantation we used a gamma distribution with the same value for beta that was used in the distributions of IOP's after trabeculectomy. The resulting distribution is presented in Figure 11.

Table 17 Literature review for implantation results.

Article	Year	Patients	N	IOP baseline (mmHg)	IOP after surgery (mmHg)	Follow-up
Wilson <i>et al.</i> ¹⁹	2003	POAG or PACG	59	25.9 ± 7.6	16.2	6 months
Gedde <i>et al.</i> ²²	2007	Glaucoma	107	25.6 ± 5.3	12.4 ± 3.9 (1.3 ± 1.3 co-medications)	12 months
Goulet <i>et al.</i> ²³	2007	Glaucoma	62	35.3 ± 12.9	14.7 ± 6.8 (0.8 ± 0.9 co-medications)	12 months

Wilson *et al.* studied the effects of Ahmed rather than Baerveldt devices.

Figure 11 Histogram of the intra-ocular pressure after Baerveldt implantation, derived from a gamma distribution with alpha 75 and beta 0.2.

Conversion risk

Baseline risk

The estimate of the baseline risk of conversion is based on the Kaplan-Meier results of the Ocular Hypertension Treatment Study where 78 untreated patients converted to POAG within 5 years and 741 patients did not convert, with an average IOP during follow-up of 23.9 ± 2.9 mmHg and an average age of 54.9 ± 9.5 years.⁴ In 50-57%

of the patients the diagnosis of conversion was based on the appearance of the optic disc, in 32-42% it was based on visual field measurements, and in 8-10% it was based on both the appearance of the optic disc and visual field measurements.

A recent systematic review of randomized controlled trials in untreated OHT patients found a higher conversion risk in several trials other than in the OHTS (10% -37% in approximately 5 years), but all these trials differed in the definition of conversion, follow-up time and population base.¹ It is therefore hard to compare the results. However, in the systematic review the reported cumulative risks were based on the total number of events in the total follow-up period, while our model uses the Kaplan-Meier estimates at 60 months exactly. For example, in the systematic review the cumulative risk reported for the OHTS study was 10.9% in an average follow-up of 60 (and median 76.5) months, while our model uses 9.5% after 60 months exactly. This could partially contribute to the higher cumulative risks found in literature compared to the estimate used in the model.

Relative risks

The investigators of the OHTS and the EGPS study have joined the data of untreated patients in both studies to develop a prediction model for the development of POAG.⁵ The results of the final multivariate hazard model are presented in Table 18.

Table 18 Multivariate hazard ratios (HR) in the pooled OHTS and EGPS control groups.⁵

Variables	Hazard ratio	95% confidence interval
Age (per decade higher)	1.26	1.06; 1.50
Mean IOP (per mmHg higher)	1.09	1.03; 1.17
Mean CCT (per 40 μ m higher)	2.04	1.70; 2.45
Mean vertical C/D ratio (per 0.1 higher)	1.19	1.09; 1.31
Mean PSD (per 0.2 dB higher)	1.13	1.04; 1.24

IOP = intra-ocular pressure, CCT = central corneal thickness, C/D ratio = cup/disc ratio, PSD = pattern standard deviation.

In our model, the relative risk of age and intra-ocular pressure are updated continuously, and are based on the actual age and intra-ocular pressure of the simulated patient. The other prognostic factors are aggregated into one additional factor in the model ('Other risk factors')

Relative risk of intra-ocular pressure

The point-estimate for the relative risk of IOP above 23.9 mmHg is 1.09, based on the results of the pooled OHTS/EGPS risk model.⁵ This estimate was further supported by a meta-analysis performed in the University Eye Clinic Maastricht.²

Relative risk of age

The point-estimate for the relative risk of age above 54.9 years is 1.26, based on the results of the pooled OHTS/EGPS risk model.

Other prognostic factors

The presence of other risk factors (or the relative risk of the other prognostic factors in Table 18) is in the model simulated by a single variable. As a model input an estimate is needed for the distribution of the 'additional risk' in the typical population of OHT patients. The average of this value is 1, since the average population of the OHTS and the EGPS studies has the average risk of conversion, i.e. no additional risk (or risk reduction). The distribution of the value of this variable however could not be derived from the OHTS or the EGPS studies, because the risk model has never been applied to the actual study populations themselves. The OHTS investigators have however used a cohort of patients of the "Diagnostic innovations in glaucoma study" (DIGS) to validate their predication model for the development of POAG.³⁷ They present the distribution of predicted probabilities for the 5-year risk of glaucoma development among the 126 untreated patients with OHT.

We have used the risk distribution in the DIGS cohort to deduct the distribution of additional risk in an OHT population. The distribution of the natural logarithm of the additional risk was assumed to be normal with an average 0 (since $e^0=1$). A population was simulated with an age and IOP distribution similar to that reported for the DIGS population, and hazard ratio's for age and IOP as reported by the OHTS/EGPS investigators.³⁷ Subsequently a normal distribution was used to simulate the additional risk, and the standard deviation of this distribution was fine-tuned in such a way that the resulting distribution of risk in the population resembled the distribution reported for the DIGS cohort. With a standard deviation of 0.7 (Figure 12), the resulting distribution of predicted risk of conversion resembled the DIGS cohort best (Figure 13).

Figure 12 Probability density function of the relative risk of factors other than age and IOP in the simulated OHT population.

Figure 13 Distribution of the risk of glaucoma development in 5 years in a simulated OHT population with age 56.3 ± 13.1 years, IOP 25.7 ± 3.5 mmHg, and $\text{LN}(\text{additional risk}) = \text{normal}(0, 0.7)$, compared to the reported distribution of predicted conversion risk in the DIGS cohort.

Equations

The baseline risk and the relative risks of age, IOP, and other risk factors are aggregated in the model into the following equation for the current hazard rate for conversion from OHT to POAG of individual i .

$$h_i = HR_i \cdot h = HR_{Age}^{\left(\frac{\langle Age \rangle_A - Age_{av}}{10}\right)} \cdot HR_{IOP}^{(\langle IOP \rangle_A - IOP_{av})} \cdot HR_{other_i} \cdot h$$

$$h_i = 1.26^{\left(\frac{\langle Age \rangle_A - 55}{10}\right)} \cdot 1.09^{(\langle IOP \rangle_A - 24)} \cdot HR_{other_i} \cdot 0.02$$

h_i = current hazard rate of individual i at current event

h = hazard rate in reference OHT population

HR_i = Total hazard ratio of individual i at current event

HR_{age} = Hazard ratio of age (per 10 years older)

HR_{IOP} = Hazard ratio of IOP (per mmHg higher)

$\langle Age \rangle_A$ = Age of individual i at current event

Age_{av} = Average age of reference OHT population

$\langle IOP \rangle_A$ = IOP of individual i at current event

IOP_{av} = average IOP in the reference OHT population (mmHg)

HR_{other} = Hazard ratio of other risk factors

The individual hazard is entered into the survival function $P = 1 - S = 1 - e^{-h_i \cdot t}$, from which a random draw is made to arrive at the new value for time-to-conversion. Figure 14 shows two examples of such cumulative probability distributions for conversion.

Figure 14 Examples of cumulative survival distributions for time-to-conversion in an untreated patient (black line) and a treated OHT patient (grey line).

Progression

Progression of POAG in the model is simulated via the level of the Mean Deviation (Humphrey Field Analyzer, Carl Zeiss Meditec, Jena, Germany) of the simulated patient. A decrease in the Mean Deviation signifies a decrease in the quality of the visual field, which is the pivotal feature of functional glaucomatous progression.

Glaucomatous progression is the mechanism where nerve fibers in the optic nerve continue to degenerate, which leads to a loss of functional nerve fibers, which in turn leads to a desensitization of specific areas of the retina, resulting in localized 'gaps' in the visual field, which can ultimately lead to a loss of visual functioning. The translation of glaucoma progression into a value of the Mean Deviation in the model is not straightforward. Mean Deviation is calculated as the average deviation of the retinal sensitivity from the age-corrected normal values. The sensitivity is the threshold value of light intensity that is no longer perceived by the patient, and is expressed in terms of apostilbs. A 10-fold decrease in average sensitivity equals a loss of 10 decibels in the Mean Deviation, and a 1000-fold decrease in average sensitivity equals a loss of 30 decibels in the Mean Deviation. The consequence of this conversion is that Mean Deviation is actually a logarithmic parameter and this might be reflected in the natural course of the Mean Deviation in glaucomatous patients.

In a systematic review the available data on the characteristics of glaucomatous progression in time was investigated, and no evidence was found that indicated that progression measured by the Mean Deviation is not linear in time. The model therefore assumes the existence of a baseline progression rate (in dB per month) which can be influenced by the level of the intra-ocular pressure.

Systematic review of glaucomatous progression (and rate of progression)

Several of the assumptions made in the model concerning the progression and speed of progression, were based on a systematic literature review. The method and results of this review will be briefly described here.

The purpose of the systematic review was to collect information regarding the progression of visual fields in time and to estimate the rate of progression in glaucoma patients.

Sources of references:	Embase Pubmed Bibliography of included articles
Search Terms:	"Open-angle glaucoma" AND "Progression" AND "Visual field" OR "optic disc" OR "optic nerve"
Restrictions:	English or Dutch Adult population Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Case Reports, Classical Article, "Clinical Trial, Phase I", "Clinical Trial, Phase III", "Clinical Trial, Phase IV", Controlled Clinical Trial, Journal Article, Multi center Study

Exclusion criteria during title and abstract screening:

1. Not OAG
2. Technical report about visual field measurement
3. Cross-sectional study
4. Follow-up < 4.5 years AND no reference to progression rates (xx/month) in the abstract
5. Does not concern OAG progression (e.g. IOP monitoring, screening, prevalence etc.)
6. Review or case report.

Exclusion criteria during full-text screening:

1. The rate of visual field progression is not quantified and reported directly, AND
2. The rate of visual field progression cannot be derived from the change in score and mean follow-up time.

Figure 15 Flow diagram of article selection and inclusion. Numbers in the boxes of excluded references refer to the exclusion criteria listed above.

Glaucomatous progression (or glaucoma severity) was measured with several different methods in the included studies, as can be seen in the rightmost column of Table 19. The reported rates of progression with each of these methods are presented in Table 20 to Table 27. Some articles did not report the actual observed rate of progression. In these cases the rate was derived from the difference between the average final and the average baseline visual field parameter divided by the average length of follow-up. Most authors reported results divided in groups based on the occurrence of progression.

Table 19 Included studies in systematic literature review for glaucomatous progression rate.

	Population	N	FU (yrs)	A	B	Intervention	Outcomes
Chen <i>et al.</i> , 2002 ⁶	POAG, NTG, PEX, PDG	152 pts	7.5	N	N	Usual care	MD/year ± SD, PSD/year ± SD, AGIS, c/d ratio.
Chen <i>et al.</i> , 2000 ⁷	POAG, NTG, PEX, PDG	36 pts	5.6	N	N	Usual care	MD/year ± SD, PSD/year ± SD, AGIS, c/d ratio.
Feiner <i>et al.</i> , 2003 ³⁸	POAG, PDG, PEX	607 pts	5	Y	N	1) Medical 2) Surgical	CIGTS
Heijl <i>et al.</i> , 2002 ¹⁰	POAG, NTG, PEX	255 pts	5.7	Y	N	1) LT 2) No Tx	MD/year ± SD
Lee <i>et al.</i> , 2004 ³⁹	POAG, PACG	48 eyes	11.7	N	N	Usual care	%/year ± SD, c/d ratio
Mayama <i>et al.</i> , 2004 ⁴⁰	OAG	105 eyes	7.5	N	Y	Usual care	MD
Mikelberg <i>et al.</i> , 1986 ⁴¹	OAG (not NTG)	45 eyes	7.6	N	N	Usual care	Scotoma mass/month
Oliver <i>et al.</i> , 2002 ⁴²	POAG, PEX, PDG, NTG	290 pts	15	N	Y	Usual care	Stages/year
Pereira <i>et al.</i> , 2002 ⁴³	POAG	40 eyes	16.2	N	N	Usual care	%/year ± SD, c/d ratio
Rasker <i>et al.</i> , 2000 ⁴⁴	POAG, NTG, OHT	227 pts	9	Y	N	Usual care	%/year ± SD
Schwartz <i>et al.</i> , 2004 ⁴⁵	OAG	30 eyes	6.7	N	N	Usual care	MS/year ± SD
Soares <i>et al.</i> , 2003 ⁴⁶	OAG	44 eyes	4.9	Y	N	Usual care	MD/year
Vest <i>et al.</i> , 2003 ⁴⁷	OAG	76 pts	7	N	N	Usual care	MD
Wilson <i>et al.</i> , 2002 ⁴⁸	Glaucoma, glaucoma suspect	287 eyes	10	Y	N	No Tx	AGIS, CIGTS
Zink <i>et al.</i> , 2003 ⁴⁹	OAG	29 eyes	2.8	N	?	Usual care	CPSD/year ± SD
Kwon <i>et al.</i> , 2001 ⁵⁰	POAG	40 eyes	15.2	N	N	Usual care	%/year ± SD, c/d ratio
Smith <i>et al.</i> , 1996 ⁸	Glaucoma	191 eyes	7.1	N	N	Usual care	MD/year ± SD, CPSD/year ± SD.
O'Brien <i>et al.</i> , 1991 ⁵¹	OAG (not NTG)	40 eyes	3.7	N	N	Usual care	MS/year ± SD
Katz <i>et al.</i> , 1997 ⁹	OAG from OHT	67 eyes	7	N	N	Usual care	MD/year ± SD, CPSD/year ± SD.

A: Prospective?, B: Selection based on progression? N = No, Y = Yes.
MD = Mean Deviation (HFA), MS = Mean Sensitivity (Octopus), % = Percentage of maximum sensitivity.

Table 20 Reported rate of MD change (dB/year).

Study	Patients	N	MD baseline (dB)	IOP (mmHg)	Mean ± SD
Chen <i>et al.</i> , 2002 ⁶	Progressed	54	Better: -3.6 ± 4.1 Worse: -7.6 ± 7.3	17	-0.64 ± 0.52
	Stable	98		-	-0.39 ± 0.53
Chen <i>et al.</i> , 2000 ⁷	Progressed	6	Better: -6.0 ± 4.8 Worse: -17.9 ± 6.0	17.6	-2.20 ± 1.40
	Stable	30		16.5	0.10 ± 0.70
Smith <i>et al.</i> , 1996 ⁸	Progressed	24	-8.7 ± 3.8	-	-1.26 ± 0.60
	Stable	167		-	0.06 ± 0.60
Katz <i>et al.</i> , 1997 ⁹	Progressed	12	-7.4	-	-0.96 ± 0.44
	Control (no treatment)	126	-4.4 ± 3.3	20.8	-0.60 ± 0.84
Heijl <i>et al.</i> , 2002 ¹⁰	Treatment	129	-5.0 ± 3.7	15.5	-0.36 ± 0.60

Table 21 Derived rate of MD change (dB/year).

Study	Patients	N	MD baseline (dB)	IOP (mmHg)	Mean ± SD*
Mayama <i>et al.</i> , 2004 ⁴⁰	Progressed	105	-4.2 ± 3.7	-	-0.72 ± 1.03
	Stable	355	-9.2 ± 7.2	-	0.03 ± 1.52
Soares <i>et al.</i> , 2003 ⁴⁶	All	44	-4.2 ± 2.9	-	-0.30 ± 0.40
Vesti <i>et al.</i> , 2003 ⁴⁷	All	76	-8.5 ± 4.7	-	-0.31 ± 0.46

*Estimates of SD

Table 22 Reported rate of PSD change (dB/year).

Study	Patients	N	Mean ± SD
Chen <i>et al.</i> , 2000 ⁷	Progressed	6	0.61 ± 0.59
	Stable	30	0.02 ± 0.51
Chen <i>et al.</i> , 2002 ⁶	Progressed	54	0.40 ± 0.30
	Stable	98	0.30 ± 0.52

Table 23 Reported rate of CPSD change (dB/year).

Study	Patients	N	Mean ± SD
Zink <i>et al.</i> , 2003 ⁴⁹	High tension glaucoma	13	-0.01 ± 0.81
Smith <i>et al.</i> , 1996 ⁸	Progressed	27	0.71 ± 0.34
	Stable	164	-0.01 ± 0.39
Katz <i>et al.</i> , 1997 ⁹	Progressed	5	0.91 ± 0.25

Table 24 Reported rate of change in mean threshold values (dB/year).

Study	Patients	N	IOP (mmHg)	Mean ± SD
Schwartz <i>et al.</i> , 2004 ⁴⁵	All	30	18 ± 2	-0.38 ± 0.56
O'Brien <i>et al.</i> , 1991 ⁵¹	Progressed	10	16.5 ± 1.8	-1.39 ± 0.78
	Stable	30	16.8 ± 2.5	-0.07 ± 0.43

Although the methods to measure the severity of glaucoma or the rate of visual field loss varied across the included studies, most methods have in common that they are based on the sensitivity measurements from the Humphrey or Octopus automated perimeters. Some authors have commented on the linearity of the relationship between the visual field and time.

Smith, 1996 (MD/year) ⁸
“We determined the type of regression function based on visual inspection of the data. This gave no indication that a better fit would be obtained with a nonlinear rather than a linear function. Because visual field data were recorded in decibels, a linear decline represents an exponential decay in retinal sensitivity.”

Table 25 Reported rate with Grids methods, (%/year).

Study	VF method	Patients	N	IOP (mmHg)	Mean ± SD
Lee <i>et al.</i> , 2004 ³⁹	Goldman, 12 th and 14 th isopter % of normal field (full field)	All	48	17.2 ± 2.8	-0.81 ± 1.00
Pereira <i>et al.</i> , 2002 ⁴³	Goldman, 14 th isopter % of normal field (full field)	All	40	18.4 ± 2.5	-1.29 ± 1.37
Rasker <i>et al.</i> , 2000 ⁴⁴	Peritest, screening, % of maximum possible sensitivity loss (full field)	Progressed Stable	27 41	- -	-2.5 ± 1.8 -0.45 ± 2.23
Kwon <i>et al.</i> , 2001 ⁵⁰	Goldman, 14 th isopter % of normal field (full field)	All	40	18.4 ± 2.5	-1.28 ± 1.37

Table 26 Derived rate of change in AGIS score (points/year).

Study	Patients	N	IOP (mmHg)	Mean (change points / fu)
Chen <i>et al.</i> , 2002 ⁶	Worse eye	152	-	0.4 / 7.5 = 0.05 points / year
Chen <i>et al.</i> , 2000 ⁷	Worse eye	36	-	2.1 / 5.6 = 0.38 points / year
Wilson <i>et al.</i> , 2002 ⁴⁸	Untreated	287	-	5.4 / 10 = 0.54 points / year

Table 27 Derived rate of change in CIGTS score (points/year).

Study	Patients	N	IOP (mmHg)	Mean (change points / fu)
Feiner <i>et al.</i> , 2003 ³⁸	All	607	-	0.3 / 5 = 0.06 points / year
Wilson <i>et al.</i> , 2002 ⁴⁸	Untreated	287	-	7.5 / 10 = 0.75 points / year

Katz, 1997 (MD/year) ⁹

"A linear fit appeared to adequately describe the changes occurring in the visual field over time as evidenced by a lack of relationship between the residuals and time".

Mikelberg *et al.* report that the majority of patients with progression had a linear progression of scotoma mass in time (Figure 16), and Kwon *et al.* showed that a linear model resulted in good fits for the visual field score versus time (Figure 17).

Figure 16 Graphs from Mikelberg *et al.* The authors reported that 49% of the patients had linear progression (A), 20% had curvilinear progression (B), 7% had episodic progression (C) and 24% had no progression (D). Reprinted from American Journal of Ophthalmology, 101(1). Mikelberg FS, Schulzer M, Drance SM, Lau W. The rate of progression of scotomas in glaucoma. Page 1-6. Copyright (1986), with permission from Elsevier.

Figure 17 Graphs from Kwon *et al.* of the visual field score in time. Reprinted from American Journal of Ophthalmology, 132. Kwon Y, Kim C, Zimmerman B, et al. Rate of visual field loss and long-term visual outcome in primary open-angle glaucoma. Page 47-56, Copyright (2001), with permission from Elsevier.

In addition to these data in literature, we inspected the visual field data of the patients included in our observational data from the quality-of-life study.^{29,30} Similarly to the conclusion of Smith *et al.* we found no indication that the relationship between Mean Deviation and time would be any other than linear. Some examples of patients with more than three visual field measurements are presented in Figure 18.

An evaluation of the assumption that in the natural course of disease MD decreases linearly in time, is hampered by the fact that there are no records of long-term MD progression in untreated POAG patients. The scarce data that are available typically concern short follow-up data of treated early POAG patients, with (presumably) more intensive treatment upon progression. The fact that MD decrease seems linear in these data may suggest that the actual progression in untreated patients is exponential, with an increasingly fast MD decrease as the visual field worsens. Some

Figure 18 Plots of Mean Deviation in the right eye derived from a central 30-2 or 24-2 visual field test (dB) versus time (years) since the first visual field measurement in the patient file, in four glaucoma patients from our quality-of-life study population.^{29,30}

Figure 18 Continued.

literature reports indeed suggest that baseline disease severity is an independent risk factor for progression⁵², but this is contradicted by other reports^{48, 50, 53}. The latter study results may even suggest that a more severe baseline visual field defect is associated with a *lower* risk of progression. However, this result may be observed due to the fact that there is a limit to the amount of visual field a person can lose. Patients with severe visual field defects have less to lose than patients with early visual field defects. Given the current level of evidence we concluded that it would not be implausible to assume that an individual glaucoma patient in the model has a constant rate at which the Mean Deviation decreases each year, and that the height of this rate can be influenced by the IOP level.

In order to make an estimate of the height of this natural rate, a meta-analysis was performed in Review Manager (Cochrane) with the studies from the systematic review that reported the rate of progression in MD/year with variance data (95% confidence interval, variance, SE or SD) and the reported rates were compared against a hypothetical group with no change in the Mean Deviation. The results of this meta-analysis are presented in Figure 19. The average rate of MD change per year in treated patients was -0.33 dB/year (95% CI: -0.38; -0.28).

In 2009, results from the Groningen Longitudinal Glaucoma study were reported, which showed that in an unselected cohort of OAG patients with an average IOP of 14.9 mmHg during a mean follow-up of 5.3 years, the annual change in MD was -0.25 dB/year.⁵⁴ This is in good agreement with the results from the meta-analysis and further support the estimates made for the model input.

Baseline rate of progression

In the model, each individual patient is 'assigned' a reference progression rate (MDR_{ref}) that represents the rate with which MD would decrease annually if IOP and additional risk were as in the referent POAG population. There is no information on the actual distribution of the rate of MD progression in the POAG population. For the sake of the model consistency, it was assumed that the decrease in the Mean Deviation in glaucoma patients is always larger than zero (i.e. there are no patients with an improving visual field). We therefore chose to use a gamma distribution, because values in the Gamma distribution are always higher than zero while the distribution is flexible in its shape through the shape parameter.

The estimate of the distribution of progression rates in the POAG population was initially based on the treated patient population in the meta-analysis (Figure 19). The average progression rate was 0.33 dB/year (which corresponds to 0.028 dB/month), and the standard deviation was derived from the individual studies in Table 20 and estimated at 0.63 dB/year (which corresponds to 0.053 dB/month). The formulas

Figure 19 Meta-analysis of the rate of change of the Mean Deviation in Review Manager.

in Table 15 and the estimated mean and standard deviation of 0.028 ± 0.053 dB/month for treated patients, lead to an initial estimate for alpha 0.36 and an estimate for Beta 0.08 and a population distribution as presented in Figure 20.

Figure 20 Gamma distribution of MD progression rate (dB/month) in the population with alpha = 0.36 and beta = 0.08.

Since we did not know the actual shape of the distribution of progression rates in a POAG population, we validated the initial estimates for the distribution in Figure 20 by using the only other source of information we had. The initial distribution was translated into an expected survival curve by means of simulation in order to compare it with the survival curve reported in the EMGT study. The estimated average progression rate of 0.028 ± 0.053 is very similar to the results reported for the EMGT study.¹⁰ In the EMGT study, progression was defined as either visual field progression or optic disc progression. Visual field progression was defined as at least 3 test-points significantly progressing at the same location in the EMGT Pattern Change Probability Maps (based on the PSD) in 3 consecutive tests. Optic disc progression was defined as a clear and progressive change located at the same optic disc clock-hour, confirmed in photographs 6 months later. Optic disc progression was determined by 2-3 independent graders. The authors of the EMGT study have reported that, in retrospect, progression was associated with an MD change of -2.26 dB and that progression was based on the visual field measurements in 82-91% of the cases. In Figure 21 the curve resulting from our simulation was merged with the progression curve reported for the EMGT study.

Figure 21 Expected curve of progression in time with Gamma (0.36, 0.08) (red dotted line) compared to EMGT results for treated patients (solid light grey line).

From Figure 21 it is clear that the expected incidence of progression with the initial Gamma distribution in Figure 20 was much lower than the incidence observed in the EMGT study. Moreover, the shape of the survival curve did not match the observed curve. Therefore the parameters of the Gamma distribution were adjusted, restricted by the mean of 0.028 dB/month, in order to fine-tune the survival curve towards one that would resemble the results of the EMGT study. The result is presented in Figure 22 which shows a Gamma distribution with $\alpha = 2$ and $\beta = 0.014$. This distribution has an expected value of 0.028 ± 0.02 . It was not possible to find a Gamma distribution that lead to survival curves that matched the EMGT results exactly, but the distribution in Figure 22 lead to survival curves that matched the shape of the EMGT survival curves best. We valued a match in the shape of the curve higher than a match (over a small range) in the absolute values of the incidence of progression with a curve shape that does not match. The reason for this is that the difference between two curves with a similar shape corresponds with a time-shift, or a delay in the onset of progression in the simulated cohort relative to the observed cohort (in this case approximately 18 months), whereas the difference between two curves with a different shape corresponds to a different relationship between time and risk.

Figure 22 Gamma distribution of MD progression rate (dB/month) in the population representing a treated population with $\alpha = 2$ and $\beta = 0.014$ (top graph), and the expected curve of progression in time with Gamma (2, 0.014) (dotted red line) compared to EMGT results for treated patients (solid light grey line) (bottom graph).

Relative risk of intra-ocular pressure

Lowering intra-ocular pressure reduces the risk of progression in POAG patients.^{10, 55, 56} However, the magnitude of risk reduction per unit of pressure lowering has not been established in systematic reviews or meta-analyses. The only source for an estimate of the relative risk of the intra-ocular pressure on progression is the EMGT study.

The EMGT authors have performed a multivariate Cox proportional hazards models and found a hazard ratio of 1.13 (95% CI: 1.07; 1.19) per mmHg higher during a median follow-up of 6 years, corrected for age, baseline IOP, exfoliation, number of eligible eyes and MD.¹⁰ The reference value of the intra-ocular pressure in the model is the average value of the intra-ocular pressure in the treated EMGT group (15.5 mmHg).

The relative risk (odds ratio) of progression per mmHg was derived from logistic regression analysis, with the occurrence of progression as a dichotomous outcome. However, in the model progression is not modeled as an event but rather as a continuous process. The relative risk of IOP works on the progression rate, not on progression risk. Still, in the absence of any other data on the relative risk of IOP on the rate with which MD decreases in time, we have applied the reported odds ratios to the MDR directly. This means that, for example, an odds ratio of 2 results in an MD-change that is twice as fast as the MDR_{ref} . We have checked this assumption by creating survival curves from hypothetical distributions of MDR and calculating the relative risk of progression (i.e. a total MD decrease of 2.3 dB or more) compared to the reference MDR distribution. The reference MDR distribution was the Gamma(2, 0.014) distribution described in the previous paragraph. The hypothetical distributions were created by increasing the expected value with a factor 2, 4, and 6. The relative risks of progression derived from these distributions depend on time, because the cumulative event curves converge and the relative risks ultimately all approach 1. However, when we looked at the time-period from which the odds ratio in the EMGT study was derived (i.e. 6 years), the relative risks of progression in the hypothetical distributions were 2.6, 4.8 and 6.3 respectively. These numbers resemble the multiplication factors of the distributions (2, 4 and 6), and we concluded that the direct extrapolation of relative risks into MDR multiplication factors in the model does not lead to unlikely results.

The construction described above, where each simulated patient is assigned a random reference MDR which is subsequently adjusted to the actual IOP of the patient, has the consequence that the MDR in the model can *approach* zero, but it can never *become* zero. After all, the reference MDR drawn from a Gamma distribution is always higher than 0, and so is the relative risk, even at low IOP values. As a result of this, a POAG patient in the model will never reach a stable disease stage. Some reports in literature indicate that in POAG the rate of progression might decrease to zero if the intra-ocular pressure is low enough, although it remains an issue of some dispute.^{55, 57, 58} In the AGIS study the investigators found that very few of the patients with an intra-ocular pressure that was always below 18 mmHg in the first six years of follow-up (on average 12.3 mmHg) showed progression in ten years.⁵⁵ Shirakashi *et al.* found that patients

without progression in a follow-up of fifteen years had an average intraocular pressure of 13.4 ± 1.3 mmHg.⁵⁷ It may therefore be reasonable to assume that there is something like a threshold IOP below which no progression occurs. In the base case model we assumed that the MDR will become 0 dB/months if the intraocular pressure is lower than 13 mmHg.

Equations

The baseline rate of progression and the relative risks of IOP are aggregated in the model into the following equation for the current MDR of individual i .

*When $IOP \geq IOP_{no\ progression}$

$$MDR = MDR_{ref} \cdot HR_i = MDR_{ref} \cdot HR_{IOP}^{((IOP)_A - IOP_{av})} \cdot HR_{other} = MDR_{ref} \cdot 1.13^{((IOP)_A - 15.5)} \cdot HR_{other}$$

*When $IOP < IOP_{no\ progression}$

$$MDR = 0$$

MDR = Mean Deviation Rate of individual i at current event

MDR_{ref} = Mean Deviation Rate of individual i if IOP and HR_{other} were as the average in the reference POAG population.

HR_i = Total hazard ratio of individual i at current event

HR_{IOP} = Hazard ratio of IOP (per 1 mmHg higher than average IOP in the reference POAG population)

HR_{other} = Hazard ratio of other risk factors (<progression risk>_A)

$\langle IOP \rangle_A$ = IOP at current event (mmHg)

IOP_{av} = average IOP (mmHg) in the reference POAG population (15.5 mmHg)

$IOP_{no\ progression}$ = IOP threshold for disease progression.

Criterion for progression in the model

The disease progression of POAG patients is modeled via the gradual decrease of MD in time. Whether or not a simulated patient experiences 'clinical progression' in the sense that it calls for a treatment adjustment therefore depends on the definition of progression in any particular analysis. The occurrence of progression is not an outcome of the model, but rather it is a tool to guide treatment decisions throughout the simulated life of POAG patients. When progression occurs in a simulated patient, the target pressure will be adjusted, and (if possible) a treatment change will occur.

In real clinical practice the establishment of progression is a process that involves multiple measurements and clinical judgment. It is not only important to establish objectively whether the optic nerve or the visual field has worsened, but also whether this worsening calls for a treatment change. Not only the absolute change

may play a role, but also the time-frame in which this absolute change was observed relative to the life-expectancy of the patient.

In the base case model presented here, an absolute MD decrease of 2 dB was set as the criterion for progression, irrespective of the time-frame and life-expectancy of the patient. The threshold of 2 dB was based on the literature reports by Wesselink *et al.* and Heijl *et al.*, where POAG patients with confirmed progression had an average MD decrease of 2.4 dB and 2.3 dB respectively.^{10, 54} The criterion for progression in this base case model may be rather stringent compared to clinical practice.

It is important to note that the base case model does not directly take inter-test variability of visual field measurements into account. The modeled MD value is the 'real' MD value, and it is assumed that the ophthalmologist can measure this value with a 100% sensitivity and specificity. In that context, the progression criterion of 2 dB defines the threshold for the absolute reduction in MD that will, in the model, call for a treatment change, given that it has been established that the real MD decrease is indeed more than 2 dB. The 2 dB threshold should not be confused with the threshold that will in clinical practice trigger a suspicion of progression and call for extra visual field measurements to confirm or invalidate this suspicion.

The base case model adds the costs of an extra visual field measurement to a visit in which progression is observed, to take account of the extra visual field measurement that is in clinical practice performed to confirm a suspected progression.

In the model, the absolute MD decrease is measured relative to either the first MD measurement in the model, or the MD value at the moment the previous progression was observed.

For example:

Visit	MD measured	Progression?	
1	- 3.0	No	3.0 dB
2	- 4.5	No	
3	- 6.0	Yes	2.2 dB
4	- 7.0	No	
5	- 8.2	Yes	

Cataract

POAG and cataract are related by the fact that the risk of developing cataract is higher in patients that received a trabeculectomy in the past. Conversely, a laser trabeculoplasty is contraindicated if a patient has undergone a cataract extraction in the past. For this reason, the occurrence and treatment of cataract is included in the disease progression model of OHT and glaucoma.

Baseline risk of cataract formation

The age-related incidence of cataract was derived from medical statistics provided by the National Institute for Public Health and the Environment (RIVM).⁵⁹ The incidence numbers were used to estimate the age-related hazard of cataract formation for the patients in the model.

Table 28 Estimated prevalence and incidence of cataract in The Netherlands.

Age	Year prevalence (per 1000)		Incidence (per 1000 per year)	
	Male	Female	Male	Female
0-4	0,74	0,00	0,27	0,00
5-9	0,37	0,16	0,00	0,00
10-14	0,63	0,53	0,00	0,00
15-19	0,69	0,19	0,00	0,00
20-24	0,65	0,18	0,00	0,00
25-29	0,36	0,73	0,00	0,00
30-34	0,43	0,90	0,00	0,13
35-39	0,95	0,62	0,00	0,47
40-44	2,11	0,99	0,20	0,00
45-49	2,28	4,13	0,56	0,77
50-54	2,73	4,91	0,61	1,67
55-59	7,29	8,52	2,44	3,01
60-64	16,95	19,27	3,67	4,82
65-69	40,45	52,20	9,95	14,62
70-74	84,84	113,91	18,65	22,46
75-79	153,00	183,46	32,16	33,16
80-84	205,98	237,24	35,85	35,78
85+	283,92	296,89	20,21	22,14

At baseline the model establishes whether a patient has experienced cataract formation in the past, based on the cumulative risk at the baseline age of the patient. If a patient has not developed cataract in the past, the model uses the age-related hazard of cataract formation to simulate cataract development during the simulation.

Relative risk of trabeculectomy for cataract formation

Trabeculectomy may enhance cataract formation. In the Collaborative Initial Glaucoma Treatment Study (CIGTS) the authors found a relative risk of cataract extraction of approximately 3.0 after trabeculectomy relative to medication only.⁵⁶ The CIGTS study was also referred to in a Cochrane systematic review.⁶⁰ The authors of the review reported a relative risk of cataract extraction after surgery of 2.72 at up to three years follow-up (95% CI: 1.51; 4.89).

In the Advanced Glaucoma Intervention Study (AGIS), the authors reported an increased risk of cataract surgery in the group that was initially treated with trabeculectomy versus the group that was initially treated with laser trabeculoplasty (1.1 to 1.3) after ten years.⁶¹ It should be noted however that 50% of the patients in the laser trabeculoplasty group also received trabeculectomy within the first 10 years (hence perhaps the lower relative risk).

In the model the default estimate of the relative risk of cataract formation after trabeculectomy was 2.7.

Cataract extraction

Cataract is often surgically removed. However, the model takes account of a small percentage of patients that can, for any reason, not undergo cataract extraction. A baseline attribute (yes/no) informs the model whether a patient will undergo cataract extraction if cataract develops during the model, or whether the patient has undergone cataract extraction if the baseline attribute 'Cataract in the past' is positive.

Utility outcomes

Estimates for the relationship between disease, treatment and utility were derived from observational research among 531 OHT and glaucoma patients in the University Eye Clinic Maastricht and five other Dutch ophthalmology centers. The methods and results of this observational research are described elsewhere.^{29,30} In this document only the results relevant for the parameter estimates of utilities are described.

Visual Functioning Questionnaire

A multivariable linear regression model was used with the measured value of the patients' score on the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25).

Table 29 Results of multivariable linear regression analysis with VFQ-score.

	Unstandardized coefficient	Standard error	Significance
Constant	94.246	1.189	.000
Co-morbidities (yes vs. no)	-2.014	.424	.000
Side-effects score (per point)	-.194	.034	.000
MD in worse eye (per dB)	.496	.099	.000
MD in better eye (per dB)	1.050	.152	.000
Cataract in worse eye (yes vs. no)	-6.891	3.196	.032
Cataract in better eye (yes vs. no)	-2.301	2.921	.431

Parameters that occur in the model are: side-effects, MD and cataract. The number of co-morbidities was included in the regression model because it had an effect on the coefficients of cataract. Side-effects in the model represent the occurrence of side-effects that necessitate a change in medical therapy. In the data from the observational study, the participants were divided into two groups based on their answer to the question "How much do side-effects from medication impact your quality-of-life". One group consisted of patients who answered "Not at all", "Hardly", "Somewhat" or "Quite a bit", and the other group consisted of patients who answered "Much" or "very much". The average side-effects score of the first group was 13, and the average score of the second group was 49. It was therefore assumed that the occurrence of side-effects severe enough to warrant a change in medication was associated with a side-effects score of 50. This is subsequently associated with a loss of $50 \times 0.194 = 9.7$ VFQ points. The model only simulates the MD in the better eye, but it is assumed that the disease progression is reasonably symmetric, and the coefficient of both MD in the worse eye as well as MD in the better eye was applied to the current MD in the model. The same goes for the presence of cataract.

Therefore, the current VFQ-score in the model is calculated with the formula:

$$\text{VFQ} = 94 - 9.7 \times \text{side-effects} + 1.54 \times \text{MD} - 9.2 \times \text{cataract}.$$

The VFQ-25 scores is a value on a scale from 0 (worst) to 100 (best). This scale was converted directly into a utility scale from 0 to 1 by dividing the VFQ-25 score by 100. The life-years in the model adjusted for the VFQ-25 score therefore represent 'visual functioning quality adjusted life-years (VFQaly).

Health Utilities index

To estimate the relationship between disease, treatment and utility by the Health Utilities Index Mark 3 (HUI3), the same linear regression model that was used for the VFQ scores was employed for HUI. The resulting coefficients for the model parameters are presented in Table 30.

Table 30 Results of multivariable linear regression analysis with HUI utility.

	Unstandardized coefficient	Standard error	Significance
Constant	.878	.020	.000
Co-morbidities (yes vs. no)	-.046	.007	.000
Side-effects score (per point)	-.002	.001	.000
MD in worse eye (per dB)	.004	.002	.009
MD in better eye (per dB)	.006	.003	.019
Cataract in worse eye (yes vs. no)	-.056	.055	.306
Cataract in better eye (yes vs. no)	-.003	.050	.946

Therefore, the current HUI utility in the model is calculated with the formula:

$$\text{HUI3} = 0.88 - 0.1 \cdot \text{side-effects} + 0.01 \cdot \text{MD} - 0.059 \cdot \text{cataract}.$$

EQ-5D utility

To estimate the relationship between disease state and utility by the EuroQol 5 dimensions questionnaire (EQ-5D), the same linear regression model that we used for the VFQ scores was employed. The resulting coefficients for the model parameters are presented in Table 31.

Table 31 Results of multivariable linear regression analysis with EQ-5D utility.

	Unstandardized coefficient	Standard error	Significance
Constant	.972	.013	.000
Co-morbidities	-.036	.005	.000
Side-effects score	-.001	.000	.000
MD in worse eye	.002	.001	.056
MD in better eye	.002	.002	.206
Cataract in worse eye	.007	.036	.853
Cataract in better eye	.028	.033	.397

Therefore, the current EQ-5D utility in the model is calculated with the formula:

$$\text{EQ-5D} = 0.97 + 0.05 \cdot \text{side-effects} + 0.004 \cdot \text{MD}.$$

The coefficients for cataract surgery are not included because they were positive. It is however highly unlikely that cataract would lead to a higher quality-of-life, so the cataract parameters were excluded for reasons of face validity.

Survival

The survival of patients entering the model is based on their age at entry and the statistics on life-expectancy in The Netherlands from Statistics Netherlands (Centraal Bureau voor de Statistiek) (Table 32).⁶²

Table 32 Risk of death 2004-2050.

Age	Risk of death		Age	Risk of death	
	Men	Women		Men	Women
0 years	0,00457	0,00262	38,5 years	0,00109	0,00075
0,5 years	0,00071	0,00039	39,5 years	0,00122	0,00099
1,5 years	0,00031	0,00029	40,5 years	0,00137	0,00109
2,5 years	0,00029	0,00014	41,5 years	0,00141	0,00115
3,5 years	0,00020	0,00013	42,5 years	0,00162	0,00124
4,5 years	0,00016	0,00019	43,5 years	0,00178	0,00138
5,5 years	0,00011	0,00011	44,5 years	0,00189	0,00157
6,5 years	0,00012	0,00024	45,5 years	0,00233	0,00174
7,5 years	0,00017	0,00009	46,5 years	0,00239	0,00190
8,5 years	0,00016	0,00013	47,5 years	0,00252	0,00203
9,5 years	0,00014	0,00007	48,5 years	0,00289	0,00233
10,5 years	0,00021	0,00011	49,5 years	0,00318	0,00255
11,5 years	0,00017	0,00014	50,5 years	0,00352	0,00280
12,5 years	0,00019	0,00016	51,5 years	0,00389	0,00277
13,5 years	0,00023	0,00011	52,5 years	0,00426	0,00330
14,5 years	0,00028	0,00017	53,5 years	0,00464	0,00341
15,5 years	0,00025	0,00012	54,5 years	0,00514	0,00382
16,5 years	0,00037	0,00022	55,5 years	0,00586	0,00411
17,5 years	0,00028	0,00018	56,5 years	0,00625	0,00454
18,5 years	0,00040	0,00023	57,5 years	0,00700	0,00483
19,5 years	0,00054	0,00027	58,5 years	0,00801	0,00530
20,5 years	0,00040	0,00019	59,5 years	0,00857	0,00602
21,5 years	0,00042	0,00021	60,5 years	0,00946	0,00654
22,5 years	0,00052	0,00028	61,5 years	0,01085	0,00678
23,5 years	0,00048	0,00022	62,5 years	0,01184	0,00808
24,5 years	0,00049	0,00029	63,5 years	0,01329	0,00845
25,5 years	0,00047	0,00032	64,5 years	0,01483	0,00895
26,5 years	0,00063	0,00027	65,5 years	0,01633	0,01013
27,5 years	0,00048	0,00032	66,5 years	0,01852	0,01160
28,5 years	0,00061	0,00036	67,5 years	0,02013	0,01231
29,5 years	0,00070	0,00039	68,5 years	0,02293	0,01303
30,5 years	0,00057	0,00043	69,5 years	0,02540	0,01445
31,5 years	0,00070	0,00035	70,5 years	0,02790	0,01677
32,5 years	0,00066	0,00052	71,5 years	0,03136	0,01778

Table 32 Continued.

Age	Risk of death		Age	Risk of death	
	Men	Women		Men	Women
33,5 years	0,00076	0,00056	72,5 years	0,03681	0,02069
34,5 years	0,00085	0,00052	73,5 years	0,04124	0,02330
35,5 years	0,00084	0,00065	74,5 years	0,04624	0,02525
36,5 years	0,00095	0,00068	75,5 years	0,05112	0,02871
37,5 years	0,00095	0,00080	76,5 years	0,05743	0,03278

Table 33 Risk of death 2004-2050 (continued).

Age	Risk of death	
	Men	Women
77,5 years	0,06489	0,03683
78,5 years	0,07290	0,04310
79,5 years	0,08013	0,04630
80,5 years	0,09210	0,05452
81,5 years	0,09725	0,06029
82,5 years	0,10879	0,06669
83,5 years	0,12338	0,07789
84,5 years	0,13710	0,08854
85,5 years	0,14379	0,09733
86,5 years	0,16263	0,10813
87,5 years	0,17247	0,12067
88,5 years	0,18968	0,13391
89,5 years	0,20338	0,14886
90,5 years	0,22488	0,16526
91,5 years	0,23400	0,18138
92,5 years	0,25564	0,19979
93,5 years	0,27089	0,21944
94,5 years	0,29603	0,23855
95,5 years	0,31900	0,25889
96,5 years	0,33790	0,28367
97,5 years	0,35492	0,30608
98,5 years	0,37804	0,33156

For each simulated patient the model determines at baseline at which age he or she will die. The method to determine this final age was the following. For each age in Table 32 and Table 33 a random draw is made from a Bernoulli distribution with p equal to the risk of death at that age (depending on the gender). The result (0 or 1) is added to the table in an additional column. Subsequently the model searches for the first occurrence of the value 1 in this column starting at the baseline age of the patient in the table. The age that corresponds to this first occurrence of '1' is the age-at-death.

Average OHT/POAG population

The cost-effectiveness analyses that were performed with the model focused on the average OHT/POAG population. In order to simulate the average OHT/POAG population, several estimates were made of the expected values and distributions of patient characteristics in this population. The sources of these estimates are described below.

Ocular hypertension population

Age

The age distribution of patients with OHT in the disease progression model was derived from the Ocular Hypertension Treatment Study and the European Glaucoma Prevention Study.^{4, 63} The average age of the patients with OHT in those studies was 55 ± 12 years (skewed to the right) and 57 ± 10 (skewed to the left) respectively. In the disease progression model the age distribution of OHT patients was assumed to be normal with average 55 and standard deviation 10.

Gender

The gender distribution of patients with OHT in the disease progression model was derived from the Ocular Hypertension Treatment Study and the European Glaucoma Prevention Study.^{4, 63} The percentage of men in these studies was 43% and 46% respectively. In the disease progression model the gender distribution of OHT patients was assumed to be dichotomous with a 40% probability of the male gender.

Baseline IOP

The distribution of intra-ocular pressure of new patients in the model was based on the average intraocular pressure found in the OHTS (25 mmHg), the EGPS (24 mmHg) and the Groningen longitudinal glaucoma study (27 mmHg), and on the reported distribution of IOP's in the patient population in the European Glaucoma

Prevention Study (EGPS).^{4, 63, 64} The average IOP in the EGPS population was 23.6 ± 1.7 mmHg, but the distribution was strongly skewed to the right and truncated at 29 mmHg. In the disease progression model the distribution of intraocular pressure at baseline in the average population of OHT patients was assumed to be a normal distribution with average of 22 mmHg and standard deviation 4, but truncated on the left at 22 mmHg. The resulting distribution has an average IOP of 25 mmHg is skewed to the right, and includes intra-ocular pressures up to the high thirties.

MD after conversion

The value of the Mean Deviation after conversion in the disease progression model was based on the Groningen longitudinal glaucoma study, where the average MD in recently converted patients was -3.6 dB with a range of -0.8 dB to -7.6 dB (personal communication).⁶⁴

The OHT population distribution of MD after conversion in the model was represented by a (negative) gamma distribution, which cannot take a value higher than zero. The latter restriction was built into the model because it was precluded that POAG patients can have MD values higher than zero. The parameters of the distribution were iterated to obtain a gamma distribution with an average of 3 dB and a standard deviation of 1 dB. The parameters of the final distribution were - Gamma (6, 0.5), which has an average of -3 dB and a range of -0.5 to -7.5 dB.

Note: the MD value in an OHT patient only becomes relevant at (and after) a conversion event. This does not mean that the model assumes that the establishment of conversion was based on the visual field only. Rather, conversion is modeled as an event, as a given fact, that is not necessarily observed by the ophthalmologist. The model's determination of the MD value in the converted patient is a consequence of the fact that the patient has converted, because the model needs an MD value to be able to further simulate the disease progression. The chosen distribution of MD values in newly converted patients includes MD values that are close to zero, which represent the patients with glaucomatous changes in optic disc but without apparent defects in their visual field.

Primary open-angle glaucoma population

A problem with trial based averages for POAG patients is that the study population usually represents only a small selection of patients (based on the in- and exclusion criteria). It is therefore actually quite difficult to estimate the baseline clinical characteristics for glaucoma patients. Here we report the parameters and the reasoning behind the parameter derivation that we used in the base case model presented in the article.

Age

The age distribution of the average population of POAG patients was based on the study population in the Early Manifest Glaucoma Trial.¹⁰ The average age was 68 ± 5 years and the distribution was slightly skewed to the left. In the disease progression model a normal distribution was used with average 68 and standard deviation 5. Several other sources were consulted for a typical age distribution of the average population of new POAG patients. The DURING study included 518 new POAG patients with an average age of 62 ± 11 , while in the CIGTS it was 57 ± 11 .^{36, 56}

Gender

The gender distribution of the average POAG population in the model was based on the EMGT population.¹⁰ In this population, 34% were men.

Baseline IOP

In the EMGT population the average intra-ocular pressure at baseline was 21 ± 4 mmHg, whereas the CIGTS population had an average intra-ocular pressure of 28 ± 6 at baseline.^{10, 56} The unselected POAG population (including normal tension glaucoma patients) in the Groningen longitudinal glaucoma study had a baseline IOP of 30.3 ± 9.5 mmHg.⁵⁴ The differences were likely to be caused by the eligibility criteria of the trials: the EMGT excluded patients with an average IOP (in both eyes) higher than 30 mmHg, while the CIGTS excluded patients with an IOP lower than 20 mmHg. In the disease progression model, the baseline IOP in the POAG population was described by a normal distribution with mean 28 mmHg and standard deviation 3 mmHg, truncated on the left at 22 mmHg. The resulting distribution has an average of 29 ± 3 mmHg.

MD at baseline

The value of the Mean Deviation in the average (newly diagnosed) POAG population in the disease progression model was based on the baseline MD value of the participants in the Early Manifest Glaucoma Trial (EMGT) and the Collaborative Interventional Glaucoma Treatment Study (CIGTS).^{10, 56} In both trials, early glaucoma patients were included. The average baseline MD in the EMGT study was -4.7 ± 3.5 dB, in the CIGTS -5.5 ± 4.2 dB, and the distributions were skewed to the left. Considering that the distribution of MD values was skewed to the left, and the fact that the MD in a converted patient cannot take on a positive value, the population distribution of MD in the average population of POAG patients in the model was based on a (negative) gamma distribution. The distribution was truncated at -3 dB because patient with POAG at the first presentation to an ophthalmologist will generally not have MD values higher than -3 dB. The base case distribution (- Gamma (2, 2.5, truncated at 3 dB) has an average of -7.2 ± 3.2 dB and ranges from -4 to -20 dB.

Response to trabeculectomy

An attribute of the simulated patient is the type of reaction this patient has to trabeculectomy. There are three options:

1. Immediate failure
2. Late failure
3. Never failure

In order to estimate the incidence of these three types of responses among patients with a primary trabeculectomy, a review of the literature was performed. From the articles thus considered it was apparent that the necessary information for the model could not directly be retrieved from the reported results. The articles generally report the failure rates of trabeculectomy, but 'failure' is not uniformly defined. Usually 'failure' of trabeculectomy is defined as an intra-ocular pressure persistently over a certain threshold (e.g. 15 mmHg, 18 mmHg or 21 mmHg) despite co-medication, whereas in the disease progression model, failure of trabeculectomy signifies a return to the pre-surgical intra-ocular pressure in the absence of co-medication. A second issue is the duration of follow-up. Long follow-up data are very scarce, and short term failure is reported only after 6 months (rather than a more immediate term such as 6 weeks). Still, several articles were consulted to inform our estimate of the incidence of trabeculectomy responses. The included articles are listed in Table 34.

The estimated intra-ocular pressure after trabeculectomy in the disease progression model is 12.5 mmHg with a distribution such that 94% of the cumulative function is lower than 15 mmHg (see paragraph 6.1 |). The only results on short-term failure rates with a threshold of 15 mmHg are from Beckers *et al.* and Wudunn *et al.* which were 13% and 12% respectively. In the base-case model, an incidence of 'immediate failure' of 12% was assumed.

Due to the lack of long-term data of the results of trabeculectomy without co-medication, an estimate of the incidence of 'never failure' was made by two glaucoma surgeons (HB, NJ) at 40%. This estimate implies that in the model it is assumed that 60% of the patients who receive trabeculectomy will go back to the pre-surgical intraocular pressure within 10 years if they would not receive additional medication or laser treatment: 12% within 6 weeks (immediate failure), the remaining 48% gradually during the ten years after surgery.

Table 34 Literature review for response to trabeculectomy. Failure rates (%).

Failure is...	Follow-up (months)	Beckers <i>et al.</i> 2003 ^{18 a)}	Wudunn <i>et al.</i> 2002 ^{21 a)}	Singh <i>et al.</i> 2000 ^{20 c)}	
IOP > 15 mmHg	6	13%	12%		
	12	17%		17% (10 months)	
	48	30%			
	72	40%			
Failure is...		AGIS investigators. 2002 ^{65 a)}	Wudunn <i>et al.</i> 2002 ^{21 a)}	Singh <i>et al.</i> 2000 ^{20 c)}	Lichter <i>et al.</i> 2001 ^{56 b)}
IOP > 18 mmHg	6	3%	5%		
	12	5%		4% (10 months)	12%
	48				21%
	60	10%			
	120	18%			

a) IOP with comedication or LTP
b) IOP without comedication or LTP
c) IOP with or without medication unknown

Costs

Costs were calculated in 2006 euro's. Cost prices retrieved from older sources were indexed to 2006 euro's with the percentages listed in Table 35.

Table 35 Annual indexation relative to the previous year.

	CBS ⁶⁶	Manual for costing research ²⁶
1996		2.0%
1997		2.2%
1998		2.0%
1999		2.2%
2000		2.6%
2001	3.1%	
2002	3.2%	
2003	1.9%	
2004	0.9%	
2005	1.4%	
2006	1.5%	

Medication Costs

The cost prices of eye-drops were collected from the Pharmacotherapeutic Compass, which listed the monthly costs of eye-drops based on the defined daily dosis (DDD) and the prices listed in the Z-index on 1 November 2007 (table 2).²⁴ The cost prices represent the declaration costs including claw-back, and excluding VAT (19%) and dispensing fee. None of the registered pharmaceuticals for glaucoma treatment are subject to co-payment in the Netherlands.

A pharmacist receives € 6.10 per dispensed drug, irrespective of the quantity.²⁵ The average annual amount of recipes for a glaucoma patient in the Netherlands ranged from 3.2 to 4.0 (depending on the type of drug) in 2006.³² The average frequency of recipe collection was assumed to be every 3 months for all patients. The monthly cost for the pharmacists' fee was therefore estimated at € 2.

The all-in monthly costs of medication were calculated by adding VAT and the pharmacists' fee to the costs listed in the Pharmacotherapeutic Compass (Table 36).

The cost price of timolol was based on Timoptol eye drops 0.5%. The costs for combination therapy and triple therapy were calculated by a summation of the cost prices of the monotherapies of the medications in the combination. The differences between prices of fixed combinations and the sum of the separate monotherapies are negligible.

Table 36 Medication costs per month.

Pharmacon	Product	Costsprice per package	Costs per month
Timolol	Nyogel eyegel; 0.1%, 5 ml	€ 3.53	€ 3.32 * 1.19 + € 2.03 = € 6.0
	Timo-COMOD eyedrops; 0.25%, 10 ml	€ 6.50	
	Timo-COMOD eyedrops; 0.5%, 10 ml	€ 6.64	
	Timolol eyedrops; 0.1%, 5 ml	€ 2.87	
	Timolol eyedrops; 0.25%, 5 ml	€ 2.68	
	Timolol eyedrops; 0.5%, 5 ml	€ 2.68	
	Timoptol Ocudose eyedrops; 0,25%, 0.2 ml, 20 pc.	€ 1.84	
	Timoptol Ocudose eyedrops; 0.5%, 0.2 ml, 20 pc.	€ 1.88	
	Timoptol eyedrops; 0.25%, 5 ml	€ 3.25	
	Timoptol eyedrops; 0.5%, 5 ml	€ 3.32	
	Timoptol XE eyedrops; 0,25%, 2.5 ml	€ 4.52	
	Timoptol XE eyedrops; 0.5%, 2.5 ml	€ 4.52	
Latanoprost	Xalatan eyedrops; 0.005%, 2.5 ml	€ 15.24	€ 15.24 * 1.19 + € 2.03 = € 20.2
Dorzolamide	Trusopt eyedrops; 2%, 5 ml	€ 9.98	€ 9.98 * 1.19 + € 2.03 = € 13.9
Brimonidine	Alphagan eyedrops; 0.2%, 5 ml	€ 10.10	€ 10.10 * 1.19 + € 2.03 = € 14.0

Costs of ophthalmologist, procedures and interventions

Three sources were identified for the estimation of costs associated with ophthalmologist visits, procedures and interventions.

The Dutch Manual for costing research lists several integral standard cost prices in 2003 euro's.²⁶ These were based on bottom-up cost research in twenty Dutch hospitals and include materials, equipment, housing, wages, and overhead costs such as interest and depreciation costs.

Oostenbrink *et al.* have investigated the resource utilization and associated costs during the first two years after diagnosis of OHT or glaucoma in 200 to 500 patients in 5 to 10 Dutch hospitals.^{27, 67} Cost prices in this study were based on detailed micro-costing studies in two participating (one peripheral and one university) hospitals, and can be regarded as integral cost-prices.

Peeters *et al.* have based their cost-estimates for glaucoma treatment on bottom-up costing research in the University Hospital Maastricht.²⁸ It is uncertain whether the authors have included overhead costs in their cost calculations, and the reported cost-prices may therefore not be integral.

The cost prices listed in the manual for costing research were the primary sources for the cost estimates in the OHT/POAG disease progression model, because they were derived from micro-costing studies, based on a large number of hospitals, and were transparently described in the manual. In addition, the standard cost prices listed in the manual are frequently used in Dutch health economic evaluations, increasing the comparability of our study results with others.

Ophthalmologist visit

Table 37 Cost prices of ophthalmologists consults in various sources.

	In source	In 2006
Manual for costing research, 2003. ²⁶		
Peripheral hospital, 10 minutes	€ 56	€ 58
University hospital, 5 minutes	€ 100	€ 104
Oostenbrink <i>et al.</i> , 2000 ^{27, 67}	US\$ 47	€ 46
Peeters <i>et al.</i> , 2001. ²⁸		
Consult 10 minutes	€ 24	€ 26
Consult 15 minutes	€ 26	€ 28

According to the manual for costing research the ratio of peripheral and university hospitals is 84:16. This ratio was applied to the manual's cost prices and the resulting average estimate of € 65 was used in the base case model.

Visual field measurement

Table 38 Cost prices of visual field examinations in various sources.

	In source	In 2006
Manual for costing research, 2003. ²⁶		
Static perimetry	€ 124.50	€ 129
Visual field testing	€ 128.30	€ 133
Oostenbrink <i>et al.</i> , 2000 ^{27, 67}	US\$ 47	€ 46
Peeters <i>et al.</i> , 2001. ²⁸	€ 81	€ 88

The cost prices in the various sources range from € 46 to € 133. The estimate based on the manual for costing research (€ 133) was used in the base case model.

Laser trabeculoplasty (LT)

The estimate of the cost price for laser trabeculoplasty (LT) must include all resources that are needed to perform the procedure:

- Medical staff
- Equipment
- Housing
- Day stay or hospital admission (usually not required)

Table 39 Cost price of laser trabeculoplasty (LT) in various sources.

	In source	In 2006
Manual for costing research, 2003. ²⁶	n.a.	n.a.
Oostenbrink <i>et al.</i> , 2000 ^{27, 67}	US\$ 77	€ 75
Peeters <i>et al.</i> , 2001. ²⁸	€ 279	€ 305

There is a very big difference between the cost price estimates, which may be the result of a difference in the resources that were included in the estimate. The sources do however not contain a detailed account of the resources that were included in their estimates of the cost price for LT. We reasoned that the costs of medical staff and housing for LT are comparable to a regular ophthalmologist consultation, that there are additional costs for the equipment and that the costs of hospital admission are negligible since LT is performed on an outpatient basis. Since the base case estimate for an ophthalmologist consultation was € 65, the base case estimate for LT was kept at € 75.

Trabeculectomy

The estimate of the cost price for trabeculectomy must include all resources that are needed to perform the procedure:

- Medical staff
- Equipment
- Housing
- Day stay (usually) or hospital admission (occasionally)

Table 40 Cost prices of trabeculectomy in various sources.

	In source	In 2006
Manual for costing research, 2003. ²⁶		
Glaucoma surgery	€ 940	€ 976
Day stay	€ 229	€ 238
Admission university hospital	€ 476	€ 494
Oostenbrink <i>et al.</i> , 2000 ^{27, 67}		
Glaucoma surgery	US\$ 905	€ 875
Day stay	US\$ 118	€ 111
Admission day	US\$ 179	€ 170
Peeters <i>et al.</i> , 2001. ²⁸	€ 1282	€ 1400

The estimate for the cost price of trabeculectomy in the base case model was based on the standard cost prices in the manual for costing research. It was assumed that all patients are admitted on a day stay basis. Therefore the base case estimate for the cost price of trabeculectomy is € 1214. Follow-up visits after trabeculectomy are modeled as separate events starting on the third day after

surgery. However, in practice the first check-up after surgery will occur on the first post-operative day. To account for the costs of this consultation, the cost price of an ophthalmologist consultation is added to the cost price of trabeculectomy (€ 65) to reach a total of € 1279. This represents the cost price of trabeculectomy including day stay and a next day check.

Re-trabeculectomy

The estimated cost price of a second trabeculectomy in the same eye is similar to the cost price of the first trabeculectomy.

Baerveldt implant

The implantation of a filtering device is a surgical procedure (like trabeculectomy) that usually involves a day stay, and very occasionally an overnight stay. The cost price of an implantation procedure includes the costs of:

- Medical staff
- Equipment
- Device
- Housing
- Day stay (usually) or hospital admission (occasionally)

The cost price of a Baerveldt implantation procedure has not been reported in any of the previously consulted sources.^{26-28, 67} It is likely that the costs of medical staff and housing for implantation surgery are slightly higher than with trabeculectomy because the procedure takes more time. It is however unclear how much more time is required. Therefore the estimate of the cost price for implantation surgery was based on the estimate for trabeculectomy (€ 1214) and € 500 was added to account for the implanted device (personal communication with a glaucoma specialist, HB).

The final estimate for the integral cost price of implantation surgery, including day stay and a next day check is € 1779.

Cataract extraction

Cataract surgery is performed on an outpatient basis with local anesthetics. The cost price for cataract surgery consists of the procedure itself (medical staff, equipment, housing) and the costs of two post-surgery follow-up visits.

Cataract surgery is a procedure for which the costs have been calculated quite precisely by hospital administrations, in view of the new billing system based on diagnose related groups (Diagnose Behandel Combinatie, DBC). The cost price of cataract surgery in the university hospital Maastricht has been communicated to

Table 41 Cost prices of cataract extraction in various sources.

	In source	In 2006
Manual for costing research, 2003. ²⁶	€ 1525	€ 1584
University hospital Maastricht (personal communication with hospital financial administration)		€ 1100

us in 2008. Considering the recentness of this information the cost price of cataract surgery in the base case model was based on the estimate of € 1100.

Costs of low-vision rehabilitation services

Low-vision rehabilitation services entail the services that are available to the visually impaired and blind to help them cope with their visual impairment, both on a physical, social and mental level. There is no scientific literature on the use of such services by glaucoma patients, nor do the institutions providing the services have information on the degree of service utilization by glaucoma patients. Therefore we have asked over 500 OHT and glaucoma patients to complete a questionnaire collecting information on resource utilization related to (impaired vision as a consequence of) glaucoma.^{29, 30}

Resource utilization

The questionnaire included a question asking about the utilization of services provided by revalidation institutions for the visually impaired or blind, e.g. Sensus, Vision and Bartiméus, during the last three months. The results, stratified by the Mean Deviation averaged over both eyes, are presented in the table below. This table indicates the number of patients in each stratum, the number (and %) of patients reporting the utilization of services during the last three months, and the type of service the patients received.

The translation of this information to cost price estimates is hampered by the fact that the questionnaire only asked for service utilization during the past three months, whereas these services are typically offered only once during a patients disease progression. It is virtually impossible to translate the three-month incidences to life-time incidences, so the model uses monthly costs for rehabilitation services based on the observed three month incidence numbers.

Table 42 Utilization of low-vision rehabilitation services in he last three months.

Average MD in both eyes (dB)	Total n	Utilized services	SEM	95% CI	Type of service
MD ≥ 0	68	1 (1%)	1.2%	0%; 3.4%	Low vision investigation
-5 ≤ MD < 0	204	2 (1%)	0.7%	0%; 2.4%	Habits of living investigation Habits of living investigation
-10 ≤ MD < -5	74	2 (3%)	2.0%	0%; 6.9%	Low vision examination Habits of living investigation
-15 ≤ MD < -10	60	1 (2%)	1.8%	0%; 5.5%	Mobility instruction
-20 ≤ MD < -15	46	3 (7%)	3.8%	0%; 9.4%	Low vision examination Low vision examination Habits of living investigation
-25 ≤ MD < -20	29	1 (3%)	3.2%	0%; 9.3%	Audio book Daisy player Computer course
MD < -25	21	0 (0%)	0%	0%; 0%	.
Total	502	10 (2%)	0.6%		

SEM = Standard error of the mean, 95% CI = 95% confidence interval

Cost prices

Cost prices for low-vision rehabilitation services were derived from the maximal tariffs set by the Dutch Healthcare Authority (NZA) in 2007. From personal communication with employees at Sensis we have learned that low-vision and habits of living examinations fall under 'Basic treatment' with a maximal tariff of € 96.20 per hour. Services such as independence training, mobility training, revalidation and social services fall under 'Activating guidance, level 3' with a maximal tariff of € 104.60 per hour. Low-vision examinations usually take 2 to 2.5 hours, the other examinations take approximately 1.5 hours and the activating guidance sessions take on average 2 hours.

The cost prices per hour and the average durations of the services were aggregated into an estimate of € 192 per low-vision rehabilitation service. This was multiplied with the observed three-month incidence of the utilization of services to obtain an estimate of the average costs of rehabilitation services per three months. Finally, the thus estimated costs were divided by three to obtain the monthly costs (Table 43).

Table 43 Calculation of average costs for low-vision rehabilitation services depending on MD in the better eye.

MD in the better eye (dB)	Incidence in three months	Average cost per three months	Average cost per month	95% CI
MD ≥ 0	1%	€ 3.10	€ 1.03	0; 2.9
-5 ≤ MD < 0	1%	€ 2.10	€ 0.69	0; 2.0
-10 ≤ MD < -5	3%	€ 5.70	€ 1.89	0; 5.8
-15 ≤ MD < -10	2%	€ 3.50	€ 1.17	0; 4.6
-20 ≤ MD < -15	7%	€ 13.70	€ 4.57	0; 7.9
-25 ≤ MD < -20	3%	€ 7.20	€ 2.41	0; 7.8
MD < -25	0%	€ 0	€ 0	0

Costs of low-vision aids

Low-vision aids for glaucoma patients entail both devices that aid the patient to see better, but also devices that aid to improve activities of daily living and mobility.

Resource utilization

The degree of low-vision aid utilization in glaucoma patients was captured with a questionnaire.^{29, 30} The participants were asked to indicate whether they currently used a specific aid, or whether specific adjustments were made to their house (e.g. lighting). The prevalence of optical aid utilization is presented in the next table, stratified by the average MD in both eyes.

Table 44 Prevalence of low-vision aid utilization in seven strata of average MD in both eyes.

Type aid	MD ≥ 0	-5; 0	-10 ; -5	-15 ; -10	-20 ; -15	-25 ; -20	MD < -25
Total patients (n)	61	114	14	133	37	105	64
Glasses	49 %	49 %	69 %	63 %	72 %	75 %	62 %
Hand loupe	3 %	5 %	16 %	18 %	24 %	36 %	24 %
TV reading loupe	2 %	1 %	0	2 %	4 %	4 %	10 %
Loupe lamp	0	1 %	1 %	3 %	4 %	14 %	10 %
Loupe glasses	0	1 %	0	2 %	3 %	8 %	6 %
Filter glasses	3 %	0	2 %	5 %	0	0	0
Daisy player	2 %	0	0	0	0	17 %	0
Contacts	0	0	0	2 %	2 %	0	0
Nightglasses	0	0	0	2 %	0	0	0
Adjusted lighting	0	0	3 %	0	0	7 %	5 %
White cane	0	1 %	0	2 %	9 %	18 %	24 %
Telephone	0	1 %	0	0	2 %	14 %	14 %
Software	0	0	3 %	0	0	4 %	0
Monitor	0	0	1 %	0	2 %	4 %	14 %
Monitor magnifier	0	0	1 %	0	0	0	0
Dictaphone	0	0	0	0	0	3 %	0
Walking stick	0	0	0	0	0	0	5 %
Keyboard	0	0	0	0	0	0	5 %

The utilization of low-vision aids other than glasses is generally low. For the purpose of the model it was important to establish whether the utilization of a specific aid differed between groups based on glaucoma severity (MD). Such a difference was seen with:

- Glasses
- Loupe
- TV reading loupe
- Loupe lamp
- Loupe glasses
- Daisyplayer
- White cane
- Telephone
- Monitor

Patients with the worse average MD also indicated a higher utilization of adjusted lighting. However, the cost price of adjusted lighting was estimated to be negligible.

In order to translate the survey results to model input we reasoned that the purchase of a low-vision aid is usually a one-time event that occurs when glaucoma severity has crossed a certain threshold. Over the whole of the low-vision aids, the largest increase in the prevalence of utilization was seen at MD values lower than -15 dB. Therefore the MD threshold to incur low-vision aid costs in the model was set at -15 dB. Next the study population was divided in two groups based on the average MD in both eyes: higher than -15 dB and lower than -15 dB. The difference in the observed prevalence of aid utilization was assumed to be an estimate of the incidence of glaucoma-related low-vision aid utilization.

Table 45 Prevalence of low-vision aid utilization in two strata of average MD in both eyes.

Low-vision aid	MD > -15	MD ≤ -15	Difference
Total patients (n)	405	97	
Glasses	55%	71%	16%
Loupe	9%	27%	18%
TV reading loupe	1%	5%	4%
Loupe lamp	1%	8%	7%
Loupe glasses	1%	5%	5%
Daisyplayer	0%	5%	5%
White cane	1%	15%	14%
Telephone	0%	8%	8%
Monitor	0%	5%	5%

Cost prices

Various sources were consulted to obtain estimates of the cost prices of the most important low-vision aids for glaucoma patients.

Ergra Low vision catalogue 2007

	Price
White cane	€ 20.50
Telephone	€ 35 - € 150 (wireless)

Internet

	Source	Price
Reading loupe with lamp	www.seniorenthuiszorgwinkel.nl	€ 50 - € 125
Daisyplayer	www.lexima.nl	€ 300 - € 400
Loupe glasses	www.lvbc.nl/produkt/view/607/print	€ 80 - € 270
TV reading loupe	http://kobavision.be/nl/prijzen.html	€ 3000 - € 4000
Monitor	http://kobavision.be/nl/schermmpc.html	€ 750 - € 1000
Portable loupe	http://kobavision.be/nl/hulpmid.html	€ 70

The cost prices per item were multiplied by the estimated incidence of glaucoma related low-vision aid utilization. The resulting total costs of low-vision aids (Table 46) were incurred in the model when a simulated patient's better eye progressed to an MD value lower than -15 dB.

Table 46 Calculation of the average costs of low-vision aids.

Low-vision aid	Prevalence	Cost price	Costs
Glasses	16%	€ 500	€ 80
Loupe	18%	€ 70	€ 13
TV reading loupe	4%	€ 3500	€ 140
Loupe lamp	7%	€ 75	€ 5
Loupe glasses	5%	€ 175	€ 9
Daisyplayer	5%	€ 350	€ 18
White cane	14%	€ 21	€ 3
Telephone	8%	€ 150	€ 12
Monitor	5%	€ 900	€ 45
Total			€ 325

Costs of homecare, grooming and nursing

The degree to which progression of glaucoma leads to costs related to homecare or nursing homes was estimated based on the results of the questionnaire survey among OHT and glaucoma patients.

Resource utilization, nursing home

The questionnaire asked whether the patient had ever needed to move as a result of OHT or glaucoma.

Table 46 Incidence of moving as a result of OHT or glaucoma in seven strata of MD in both eyes.

Average MD in both eyes (dB)	Total patients (n)	Moved to other house	Moved to service flat	Moved to retirement home	Moved to nursing home
MD ≥ 0	68	1 (1%)	0	0	0
-5 ≤ MD < 0	204	0	1 (0%)	0	0
-10 ≤ MD < -5	74	0	1 (1%)	1 (1%)	0
-15 ≤ MD < -10	60	0	1 (2%)	1 (2%)	1 (2%)
-20 ≤ MD < -15	46	2 (4%)	0	1 (2%)	0
-25 ≤ MD < -20	29	0	1 (3%)	2 (7%)	0
MD < -25	21	1 (5%)	0	0	1 (5%)
Total	502	4 (1%)	4 (1%)	4 (1%)	2 (0%)

The percentage of patients indicating that they have had to move as a result of OHT or glaucoma was very low (Table 47). However, since long-term stay in retirement homes and nursing homes can be associated with high costs, we have calculated how much of the habituation of nursing homes and retirement homes can be attributed to progressing glaucoma. The total population was divided in two groups based on the average MD in both eyes: higher than -20 dB and lower than -20 dB. The difference in prevalence of nursing- or retirement home habituation was assumed to be attributable to glaucoma progression to a visual field with an MD lower than -20 dB (Table 48).

Table 48 Incidence of moving as a result of OHT or glaucoma in two strata of MD in both eyes.

	MD > -20	MD ≤ -20	Difference
Total patient in group (n)	452	50	
Moved to retirement home	1%	4%	3%
Moved to nursing home	0%	2%	2%

Resource utilization homecare

The questionnaire asked the participants how many hours a week (on average) they had received homecare in the last three months. We distinguished the following types of homecare:

- Family help
- Household help
- Grooming
- Nursing
- Other paid help

If patients had indicated not to have received homecare, the amount of hours per week was set at 0. The average time the study population had received each type of homecare, stratified by the average MD in both eyes, is presented in the next table.

Overall the utilization of paid help appeared to be higher in patients with an average MD lower then -10 dB. The total study population was divided in two groups based on the average MD, and the difference in the utilization of paid help was considered the to glaucoma attributable amount of paid help utilization.

Table 49 Average utilization of home care in seven strata of MD in both eyes (hours/week).

Average MD in both eyes (dB)	Family (hrs/week)	Household (hrs/week)	Grooming (hrs/week)	Nursing (hrs/week)	Paid help (hrs/week)	Total (hrs/week)
MD ≥ 0	0.1 ± 1.2	0.3 ± 0.7	0	0	0.2 ± 1.2	0.3 ± 2.7
-5 ≤ MD < 0	0.0 ± 0.4	0.0 ± 0.4	0.1 ± 0.5	0	0.1 ± 0.7	0.2 ± 1.3
-10 ≤ MD < -5	0.1 ± 0.6	0.1 ± 0.4	0.1 ± 0.5	0.0 ± 0.1	0.0 ± 0.2	0.3 ± 1.1
-15 ≤ MD < -10	0.1 ± 0.4	0.1 ± 0.4	0	1.4 ± 10.8	0.5 ± 3.0	2.0 ± 11.2
-20 ≤ MD < -15	0.4 ± 2.2	0.1 ± 0.4	1.2 ± 6.2	0	0.3 ± 0.9	2.0 ± 7.1
-25 ≤ MD < -20	0.4 ± 1.1	0	0.5 ± 1.4	0.4 ± 1.9	0.5 ± 1.6	1.8 ± 4.1
MD < -25	1.1 ± 2.9	0	0	0	0.2 ± 0.9	0.4 ± 1.9
Total	0.2 ± 1.1	0.1 ± 1.0	0.2 ± 2.0	0.2 ± 3.8	0.2 ± 1.3	0.7 ± 4.8

Table 50 Average utilization of family help and grooming in two strata of MD in both eyes (hours/week).

	MD > -15	MD ≤ -15	Difference
Total patients (n)	404	94	
Family help (hours/week)	0.08 ± 0.03	0.55 ± 0.22	0.47
Grooming (hours/week)	0.04 ± 0.02	0.71 ± 0.45	0.67

Table 51 Average utilization of other paid help and nursing in two strata of MD in both eyes (hours/week).

	MD > -10	MD ≤ -10	Difference
Total patients (n)	345	154	
Other paid help (hours/week)	0.08 ± 0.04	0.39 ± 0.17	0.31
Nursing	0.003 ± 0.003	0.61 ± 0.55	0.61

Cost prices

The cost price per unit of the various types of homecare, retirement homes and nursing homes were derived from the Manual for costing studies and multiplied by the utilization estimates (Table 52).²⁶

Table 52 Calculation of the average costs of homecare.

Type	MD threshold	Utilization per week	Utilization per month	Cost price	Cost per month
Other paid help	-10 dB	0.31 hrs	1.3 hrs	€ 27.70/hour	€ 37
Nursing	-10 dB	0.61 hrs	2.6 hrs	€ 61.20/hour	€ 159
<i>Subtotal</i>	<i>-10 dB</i>				€ 196
Family help	-15 dB	0.47 hrs	2.0 hrs	€ 27.70/hour	€ 56
Grooming	-15 dB	0.67 hrs	2.9 hrs	€ 35.40/hour	€ 103
<i>Subtotal</i>	<i>-15 dB</i>				€ 159
Retirement home	-20 dB		3%	€ 88/day	€ 80
Verpleeghuis	-20 dB		2%	€ 214/day	€ 130
<i>Subtotal</i>	<i>-20 dB</i>				€ 210

Costs of transportation

Resource utilization

The questionnaire survey among patients with OHT and glaucoma collected information on the means of transportation to various types of caregivers. The results are presented in the next tables. The study population was stratified according to the average MD in both eyes (Table 53 to Table 55). For example: 21% of the patients with an average MD higher than 0 dB usually walk or take their bike to visit the ophthalmologist, and 12% uses public transportation.

Table 53 Usual means of transportation to ophthalmologist in seven strata of MD in both eyes.

Average MD in both eyes (dB)	Walking / cycling	Car	Public transportation	Taxi	Came to the house
MD ≥ 0	21%	66%	12%	2%	0%
-5 ≤ MD < 0	17%	66%	13%	4%	0%
-10 ≤ MD < -5	16%	58%	19%	7%	0%
-15 ≤ MD < -10	12%	56%	15%	19%	0%
-20 ≤ MD < -15	11%	56%	22%	11%	0%
-25 ≤ MD < -20	4%	44%	26%	26%	0%
MD < -25	5%	48%	29%	19%	0%

Table 54 Usual means of transportation to the pharmacy in seven strata of MD in both eyes.

Average MD in both eyes (dB)	Walking / cycling	Car	Public transportation	Taxi	Came to the house
MD ≥ 0	72%	27%	0%	0%	2%
-5 ≤ MD < 0	63%	32%	2%	0%	4%
-10 ≤ MD < -5	70%	25%	2%	0%	3%
-15 ≤ MD < -10	56%	31%	0%	4%	10%
-20 ≤ MD < -15	55%	31%	2%	2%	10%
-25 ≤ MD < -20	59%	14%	9%	0%	18%
MD < -25	50%	28%	11%	6%	6%

Table 55 Usual means of transportation to the hospital in seven strata of MD in both eyes.

Average MD in both eyes (dB)	Walking / cycling	Car	Public transportation	Taxi	Came to the house
MD ≥ 0	12%	72%	16%	0%	0%
-5 ≤ MD < 0	18%	64%	14%	4%	0%
-10 ≤ MD < -5	13%	64%	13%	8%	2%
-15 ≤ MD < -10	14%	61%	8%	18%	0%
-20 ≤ MD < -15	15%	56%	18%	10%	0%
-25 ≤ MD < -20	4%	48%	20%	28%	0%
MD < -25	10%	57%	14%	19%	0%

Cost prices per unit

Cost prices per unit for each type of transportation were derived on the Manual for costing research (Table 56).²⁶

Table 56 Cost prices for transportation.

	In source	In 2006
Car (per km)	€ 0.16/km	€ 0.17/km
Parking	€ 2.50	€ 2.50
Public transport (per km)	€ 0.16	€ 0.17
Taxi (per km)	€ 2.80 + € 1.75/km	€ 2.90 + € 1.80/km

Average distance to hospital: 7 km

Average distance to general practitioner: 1.8 km

It was assumed that the ophthalmologist is located in the nearest hospital, and that the distance to the nearest pharmacy is equal to the distance to the nearest general practitioner. The total cost prices were based on a two-way journey, plus parking costs if the journey was made by care. If the caregiver paid a home-visit to the patient the costs of transportation were assumed to be were similar to a car-ride to the caregiver, minus the parking costs. The cost prices that were used for the various types of transportation are the following:

Table 57 Calculation of cost prices for transportation to ophthalmologist, pharmacy and hospital.

	Walking / cycling	Car	Public transportation	Taxi	Came to the house
Ophthalmologist	0	€ 2.4 + € 2.5 = € 4.9	€ 2.4	€ 31	€ 2.4
Pharmacy	0	€ 0.6	€ 0.6	€ 12	€ 0.6
Hospital	0	€ 2.4 + € 2.5 = € 4.9	€ 2.4	€ 31	€ 2.4

Total costs of transportation

The observed percentage of patients using a particular type of transportation was multiplied by the cost price for that type of transportation to obtain an estimate of the average costs of transportation for a visit to the ophthalmologist, pharmacy and hospital.

Table 58 Average cost of transportation to ophthalmologist, pharmacy and hospital in seven strata of MD in both eyes.

	Ophthalmologist	Pharmacy	Hospital
MD ≥ 0	€ 4.14	€ 1.37	€ 3.91
-5 ≤ MD < 0	€ 4.79	€ 1.71	€ 4.71
-10 ≤ MD < -5	€ 5.47	€ 1.35	€ 5.98
-15 ≤ MD < -10	€ 8.99	€ 3.00	€ 8.76
-20 ≤ MD < -15	€ 6.68	€ 2.43	€ 6.28
-25 ≤ MD < -20	€ 10.84	€ 1.33	€ 11.51
MD < -25	€ 8.94	€ 3.64	€ 9.02

In order to reduce the number of categories with different transportation costs in the model, the final number of strata was reduced to two, based on the average MD in both eyes: higher than -10 dB and lower than -10 dB (Table 59).

Table 59 Average cost of transportation to ophthalmologist, pharmacy and hospital in two strata of MD in both eyes.

	Ophthalmologist	Pharmacy	Hospital
MD > -10 dB	€ 4.8	€ 1.5	€ 4.9
MD ≤ -10 dB	€ 8.9	€ 2.6	€ 8.9

Costs of informal care

Resource utilization

The degree to which relatives, friends and neighbors help out with small tasks that a patient is unable to perform himself due to OHT or glaucoma was investigated with the questionnaire survey. Participants were asked to indicate how much per week they have received informal care during the past three months. The results are presented in the next table. If patients had indicated that they had not received informal care, the amount of time per week was set at 0.

Table 60 Utilization of informal care in seven strata of MD in both eyes (hours/week).

	Informal care received (hours/week)
MD ≥ 0	0
-5 ≤ MD < 0	0
-10 ≤ MD < -5	0.5 ± 2.6
-15 ≤ MD < -10	0
-20 ≤ MD < -15	0.1 ± 0.4
-25 ≤ MD < -20	2.5 ± 8.2
MD < -25	0.6 ± 2.5
Total	0.2 ± 2.2

Based on these results the total study population was divided in two groups, one with the average MD in both eyes higher than -5 dB, and one with the average MD in both eyes lower than -5 dB. The difference in the utilization of information care between the groups was assumed to be attributable to glaucoma progression (Table 61).

Table 61 Utilization of informal care in two strata of MD in both eyes (hours/week).

	MD > -5	MD ≤ -5	Difference
Total patients (n)	270	218	
Informal care (hrs/week)	0.0	0.50	0.5 hrs/week

Cost prices

The cost price for one hour of information care was derived from the Manual for costing research (Table 62).²⁶ The manual offers two possibilities to estimate the cost price of informal care: one is based on research that elicited how people would value (in monetary terms) time spent on informal care giving (willingness-to-accept). The other is based on the costs if the unpaid help would have been performed by a paid help.

Table 62 Cost price of informal care.

	In source	In 2006
Willingness-to-accept (per hour)	€ 9.80	€ 10.20
Shadow price (per hour)	€ 8.30	€ 8.60

An average price of € 9 per hour was assumed. The monthly costs of informal care attributable to glaucoma were calculated by multiplying the monthly resource utilization (2.2 hours) with the average unit price, to obtain a base case estimate of € 20 per month for informal care if the MD progresses to values below -5 dB.

Costs of productivity loss

Resource utilization

Productivity losses can be caused by either temporary productivity loss due to sick days, or permanent productivity loss due to partial or full disablement. The questionnaire survey included a question on both work disablement as well as on sick days due to OHT or glaucoma.

None of the survey participants indicated that they had had a sick day due to OHT or glaucoma during the past three months. Work disablement did however occur among the participants (Table 63). The questionnaire collected information on the degree of disablement and the age of onset. The average time since the work disablement was calculated from the current age of the participant and the age of disablement onset.

Table 63 Incidence of work disablement in seven strata of MD in both eyes.

Average MD in both eyes (dB)	Total patients (n)	Work disabled (%)	Age of onset	Degree of disablement	Time since onset (yrs)
MD ≥ 0	65	2 (3.0%)	54 ± 4	48 ± 25%	8.5 ± 0.1
-5 ≤ MD < 0	200	0 (0%)	-	-	-
-10 ≤ MD < -5	70	3 (4.1%)	50 ± 3	78 ± 38%	8.3 ± 3.4
-15 ≤ MD < -10	55	4 (6.8%)	51 ± 5	90 ± 12%	9.3 ± 3.9
-20 ≤ MD < -15	44	2 (4.3%)	48 ± 8	63 ± 53%	11.7 ± 1.3
-25 ≤ MD < -20	25	3 (10.7%)	53 ± 4	93 ± 12%	10.8 ± 1.7
MD < -25	15	6 (28.6%)	39 ± 11	92 ± 20%	12.8 ± 7.1
Totaal	502	20 (3.8%)	48 ± 9	82 ± 27%	10.6 ± 4.6

The prevalence of work disablement was higher in the two strata with the lowest average MD. Therefore the prevalence of work disablement in participants with MD lower than -20 dB (18.4%) was compared to participants with MD higher than -20 dB (2.5%). The difference (15.9%) was assumed to be the prevalence of work disablement attributable to glaucoma. The time since the onset of work disablement was approximately 10 years. With an average decrease of 0.03 dB per month and calculating back from -20 dB, the threshold MD value for the onset of work disablement was estimated at -15 dB.

In summary, in the model it is assumed that when MD progresses to values lower than -15 dB, 16% of the patients will become work disabled.

Cost prices

The costs of productivity losses was calculated according to the friction cost method, using the standards proposed in the Manual for costing research.²⁶ The average costs per working person in 2003 were € 34.98 per hour (in 2006: € 36.33). The friction period is 22 weeks, which equals 651.4 working hours. The elasticity was set at 0.8. Therefore the estimated friction costs for a full work disablement were $651.4 * 0.8 * 36.33 = € 18,932$.

The model assumes a one-time cost of $0.16 * € 18,932 = € 3,029$ as soon as a simulated patient progresses to MD values below -15 dB.

Summary of MD-related costs

During the simulation of the disease progression of an individual patient, the costs of medication, ophthalmologist consultations, procedures and interventions were added to the total based on the occurrence of visits and the treatment decisions. All other costs were calculated during the simulation based on the MD value of the simulated patient. In the previous paragraphs the derivation of the cost estimates has been described. Here an overview is presented of the costs attributed to a patient based on his MD value. Three cost-types can be discerned: direct medical costs, direct non-medical costs and indirect non-medical costs. In addition, the costs can be added to the total as one-time costs as soon as a threshold MD value is passed, or as continuous costs that are incurred as long as the MD value remains on a certain level.

Table 64 Overview of costs attributed in the model depending on the Mean Deviation in the better eye.

	Low-vision rehabilitation	Low-vision aids	Grooming/nursing	Informal care	Productivity loss
Cost type	Direct medical	Direct medical	Direct medical	Direct non-medical	Indirect non-medical
Addition	Per month	One-time	Per month	Per month	One-time
MD ≥ 0	€ 1.03		€ 0	0	
-5 ≤ MD < 0	€ 0.69		€ 0	0	
-10 ≤ MD < -5	€ 1.89		€ 0	€ 20	
-15 ≤ MD < -10	€ 1.17		€ 196	€ 20	
-20 ≤ MD < -15	€ 4.57	€ 325	€ 355	€ 20	€ 3029
-25 ≤ MD < -20	€ 2.41		€ 565	€ 20	
MD < -25	€ 0		€ 565	€ 20	

Table 64 Continued.

	Transport to Ophthalmologist	Transport to pharmacy	Transport to hospital
Cost type	Direct non-medical	Direct non-medical	Direct non-medical
Addition	Per contact	Per 3 months of medication	Per procedure / intervention
MD $\geq$ 0	€ 4.8	€ 1.5	€ 4.9
-5 $\leq$ MD < 0	€ 4.8	€ 1.5	€ 4.9
-10 $\leq$ MD < -5	€ 4.8	€ 1.5	€ 4.9
-15 $\leq$ MD < -10	€ 8.9	€ 2.6	€ 8.9
-20 $\leq$ MD < -15	€ 8.9	€ 2.6	€ 8.9
-25 $\leq$ MD < -20	€ 8.9	€ 2.6	€ 8.9
MD < -25	€ 8.9	€ 2.6	€ 8.9

From previous paragraphs it may be apparent that is uncertainty surrounding the estimates for the costs associated with increasing disease severity. The total cost estimates are the product of estimates for resource utilization and for cost-prices, which are surrounded with uncertainty themselves. The fact that there is uncertainty in the cost-estimates is a given, resulting from the reality that there are few data on resource consumption and cost-prices in ocular hypertension and glaucoma patients. However, the impact of parameter uncertainty on the results of incremental cost-effectiveness analyses can be evaluated with sensitivity analyses.

The total of costs for low-vision rehabilitation, low-vision aids, grooming, nursing, informal care and productivity loss can be interpreted as the 'costs of low-vision and blindness'. There are not many sources of literature to verify our estimates. Burr *et al.* have recently concluded the same in their research for the cost-effectiveness of screening for open-angle glaucoma, and refer to the article by Meads & Hyde in which the annual costs of blindness as a result of macular degeneration were estimated at £ 6569 in the first year and £ 6487 in later years.^{68, 69} With a 2006 conversion rate of € 1.5 for £ 1 these estimates would equal € 9700 per year. In our model a patient is considered 'blind' when the Mean Deviation in the better eye drops below -25 dB. At that time the annual costs for grooming, nursing and informal care are € 7020. This is lower than the estimates reported by Meads & Hyde. On the other hand, the model starts attributing costs for low-vision earlier in the disease progression process rather than only in case of blindness. Therefore the cost-estimates that served as input to the base case model lead to cost estimates for low-vision and blindness that resemble the few published estimates.

Abbreviations

CI	Confidence interval
EQ-5D	EuroQol 5 dimensions questionnaire
HUI3	Health Utilities Index mark 3
IOP	Intraocular pressure
OHT	Ocular hypertension
POAG	Primary open-angle glaucoma
RCT	Randomized controlled trial
SD	Standard deviation
SEM	Standard error of the mean
VFQ-25	25-item Visual Functioning Questionnaire
LT	Laser trabeculoplasty (also LTP)

References

- Maier P, Funk J, Schwarzer G, Antes G, Falck-Ytter Y. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ* 2005; 331:134.
- Peeters A, Webers C, Prins M, Zeegers M, Hendrikse F, Schouten J. Quantifying the effect of intra-ocular pressure reduction on the occurrence of glaucoma. *Acta Ophthalmol* 2010; 88:5-11.
- Heijl A, Patella V. Essential perimetry; The field analyzer primer, Third ed. Carl Zeiss Meditec: Dublin, California, USA; 2002.
- Kass M, Heuer D, Higginbotham E, Johnson C, Keltner J, Miller J, Parrish R, Wilson R, Gordon M, Group OHTs. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002; 120:701-713.
- Gordon MO, Torri V, Miglior S, Beiser JA, Floriani I, Miller JP, Gao F, Adamsons I, Poli D, D'Agostino RB, Kass MA. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. *Ophthalmology* 2007; 114:10-19.
- Chen PP. Correlation of visual field progression between eyes in patients with open-angle glaucoma. *Ophthalmology* 2002; 109:2093-2099.
- Chen P, Bhandari A. Fellow eye prognosis in patients with severe visual field loss in 1 eye from chronic open-angle glaucoma. *Arch Ophthalmol* 2000; 118:473-478.
- Smith SD, Katz J, Quigley HA. Analysis of progressive change in automated visual fields in glaucoma. *Invest Ophthalmol Vis Sci* 1996; 37:1419-1428.
- Katz J, Gilbert D, Quigley HA, Sommer A. Estimating progression of visual field loss in glaucoma. *Ophthalmology* 1997; 104:1017-1025.
- Heijl A, Leske C, Bengtsson B, Hyman L, Bengtsson B, Hussein M, for the Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression; results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002; 120:1268-1279.
- Van der Valk R, Webers C, Schouten J, Zeegers M, Hendrikse F, Prins M. Intraocular pressure-lowering effects of all commonly used glaucoma drugs - a meta-analysis of randomized clinical trials. *Ophthalmology* 2005; 112:1177-1185.
- Beckers HJ, Schouten JS, Webers CA, van der Valk R, Hendrikse F. Side effects of commonly used glaucoma medications: comparison of tolerability, chance of discontinuation, and patient satisfaction. *Graefes Arch Clin Exp Ophthalmol* 2008; 246:1485-1490.
- McIlraith I, Strasfeld M, Colev G, Hitnik C. Selective laser trabeculoplasty as initial and adjunctive treatment for open-angle glaucoma. *J Glaucoma* 2006; 15:124-130.
- Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT) and Glaucoma Laser Trial Follow-up Study: 7. Results. *Am J Ophthalmol* 1995; 120:718-731.
- Chung P, Schuman J, Netland P, Lloyd-Muhammad R, Jacobs D. Five-year results of a randomized, prospective, clinical trial of diode vs argon laser trabeculoplasty for open-angle glaucoma. *Am J Ophthalmol* 1998; 126:185-190.
- Damji K, Shah K, Rock W, Bains H, Hodge W. Selective laser trabeculoplasty versus argon laser trabeculoplasty: a prospective randomised clinical trial. *British Journal of Ophthalmology* 1999; 83:718-722.
- Juzych M, Chopra V, Banitt M, Hughes B, Kim CS, Goulas M, Shin D. Comparison of long-term outcomes of selective laser trabeculoplasty versus argon laser trabeculoplasty in open-angle glaucoma. *Ophthalmology* 2004; 111:1853-1859.
- Beckers H, Kinders K, Webers C. Five-year results of trabeculectomy with mitomycin C. *Graefes Arch Clin Exp Ophthalmol* 2003; 241:106-110.
- Wilson M, Mendis U, Paliwal A, Haynatzka V. Long-term follow-up of primary glaucoma surgery with Ahmed glaucoma valve implant versus trabeculectomy. *Am J Ophthalmol* 2003; 136:464-470.
- Singh K, Mehta K, Shaikh N, Tsai J, Moster M, Budenz D, Greenfield D, Chen P, Cohen J, GS B, Shaikh S, Group tPTAS. Trabeculectomy with intraoperative mitomycin C versus 5-fluorouracil; prospective randomized clinical trial. *Ophthalmology* 2000; 107:2305-2309.
- Wudunn D, Cantor L, Palanca-Capistrano A, Hoop J, Alvi N, Finley C, Lakhani V, Burnstein A, Knotts S. A prospective randomized trial comparing intraoperative 5-fluorouracil vs mitomycin C in primary trabeculectomy. *Am J Ophthalmol* 2002; 134:521-528.
- Gedde S, Schiffman J, Feuer W, Herndon L, Brandt J, Budenz D, group tTvts. Treatment outcomes in the Tube Versus Trabeculectomy study after one year of follow-up. *Am J Ophthalmol* 2007; 143:9-22.
- Goulet RJ, 3rd, Phan AD, Cantor LB, Wudunn D. Efficacy of the Ahmed S2 Glaucoma Valve Compared with the Baerveldt 250-mm² Glaucoma Implant. *Ophthalmology* 2007.
- Pharmacotherapeutic compass (Farmacotherapeutisch kompas). Available at: www.fk.cvz.nl. Accessed: December 2007
- Foundation for pharmaceutical statistics (Stichting Farmaceutische Kengetallen). Data and facts 2007 (Data en feiten 2007).
- Oostenbrink J, Bouwmans C, Koopmanschap M, Rutten F. Manual for costing research (Handleiding voor kostenonderzoek; Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg). Diemen, The Netherlands: Health Care Insurance Board (CVZ); 2004:164.
- Oostenbrink J, Rutten-van Mölken M, Opdenoordt T. The treatment of newly diagnosed patients with glaucoma or with ocular hypertension in the Netherlands: an observational study of costs and initial treatment success based on retrospective chart review. *Doc Ophthalmol* 2000; 98:285-299.
- Peeters A, Schouten JS, Webers CA, Prins MH, Hendrikse F, Severens JL. Cost-effectiveness of early detection and treatment of ocular hypertension and primary open-angle glaucoma by the ophthalmologist. *Eye* 2008; 22:354-362.
- Van Gestel A, Webers C, Beckers H, Van Dongen C, Severens J, Hendrikse F, Schouten J. The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye* 2010; 24:1759-1769.
- Van Gestel A, Webers C, Beckers H, Severens J, Hendrikse F, Schouten J. Does every bit of visual field loss count? , *World Glaucoma Congress*. Boston: World Glaucoma Association; 2009.
- Dutch Healthcare Authority (Nederlandse Zorgautoriteit). Maximum tariffs (Tariefbeschikking maximum-tarieven extramurale zorg in het tweede en derde compartiment). 2007.
- GIP database. Available at: www.gipdatabank.nl. Accessed: 2006
- Webers C, Beckers H, Nuijts R, Schouten J. Pharmacological management of primary open-angle glaucoma: second line options and beyond. *Drugs Aging* 2008; 25:729-759.
- Rollim de Moura C, Paranhos A, Jr., Wormald R. Laser trabeculoplasty for open angle glaucoma. *Cochrane Database Syst Rev* 2007; Cd003919.
- Committee on Ophthalmic Procedure Assessments. Ophthalmic Procedure Assessment: Laser Trabeculoplasty for Primary Open-angle Glaucoma. *Ophthalmology* 1996; 103:1706-1712.
- Van der Valk R. Thesis: Glaucoma medication; evidence from clinical trials and effects in practice. *University Eye Clinic*. Maastricht: University of Maastricht; 2005:125.
- Medeiros F, Weinreb R, Sample P, Gomi C, Bowd C, Crowston J, Zangwill L. Validation of a predictive model to estimate the risk of conversion from ocular hypertension to glaucoma. *Arch Ophthalmol* 2005; 123:1351-1360.
- Feiner L, Piltz-Seymour J. Collaborative Initial Glaucoma Treatment Study: a summary of results to date. *Curr Opin Ophthalmol* 2003; 14:106-111.
- Lee YH, Kim CS, Hong SP. Rate of visual field progression in primary open-angle glaucoma and primary angle-closure glaucoma. *Korean J Ophthalmol* 2004; 18:106-115.
- Mayama C, Araie M, Suzuki Y, Ishida K, Yamamoto T, Kitazawa Y, Shirakashi M, Abe H, Tsukamoto H, Mishima H, Yoshimura K, Ohashi Y. Statistical evaluation of the diagnostic accuracy of methods used to determine the progression of visual field defects in glaucoma. *Ophthalmology* 2004; 111:2117-2125.
- Mikelberg FS, Schulzer M, Drance SM, Lau W. The rate of progression of scotomas in glaucoma. *Am J Ophthalmol* 1986; 101:1-6.
- Oliver JE, Hattenhauer MG, Herman D, Hodge DO, Kennedy R, Fang-Yen M, Johnson DH. Blindness and glaucoma: a comparison of patients progressing to blindness from glaucoma with patients maintaining vision. *Am J Ophthalmol* 2002; 133:764-772.

43. Pereira ML, Kim CS, Zimmerman MB, Alward WL, Hayreh SS, Kwon YH. Rate and pattern of visual field decline in primary open-angle glaucoma. *Ophthalmology* 2002; 109:2232-2240.
44. Rasker M, Van den Enden A, Bakker D, Hoyng P. Rate of visual field loss in progressive glaucoma. *Arch Ophthalmol* 2000; 118:481-488.
45. Schwartz B, Takamoto T, Martin J. Increased Rate of Visual Field Loss Associated with Larger Initial Visual Field Threshold Values on Follow-Up of Open-Angle Glaucoma. *J Glaucoma* 2004; 13:120-129.
46. Soares AS, Artes PH, McCormick TA, LeBlanc RP, Nicolela MT, Chauhan BC. Retinal arterial diameter changes in progressive and nonprogressive glaucoma. *J Glaucoma* 2003; 12:243-249.
47. Vesti E, Johnson C, Chauhan B. Comparison of different methods for detecting glaucomatous visual field progression. *Invest Ophthalmol Vis Sci* 2003; 44:3873-3879.
48. Wilson M, Kosoko O, Cowan C, Sample P, Johnson C, Haynatzki G, Enger C, Crandall D. Progression of visual field loss in untreated glaucoma patients and glaucoma suspects in St. Lucia, West Indies. *Am J Ophthalmol* 2002; 134:399-405.
49. Zink JM, Grunwald JE, Piltz Seymour J, Staii A, Dupont J. Association between lower optic nerve laser Doppler blood volume measurements and glaucomatous visual field progression. *Br J Ophthalmol* 2003; 87:1487-1491.
50. Kwon Y, Kim C, Zimmerman B, Alward W, Hayreh S. Rate of visual field loss and long-term visual outcome in primary open-angle glaucoma. *Am J Ophthalmol* 2001; 132:47-56.
51. O'Brien C, Schwartz B, Takamoto T, Wu DC. Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma. *Am J Ophthalmol* 1991; 111:491-500.
52. Leske M, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E, Group EMGT. Factors for glaucoma progression and the effect of treatment. *Arch Ophthalmol* 2003; 121:48-56.
53. Nouri-Mahdavi K, Hoffman D, Coleman A, Liu G, Li G, Gaasterland D, Caprioli J. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology* 2004; 111:1627-1635.
54. Wesselink C, Heeg G, Jansonius N. Glaucoma monitoring in a clinical setting: Glaucoma Progression Analysis versus Nonparametric Progression Analysis. *Arch Ophthalmol* 2009; 127:270-274.
55. The AGIS investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000; 130:429-440.
56. Lichter P, Musch D, Gillespie B, Guire K, Janz N, Wren P, Mills R, Group TC. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001; 108:1943-1953.
57. Shirakashi M, Iwata K, Sawaguchi S, Abe H, Nanba K. Intraocular pressure-dependent progression of visual field loss in advanced primary open-angle glaucoma: a 15-year follow-up. *Ophthalmologica* 1993; 207:1-5.
58. Singh K, Shrivastava A. Early aggressive intraocular pressure lowering, target intraocular pressure, and a novel concept for glaucoma care. *Surv Ophthalmol* 2008; 53 Suppl1:S33-38.
59. Eye diseases. Scope of the problem. How often do eye diseases occur? Available at: http://www.rivm.nl/vtv/object_document/o1143n17763.html. Accessed: 18 May, 2006
60. Burr J, Azuara-Blanco A, Avenell A. Medical versus surgical interventions for open angle glaucoma. *The Cochrane Database of Systematic Reviews* 2004; Issue 2. Art.No.: CD004399.pub004392. DOI: 004310.001002/14651858. CD14004399.pub14651852.
61. Ederer F, Gaasterland D, Dally L, Kim J, VanVeldhuisen P, Blackwell B, Prum B, Shafranov G, Allen R, Beck A, AGIS investigators. The Advanced Glaucoma Intervention Study (AGIS): 13. Comparison of treatment outcomes within race: 10-year results. *Ophthalmology* 2004; 111:651-664.
62. Mortality rates by age and gender. Available at: <http://statline.cbs.nl/StatWeb/>. Accessed: 12-07-2005
63. Miglior S, Zeyen T, Pfeiffer N, Cunha-Vaz J, Torri V, Adamsons I, The European Glaucoma Prevention Study (EGPS) Group. Results of the European Glaucoma Prevention Study. *Ophthalmology* 2005; 112:366-375.
64. Heeg GP, Jansonius NM. The groningen longitudinal glaucoma study III. The predictive value of frequency-doubling perimetry and GDx nerve fibre analyser test results for the development of glaucomatous visual field loss. *Eye* 2008.
65. The AGIS investigators. The Advanced Glaucoma Intervention Study (AGIS): 11. Risk factors for failure of trabeculectomy and argon laser trabeculoplasty. *Am J Ophthalmol* 2002; 134:481-498.
66. Statline. Available at: <http://statline.cbs.nl/StatWeb/>. Accessed: 2010
67. Oostenbrink J, Rutten-van Mölken M, Sluyter-Opdenoordt T. Resource use and costs of patients with glaucoma or ocular hypertension: a one-year study based on retrospective chart review in the Netherlands. *J Glaucoma* 2001; 10:184-191.
68. Meads C, Hyde C. How much is the cost of visual impairment: caveat emptor. *Pharmacoeconomics* 2006; 24:207-209; discussion 210.
69. Burr J, Mowatt G, Hernández R, Siddiqui M, Cook J, Lourenco T, Ramsay C, Vale L, Fraser C, Azuara-Blanco A, Deeks J, Cairns J, Wormald R, McPherson S, Rabindranath K, Grant A. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007; 11.

Chapter 5

The long term outcomes of four alternative treatment strategies for primary open-angle glaucoma

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Abstract

Purpose: To evaluate the long term effects and costs of four treatment strategies for primary open-angle glaucoma (POAG) compared to usual care.

Methods: Cost-effectiveness analyses with a lifelong horizon were made from a societal perspective. Data were generated with a patient-level model based on discrete event simulation. The model structure and parameter estimates were based on literature, particularly clinical studies on the natural course of glaucoma and the effect of treatment. We simulated heterogeneous cohorts of 3000 patients, and explored the impact of uncertainty with sensitivity analyses.

Results: The incremental cost-effectiveness ratio (ICER) of initial treatment with a prostaglandin analogue compared with a beta-blocker was € 12,931 per quality-adjusted life-year (QALY) gained. A low initial target pressure (15 mmHg) resulted in 0.115 QALYs gained and € 1,550 saved compared to a gradual decrease from 21 mmHg to 15 mmHg upon progression. Visual field measurements every 6 rather than 12 months lead to health gains at increased costs (ICER € 173,486 per QALY gained), whereas measurements every 24 months lead to health losses at reduced costs (ICER € 21,516 per QALY lost). All treatment strategies were dominant over 'withholding treatment'.

Conclusions: From a cost-effectiveness point of view, it seems advantageous to aim for a low intraocular pressure in all glaucoma patients. The feasibility of this strategy should therefore be investigated. Additionally, the cost-effectiveness outcomes of initiating monotherapy with a prostaglandin analogue and reducing the frequency of VF testing may be acceptable.

Introduction

The gradual deterioration of the visual field as a result of primary open-angle glaucoma (POAG) can result in visual impairment and blindness. During the last decades, effective interventions have been developed to slow down that process, and there is ongoing development in methods to detect glaucoma earlier, to monitor progression more reliably and to treat glaucoma more effectively.¹ The added value of new treatment options in clinical practice is defined by their effectiveness in preventing visual impairment, but in the context of healthcare budget constraints it is also essential to consider their efficiency. Information from cost-effectiveness research is required to organize the care for glaucoma patients in such a way that maximum health can be achieved with the available resources. For example, the expected balance between the overall benefits and costs of glaucoma treatment according to preferred practice patterns compared to no treatment has been calculated at \$20,000 per quality-adjusted life-year (QALY) gained, which was considered good value for money.^{2, 3} Although results from cost-effectiveness studies are not directly transferable between jurisdictions and health-care systems, it is likely that glaucoma treatment according to the European guidelines is similarly cost-effective compared to no treatment at all.⁴ However, the treatment guidelines provide a general framework for the treatment approach, and the details of the treatment choices are left with the ophthalmologist. For example, it is recommended that a target intraocular pressure (IOP) is set and that treatment is directed at achieving a stable IOP below this target. However, the guidelines do not specify how low that target pressure should be to achieve the best outcome. Also, topical medications are recommended as initial therapy, but it is uncertain whether any specific order of administration of the available mono- and combination therapies is preferable in view of long term outcomes. Finally, a patient under treatment needs to be monitored for treatment response and potential further progression, but the recommended interval for follow-up visits of stable patients is somewhere between 3 and 24 months. There may be several reasons why these issues are not specified in the guidelines. For one, the patient population is heterogeneous and there must be room for the physician to make treatment decisions based on the patient's characteristics and treatment history. But secondly, there is no scientific evidence to completely support such specific recommendations, because that would require clinical trials with a multitude of treatment strategies and a lifelong follow-up. However, the evidence that *is* available can help us to make predictions of the long-term outcomes of specific treatment choices and help us to make decisions. In clinical practice a physician implicitly uses his/her knowledge to make projections of the future in order to make a treatment decision, which will be the one with the best expected outcomes for the individual patient. The aim of the research

presented in this paper was to make those forecasts explicit, and to predict the long term health and cost-effectiveness outcomes from specific choices in the treatment strategy for primary open-angle glaucoma regarding initial medication, target pressure and monitor frequency. We have used computer simulation modeling to synthesize current knowledge of glaucoma and its treatment. Although the outcomes from a model may seem less 'real' than outcomes from clinical studies, one should bear in mind that the model is entirely *based* on the outcomes of previous clinical and observational studies. Not only does it therefore make efficient use of previous research efforts, but it also provides a method to generate data that cannot otherwise be obtained. Of course there is a certain degree of uncertainty in model outcomes (as there is in any clinical decision), but this can be investigated explicitly and taken into account in the decision making process.^{5, 6}

Methods

We have developed a computer model to simulate the lifetime health and resource use of individual glaucoma patients. We then used the model to generate data on the lifelong outcomes of individual patients in a heterogeneous population under two different treatment strategies, and compared the average health and cost-effectiveness outcomes in both strategies. The simulated populations consisted of 3000 patients, because pilot runs showed that this was the best trade-off between outcomes stability and computation time. The cost-effectiveness analyses were performed according to the Dutch guidelines for pharmacoeconomic research.⁷ We used a societal perspective, which includes all benefits and all costs regardless the beneficiary and payers. Future effects and costs were discounted with 1.5% and 4.0% per year respectively.

Model structure

The following is a summary of the main model structure and parameter estimates. More detailed information is provided in the appendix. An extensive description of the development and validation of the model has been published previously.⁸ The model was programmed in Excel (Microsoft Excel 2000, Microsoft corporation, Redmond, WA) and was based on discrete event simulation.⁹ This entails that it projected when a relevant event would occur in the patient's life and subsequently made a forward jump in time towards that event. At each event the model (re)calculated the value of a number of relevant patient attributes like e.g. age and IOP, that together represent an individual patient. This (re)calculation was governed by a network of relationships that defined how all patient attributes and events are linked together. For example, the age of the patient was recalculated from the age

at the previous event plus the length of the forward jump. An event that recurred frequently during a patient simulation was the 'visit to the ophthalmologist'. At such an event, the model mimicked the treatment decision that would be made for the patient based on the attributes and the decision rules of the treatment strategy, and recalculated all treatment related attributes, like the relative pressure lowering from medication. Through the network of relationships the model also recalculated how this affected disease related attributes, like IOP. The initial event in the model represented the patient's first visit to an ophthalmologist. The initial value of each attribute in an individual patient was established with a random draw from a distribution representing the variability of that attribute in the real patient population (see appendix). This way, each new simulated patient had a unique set of initial attribute values. A patient's pathway through the model depended on these initial attributes, on the decision rules of the treatment strategy and also on coincidence as the occurrence of some events (notably the formation of cataract and death) was based on random draws.

We have simulated the disease progression and treatment in the better eye of the patient, and assumed that the other eye was only slightly worse. In terms of modeling outcomes, this was similar to modeling both eyes and assuming that disease progression is symmetrical. Costs for treatment of the other eye were included in the analyses. In a structural sensitivity analysis we have also evaluated the results of asymmetrical disease progression.

Population

The simulated population in this study was heterogeneous and representative of the case mix in first time ophthalmologist visitors. The distributions of initial age, IOP and degree of glaucomatous damage were based on the study populations in the Early Manifest Glaucoma Study and the Collaborative Initial Glaucoma Treatment Study.^{10, 11} Initial age was drawn from a normal distribution with a mean of 68 years and standard deviation of 4 years. Initial OP was drawn from a normal distribution with mean 28 and standard deviation 3 mmHg, truncated at 22 mmHg. The degree of glaucomatous damage was expressed in the standard automated perimetry global index Mean Deviation (MD). The initial value of the MD was drawn from a gamma distribution with an average of -7 dB (99% between -3 and -17 dB). Derivations and figures of the distributions are provided in the appendix.

Treatment

The model contained a network of relationships to link disease progression with treatment and vice versa. Treatment was modeled through a series of attributes representing e.g. the instillation of eye drops or the occurrence of surgery. Each

treatment type (see below) had an effect on IOP, which was in turn related to the rate of MD deterioration as described in the next paragraph. In this paper we have defined the comparator treatment strategy as 'usual care', which was based on the European treatment guidelines for glaucoma.¹² In addition, we defined four experimental strategies, and a 'no care' scenario (Table 1). The relationships to model treatment were mostly similar for all strategies. Here we first describe the simulation of treatment in the case of 'usual care', and then indicate how the alternative strategies were different.

Table 1 Treatment strategies for primary open-angle glaucoma that were compared

	Usual care	No care	Strategy 1 Latanoprost	Strategy 2 Target 15 mmHg	Strategy 3a VF 6 months	Strategy 3b VF 24 months
Start treatment	Always	Never	Always	Always	Always	Always
Target pressure (mmHg)						
initial	21		21	15	21	21
after first progression	18		18	15	18	18
after second progression	15		15	15	15	15
First choice medication	Timolol	-	Latanoprost	Timolol	Timolol	Timolol
VF measurement interval	12 months	-	12 months	12 months	6 months	24 months

VF = visual field

Treatment was initiated with one topical medication (monotherapy), and adjusted in the subsequent visits based on the occurrence of side-effects, the efficacy of the prescribed medication and the patient's IOP compared to the target. The appendix provides a detailed schedule of how the treatment decisions were regulated in the model. Briefly: If the patient experienced side-effects or if the medication had insufficient efficacy (i.e. less than 20% pressure lowering), the prescribed drug was replaced by other monotherapy. If the IOP had not dropped below the target, a

medication was added. The maximum number of medications was three. The medication schedule included medications from four different classes of pressure-lowering substances. The first choice in the 'usual care' strategy was timolol (β -blockers), followed by latanoprost (prostaglandin analogues), dorzolamide (carbonic-anhydrase inhibitors) and brimonidine (α_2 -adrenergic agonists). If medication alone was not sufficient to reduce the IOP below the target IOP, the model moved to laser trabeculoplasty (LT), trabeculectomy (TE), repeated trabeculectomy, and finally tube implant surgery. If the IOP was above target after a procedure, medication was added according to the same schedule as described above before any new procedure was executed; Medications previously associated with side-effects or low efficacy were avoided.

The initial target IOP for POAG patients in the 'usual care' strategy was 21 mmHg. Since all simulated patients in this article had an initial IOP higher than 22 mmHg, all patients were above target and therefore initiated on treatment at the first visit event. The target IOP remained 21 mmHg as long as the MD did not deteriorate beyond what was defined as progression (see below). If progression was observed during one of the visit events, the target IOP was lowered to 18 mmHg. If progression was observed again, the target IOP was lowered to 15 mmHg.

Stable patients had an ophthalmologist visit every 6 months, but the frequency of visits was temporarily increased after each treatment change and after each surgical procedure (see table 5 in the appendix). During the simulated visits, visual field (VF) measurements could take place. All simulated patients received two baseline VF test during their first visit and subsequently once every year in the 'usual care' strategy.

The effectiveness of each medication and surgical procedure in terms of pressure lowering (%) and the post-surgery IOP level respectively, was established for each patient separately with a random draw from population distributions based on observations in clinical trials (see table 3 in the appendix). Also the patient's proneness to side-effects and the presence of contra-indications for each of the medications were randomly drawn for each patient.

The alternative treatment strategies that were compared with 'usual care' are listed in table 1. The 'no care' strategy entailed a baseline ophthalmologist visit, but no subsequent visits, VF measurements, medication or surgery during the lifetime of the patient. In the 'latanoprost' strategy, latanoprost and timolol switched places as first- and second choice medication. In the 'target 15 mmHg' strategy, the target pressure was directly fixed at 15 mmHg for all patients and was no longer adjusted

upon progression. In the 'VF 6 months' and 'VF 24 months' strategies, the interval between VF measurements was set at 6 months and 24 months respectively.

Disease progression

The glaucomatous disease status of a simulated patient's better eye was defined in the model by the degree of functional damage to the visual field. The latter was quantified by the Mean Deviation (MD), a global index parameter of the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Jena, Germany). The MD was an attribute of the simulated patient, and was recalculated at each event. For each simulated patient an initial MD value (dB) was randomly drawn, as well as an intrinsic rate of MD loss (MDR, dB/year). The latter represented the rate at which the MD of that patient would deteriorate annually if the IOP of that patient were at a referent value. The intrinsic rate of MD loss was drawn from a gamma distribution with an average of 0.34 dB/year (see appendix for more details). The current rate of MD loss in a simulated patient was recalculated at each event from the MDR and the current IOP. The higher the IOP, the higher the MDR; an exception to this rule was made when IOP was below 13 mmHg, in which case MDR was assumed to be zero. This calculation of MDR was challenged in two separate structural sensitivity analyses that I) included existing visual field loss as a risk factor for MDR, and II) did not enable MDR to become zero.

The IOP at each time point was calculated from the baseline IOP and the total pressure lowering effect of current treatment. The formation of cataract in a simulated patient, before baseline and during the simulation, was based on the age-dependent cumulative incidence of cataract in The Netherlands.¹³ The relative risk of cataract formation from trabeculectomy was 2.7.¹⁴ Whether or not a cataract was surgically removed was determined in the model with a random draw from a Bernoulli distribution with a 0.8 probability of surgery.

During each visit event in which a VF test occurred, the measured MD was compared to a previous measured MD to mimic an ophthalmologist's assessment of clinical progression. We defined clinical progression in this model as an absolute decrease of 2 dB compared to either baseline (for the first occurrence of progression), or compared to the measured MD value at the previous observation of progression. Note that MD deterioration itself was modeled independent of the occurrence of visits or visual field tests, but that the detection of progression (and consequential treatment adjustment) could only occur during a visit in which a visual field test was taken.

Cost input

As per the Dutch guidelines for pharmacoeconomic research, all direct medical, direct non-medical and indirect non-medical costs were taken into account.⁷ Direct medical costs consisted of costs for ophthalmologist visits, VF measurements, medication, surgery, home care (household, grooming and nursing), low-vision rehabilitation and aids, and retirement- and nursing home. Direct non-medical costs included transportation to healthcare providers and costs for informal care. Indirect non-medical costs were the production losses as a result of POAG, which were based on the friction cost method. This entails that the period over which the production loss is calculated is limited to the friction period, i.e. the time that an employer needs to replace a sick employee.^{7, 15} The cost prices of the resources included in the analyses are listed in the appendix. The cost year was 2006. Most resource use was simulated directly (visits, medication and surgery). For the remainder we linked an estimate of the average resource utilization to POAG severity, such as in the case of home care and low-vision aids. The estimates for the latter were based on recent observational research among over five hundred Dutch POAG patients.⁸ In a structural sensitivity analysis we have assumed that costs related to POAG severity were only incurred in case of blindness (i.e. MD < -25 dB).

Utility input

Estimates for the simulated patient's quality-of-life were based on observational research in ocular hypertension (OH) and POAG patients.¹⁶ The derivation of the coefficients has been described previously.⁸ We included estimates for both disease-specific and generic quality-of-life (utility). The former was based on the National Eye Institute Visual Functioning Questionnaire (VFQ-25) with scores adjusted to a 0-1 scale representing blind and perfect vision respectively.^{17, 18} Utility estimates were based on the Health Utilities Index mark 3 (HUI3).¹⁹ Loss of quality-of-life was associated with the occurrence of side-effects from medication, the presence of cataract and the amount of visual field loss according to the following equations.⁸

$VFQ = 0.94 - 0.097 \cdot SE + 0.015 \cdot MD - 0.092 \cdot CAT$	(1)
$HUI3 = 0.88 - 0.101 \cdot SE + 0.011 \cdot MD - 0.065 \cdot CAT$	(2)

where VFQ is the score of the NEI VFQ-25, HUI3 the score of the HUI3 questionnaires, SE the presence of side-effects (0=no; 1=yes), MD the static perimetry mean deviation in dB and CAT the presence of cataract (0=no; 1=yes).

During the simulation, the length of each interval between events was multiplied with the quality-of-life during that interval to calculate QALY's. In a structural sensitivity analysis we have challenged the linearity of the relationship between MD and quality-of-life in equations 1 and 2.

Model validation

The model and its outcomes have been assessed for face validity, and for internal and external consistency.⁸ In addition, we have included a comparison of 'usual care' versus 'no care' in the analyses presented in this paper to compare the outcomes of our model with those recently reported by Rein et al. for additional validation.³

Sensitivity analyses

The sensitivity of the model outcomes to assumptions made in the model structure was evaluated with a series of univariate structural sensitivity analyses. In the first analysis (A) we modeled only the worse eye, and assumed that the other eye was unaffected (MD = 0 dB). In this case no extra treatment or monitoring costs for the better eye were included and all costs associated with disease severity were linked to the average MD in both better and worse eye. In the second analysis (B) we assumed that existing visual field damage induces further damage with a relative risk of 1.03 per dB (see appendix), which entails that the rate of MD deterioration roughly doubles between early and end-stage disease. In the third analysis (C) we assumed that the relationship between visual field loss and quality-of-life is not linear.¹⁶ The equations to calculate VFQ and utility in this sensitivity analysis were:

$$\text{VFQ} = 0.93 - 0.12 \cdot \text{SE} + 0.0022 \cdot \text{MD} - 0.00042 \cdot \text{MD}^2 - 0.051 \cdot \text{TE} - 0.088 \cdot \text{CAT} \quad (3)$$

$$\text{HUI3} = 1.1 - 0.16 \cdot \text{SE} + 0.0034 \cdot \text{MD} - 0.26 \cdot \text{MD}_{-25} - 0.091 \cdot \text{CAT} \quad (4)$$

where VFQ is the score of the NEI VFQ-25 questionnaire, HUI3 the score of the HUI3 questionnaire, SE the presence of side-effects (0=no; 1=yes), MD the static perimetry mean deviation in dB, TE the occurrence of trabeculectomy, MD₋₂₅ a Mean Deviation below -25 dB (0=no; 1=yes), and CAT the presence of cataract (0=no; 1=yes).

In the fourth sensitivity analysis (D), we assumed that all costs linked to disease severity would only occur at MD values below -25 dB in the better eye. In the final analysis (E), we assumed that there is no IOP level below which all progression halts and let the rate of MD loss diminish proportionately with decreasing IOP at all levels of IOP.

The uncertainty surrounding the cost-effectiveness outcomes of the model as a result of uncertainty in the input parameter estimates was evaluated with multivariate probabilistic sensitivity analyses (PSA).²⁰ The simulation of two treatment strategies in a cohort of patients was repeated 500 times, each time with a different set of parameter values drawn from distributions reflecting the uncertainty surrounding the base case parameter values (table 7, appendix). With the PSA outcomes we have performed analysis of covariance (ANCOVA) to investigate the impact of the input parameters on incremental costs and QALY's.

Results

The results presented in the next paragraphs were all collected from simulation runs with the model. During a simulation run, one fictitious patient was simulated according to two treatment strategies: 'usual care' and the alternative strategy. After 3000 simulation runs, the population averages were calculated and compared. This enabled us to calculate the incremental outcomes of the alternative strategy relative to the 'usual care' strategy within the same patient population. However, the composition of the heterogeneous population was different from one simulation run (i.e. comparison to 'usual care') to the next, so a direct comparison between the outcomes of the alternative strategies could not readily be made. In order to enable a wide comparability between all treatment strategies, we have recalculated the *absolute* outcomes of each strategy from one communal set of 'usual care' outcomes and the *incremental* outcomes of each strategy relative to its own 'usual care' comparator population.

The average duration of the simulated lives of the glaucoma patients, and therefore the horizon of the cost-effectiveness outcomes, was 15.4 years. Table 2 lists the population averages of several clinical outcomes that were predicted by the model for each of the treatment strategies.

The following paragraphs report the base case cost-effectiveness outcomes for each of the alternative treatment strategies. A more elaborate discussion of each strategy and a consideration of all additional analyses is provided in the discussion section of this paper.

The treatment strategy with latanoprost as the initial medication lead to health gains and extra costs on the average population level (Table 3), and a discounted incremental cost-effectiveness ratio (ICER) of € 12,931 per QALY gained.

Table 2 Average lifetime clinical outcomes in the simulated population

	Usual care	No care	Strategy 1 Latanoprost	Strategy 2 Target 15 mmHg	Strategy 3a VF 6 months	Strategy 3b VF 24 months
Mean IOP in follow-up (mmHg) ^a	17.3	29.3	17.2	15.5	17.2	17.4
Lifetime mean number of medications ^a	1.9	0.0	1.8	2.5	1.9	1.9
Occurrence of visual disability ^{a,c}	21%	74%	21%	15%	21%	23%
Occurrence of blindness ^{b,d}	2.9%	51.4%	2.7%	1.9%	2.7%	3.2%
Days with visual disability or blindness (years)	694 (1.9 yrs)	3264 (8.9 yrs)	687 (1.9 yrs)	500 (1.4 yrs)	674 (1.8 yrs)	743 (2.0 yrs)
Days with blindness (years)	61 (0.2 yrs)	1951 (5.3 yrs)	55 (0.2 yrs)	45 (0.1 yrs)	58 (0.2 yrs)	70 (0.2 yrs)
Occurrence of LT ^b	45%	0%	43%	66%	45%	44%
Occurrence of TE ^b	31%	0%	29%	46%	32%	29%
Occurrence of ReTE ^b	7%	0%	7%	12%	8%	6%
Occurrence of tube implant ^b	5%	0%	5%	9%	6%	5%
Occurrence of CE ^b	38%	32%	39%	42%	37%	38%
End of life MD (dB)	-12.0	-24.4	-11.9	-10.8	-11.9	-12.2

Yrs = years; Mo = months; LT = laser trabeculoplasty; TE = trabeculectomy; ReTE = second trabeculectomy; CE = cataract extraction; MD = Mean Deviation; dB = decibels
^a The table reports the population average of the patient-level lifetime mean; ^b Percentage of the cohort in which the event occurred during the simulated life time; ^c MD below -15 dB; ^d MD below -25 dB.

Figure 1 Cost-effectiveness plane showing the outcomes of the alternative treatment strategies compared with usual care. The bold markers indicate the base case population averages, while the small markers indicate population averages in the probabilistic sensitivity analyses. The diagonal lines represent willingness-to-pay thresholds. Points that lie under the diagonal line have an incremental cost-effectiveness ratio that is more favorable than the threshold. The south-east quadrant represents a situation in which the alternative strategy is more effective and less costly than usual care, and is therefore dominant.

In the treatment strategy with a low target IOP (15 mmHg) for all patients, the model predicted the utilization of more medications and more surgical procedures, but also a lower average IOP and a lower incidence of blindness (table 2). The incremental costs consisted predominantly of extra costs for medication and surgery but savings in low-vision related care (figure 2). The net result was that the

Figure 2 Breakdown of total incremental costs (discounted) into four categories. Transportation costs and production loss are not shown as they were all below € 10. Costs in the four treatment strategies are incremental versus 'usual care'.

strategy with a low target pressure was expected to lead to health gains and cost savings (Table 3). The outcomes were most sensitive to the costs of care, the utility loss due to progression, and the effect of IOP reduction on MD loss (Figure 3).

The treatment strategy with VF measurements every six months lead to a minor improvement in clinical results compared to VF measurements every year (table 2). The costs of the extra visual field tests were only partly compensated by lower costs for low-vision related care (figure 2), and the discounted ICER was € 173,486/QALY gained. On the other hand, the treatment strategy with VF measurements every two years resulted in cost reductions from decreased testing, but increased costs of low-vision related care, resulting in net cost savings. However, the model outcomes also indicated a loss in QALY's, and the ICER was € 21,516 per QALY lost. The incremental outcomes of a change in VF frequency were sensitive to the costs of visual field testing, the costs of care, the utility loss upon MD loss, the effect of IOP reduction on MD loss and the value of a 'safe IOP'.

The treatment strategy in which all POAG treatment was withheld ('No care') lead to the worst outcomes, both in terms of health as in terms of costs. For example, the occurrence of blindness increased from approximately 3% in all treated scenarios

Table 3 Cost-effectiveness outcomes base case model

	Usual care	No care	Strategy 1 Initial medication	Strategy 2 Target pressure	Strategy 3a VF 6 months	Strategy 3b VF 24 months
Costs	€ 37,328	€ 67,002	€ 37,401	€ 34,026	€ 38,765	€ 37,040
VFQALY's	11.90	9.67	11.91	12.12	11.91	11.87
QALY's	11.87	10.43	11.88	12.01	11.88	11.85
Discounted costs	€ 23,892	€ 42,099	€ 23,982	€ 22,343	€ 24,956	€ 23,573
Discounted VFQALY's	10.42	8.58	10.43	10.60	10.43	10.39
Discounted QALY's	10.37	9.19	10.38	10.49	10.38	10.36
Compared to 'Usual care', discounted						
Incremental Costs	€ 18,207		€ 90	-€ 1,550	€ 1,063	-€ 319
Incremental QALY's	-1.185		0.007	0.115	0.006	-0.015
ICER (/QALY)	Dominated		€ 12,931	Dominant	€ 173,486	€ 21,516

VFQALY = life years adjusted for VFQ-25 score; QALY = quality-adjusted life years; ICER = incremental cost-effectiveness ratio

Figure 3 Analysis of covariance with results from probabilistic sensitivity analyses. The bars show the percentage of variance explained by uncertainty in the model parameters. Only the most important parameters are shown.

MD= Mean Deviation; RR= Relative risk; IOP= Intraocular pressure; MDR= rate of MD deterioration; VF= visual field.

Table 4 Univariate sensitivity analyses; discounted incremental outcomes versus usual care

	Initial medication latanoprost				Target pressure 15 mmHg			
	Costs	VFQALY's	QALY's	ICER (/QALY)	Costs	VFQALY's	QALY's	ICER (/QALY)
A. Other eye unaffected	€ 204	0.011	0.008	€ 26,448	€ 806	0.053	0.042	€ 19,064
B. Non-linear progression MD	€ 64	0.007	0.005	€ 13,331	-€ 2,153	0.213	0.137	Dominant
C. Non-linear relationship MD x QOL	-€ 17	0.122	0.004	Dominant	-€ 1,504	0.213	0.029	Dominant
D. Blindness costs only if MD < -25 dB	€ 198	0.012	0.008	€ 25,511	€ 1,356	0.172	0.110	€ 12,384
E. No safe IOP	€ 41	0.013	0.009	€ 4,685	-€ 860	0.133	0.085	Dominant
	VF 6 months				VF 24 months			
	Costs	VFQALY's	QALY's	ICER (/QALY)	Costs	VFQALY's	QALY's	ICER (/QALY)
A. Other eye unaffected	€ 1,245	0.000	0.000	€ 1,828,614	-€ 637	-0.012	-0.009	€ 69,326*
B. Non-linear progression MD	€ 998	0.010	0.007	€ 144,001	-€ 55	-0.040	-0.026	€ 2,097*
C. Non-linear relationship MD x QOL	€ 1,139	0.119	0.003	€ 402,847	-€ 391	0.092	-0.009	€ 44,842*
D. Blindness costs only if MD < -25 dB	€ 1,252	0.007	0.005	€ 256,494	-€ 699	-0.031	-0.020	€ 35,453*
E. No safe IOP	€ 1,112	0.008	0.005	€ 223,278	-€ 402	-0.022	-0.013	€ 31,491*

VFQALY = life years adjusted for VFQ-25 score; QALY = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; MD = Mean Deviation; QOL = quality-of-life, IOP = intraocular pressure.

* Savings per QALY lost.

to 50% (Table 2) and patients lost around 1.5 QALY's. In spite of roughly € 10,000 worth of glaucoma treatment saved per patient, the expected expenditure related to visual impairment and blindness was estimated at € 40,000 per patient, resulting in net extra costs of almost € 30,000 per patient.

The absolute values of the incremental costs and QALY's compared to usual care in the univariate sensitivity analyses were different from the base case estimates in all treatment strategies, but in most cases this did not affect the direction of the outcomes in terms of the relative cost-effectiveness (Table 4). The outcomes of the sensitivity analyses are discussed in more detail in the discussion section.

Discussion

When cost-effectiveness outcomes are in the south-east or north-west quadrant of the cost-effectiveness plane (Figure 1), the interpretation of the outcomes is rather straightforward because one strategy is clearly dominant over the other. However, when extra effects come at surplus expenses, the interpretation of the ICER depends on the decision making context and whether or not limited resources play a role.²¹ Even if resources are unlimited there may be a limit to what society is willing to pay for an extra QALY. In several countries threshold values for willingness-to-pay have been proposed or derived. For example, in the Netherlands a tiered cost-effectiveness acceptability thresholds depending on disease burden with a maximum of € 80,000/Qaly has been recommended.²² The UK uses a range of £ 20,000 to £ 30,000 per QALY and in Canada a range of CAN\$ 20,000 to CAN\$ 100,000 has been proposed.²³

Rein *et al.* calculated an expected cost-utility of \$ 11,000 to \$ 20,000 per QALY gained for glaucoma treatment compared to 'No care'.³ In contrast, we found health gains and cost savings, indicating that glaucoma treatment is a dominant strategy compared to 'No care'. It is likely that the difference is the result of lower cost-prices of medication and surgery in our model, and the fact that we included more items of low-vision related resource utilization. Excluding the latter from our calculations lead to an incremental cost estimate of € 6,809 and an ICER of € 5,674 per QALY gained, which is comparable to Rein's lower estimate. Additionally, the validity of the model used in this paper was supported by the observation that the average resource utilization predicted for 'usual Care' in terms of medications, LT and surgery (Table 2) was comparable with those found in a retrospective chart review study in five European countries and the United States.^{24, 25}

We evaluated a prostaglandin analogue (latanoprost) versus a β -blocker (timolol) as the first-choice medication. The model results showed that this strategy is expected to cost an additional € 12,931 per QALY gained, which lies within the acceptability thresholds mentioned above and therefore might indicate an acceptable ratio. It therefore appears that initial latanoprost has a more favorable cost-effectiveness in glaucoma patients than in ocular hypertension patients.²⁶ Also, the absolute numbers of the incremental costs (€ 90) and QALY's (0.007) were very close to zero, indicating that the two strategies were actually virtually similar. This was also reflected in the probabilistic sensitivity analyses that resulted in a distribution of the expected ICER across the four quadrants (Figure 1). In order to gain insight in the uncertainty surrounding the outcome, we used the outcomes from the PSA to create a cost-effectiveness acceptability curve (CEAC, Figure 4). The CEAC showed that at acceptability thresholds higher than € 14,000/QALY, a treatment strategy with initial latanoprost had a higher probability to be cost-effective than a treatment strategy with initial timolol. Moreover, the cost-effectiveness ratio is likely to improve further if the current expiration of the patent on latanoprost results in the availability of generic latanoprost formulations with comparable effectiveness at a lower costprice. Subgroup analyses (reports listed in the appendix) showed that the most favorable cost-effectiveness ratios for latanoprost can be expected in patients with either high initial IOP (>28 mmHg) or mild to moderate glaucomatous damage (MD < -10 dB).

Figure 4 Cost-effectiveness acceptability curve showing the probability that 'Initial latanoprost' is considered cost-effective compared to 'usual Care' at increasing acceptability thresholds.

In the second alternative treatment strategy we evaluated a low target IOP for all patients. The incremental cost-utility outcome was in the south-east quadrant of the cost-effectiveness plane and was therefore dominant to usual care. The model predicted more medication use in the low target IOP strategy, which was expected, but also more surgical procedures, which might seem contradictory as (Table 2). The explanation lies in the fact that with a low initial target IOP, the timing of the TE moved forward. A simulated patient with an IOP above 15 mmHg despite maximal medication and LT would receive TE at the first incidence of progression, whereas the same patient could experience three incidences of progression in the 'usual Care' strategy before TE would be performed. By that time the patient may have died or become too old for surgery. The PSA results in Figure 1 indicate that there is uncertainty in the expected ICER, and also the ANCOVA indicated that the cost-effectiveness outcomes were sensitive to several input parameters. However, uncertainty and sensitivity are not relevant when they do not alter the conclusion. Indeed, the PSA results indicated that the probability of an acceptable cost-effectiveness ratio was 87% at a € 0/QALY threshold and reached 100% at thresholds higher than € 25,000/QALY (see CEAC in appendix). Between these threshold values, the expected value of perfect information dropped from € 62 to € 0 per patient, indicating that there is hardly any value in additional research to reduce the parameter uncertainty in the model.²⁷ These results suggest it would be worthwhile to aim for the lowest possible IOP achievable (and tolerated) with medical therapy early in POAG therapy. The subgroup analyses showed that this conclusion may even apply to the mildest group of glaucoma patients (see appendix). Because of the potential applicability of this strategy in practice, we have rerun the simulations for the other alternative treatment strategies and 'usual care', in the context of a target IOP of 15 mmHg for all patients. The results are listed and discussed in the appendix.

In the final analyses we evaluated the impact of a higher or lower frequency of visual field testing on cost-effectiveness. The outcomes of these analyses must be interpreted in the context of the assumptions made, particularly with respect to the absence of any measurement error in the VF tests. Due to this assumption the model was not fit to compare detailed regimens of visual field testing such as have been proposed by other authors, and to take into account inter-test variability and the chances of false-positives and false-negatives.^{28, 29} Some of these ideas were incorporated by adding costs for additional baseline and confirmatory VF tests, but essentially the model outcomes as presented here indicate the expected health outcomes when progression is discovered a half year earlier at the extra cost of one VF test per year, or one year later with the savings of half a VF test per year. Compared to 'usual care' a high VF test frequency was expected to cost an additional € 173,486 per QALY gained, which is considerably higher than the

acceptability thresholds mentioned earlier. This outcome was confirmed in the PSA where only 14% of ICERs was below € 80,000/QALY, and only 3% was below € 50,000/QALY. On the other hand, a low VF test frequency resulted in cost savings but lower health outcomes at a ratio of € 21,516 per QALY lost. In theory, a less effective strategy can be considered cost-effective when the compensation in terms of savings is large enough, i.e. larger than the acceptability threshold value (willingness-to-accept). If this willingness-to-accept (WTA) threshold were equal to the willingness-to-pay (WTP) threshold, the ICER of € 21,516 would probably be too low. Moreover, it is likely that the WTA threshold is much larger than the WTP threshold, or even that decision makers are not willing to accept any health loss no matter the monetary compensation.^{30, 31} Therefore it seems that annual VF testing was the most cost-effective approach.

The cost-effectiveness analyses in this paper were based on the Dutch situation. When the results are transferred to other jurisdictions, one has to consider a number of factors, such as differences in clinical practice, cost prices and the appropriate perspective.^{32, 33} This paper reports the results from a societal perspective, but many countries also employ the healthcare perspective.³⁴ The latter would differ from the outcomes reported here by exclusion of the costs for informal care, low-vision services and aids, transport and production losses. A break-down of the incremental cost per category is provided in the appendix.

The model outcomes are a direct result of the model itself, and must therefore be interpreted in the context of the uncertainties that surround the model's structure and parameter estimates. We have based our model and the parameter estimates on published literature as much as possible. We assessed the impact of remaining uncertainties on the outcomes with univariate structural sensitivity analyses (Table 4) and with the probabilistic analyses. The first univariate sensitivity analysis (A) modeled only the worse eye while the other eye was presumably unaffected. The outcomes in this scenario may be regarded as the expected cost-effectiveness of the treatment strategies in patients with an asymmetric course of glaucoma, whereas the outcomes of the base case scenario represent patient with two symmetrically affected eyes. The cost-effectiveness of a treatment strategy in any scenario with two differently affected eyes can therefore be expected to lie between the reported outcomes. In the second univariate analysis (B) we challenged the linear deterioration of MD in time. Although short-term data in untreated patients indicate a linear MD decline, there are no data in untreated POAG patients to confirm that MD continues to decline linearly. A linear deterioration of visual field has been observed in treated patients, but these patients were likely to receive more treatment and therefore have lower IOP levels with increasing disease

severity.³⁵⁻³⁸ If a linear decrease of MD in time is observed, knowing that IOP may have decreased simultaneously, we must consider that the actual MD decrease *had the IOP remained the same*, would have increased in time. Indeed, the EMGT investigators found more existing visual field at baseline to be associated with faster glaucomatous progression.³⁹ We have operationalized this in the model by introducing a positive relationship between visual field damage and progression speed (see appendix). The outcomes of the adjusted model showed that the direction of the conclusions were similar to the base case analyses (Table 4). Whether or not existing visual field damage is indeed a prognostic factor for progression remains inconclusive in current literature.^{40, 41}

In the base case model we assumed that the degree of utility loss associated with a worsening in MD was equal over all ranges of MD. However, in a recent study we have found that the impact of visual field deterioration may be larger in patients with more advanced disease.¹⁶ When we adjusted the coefficients for utility loss accordingly in the model (C), the incremental QALYs moved closer to zero in all analyses (Table 4). It is not unlikely that patients with early glaucoma are not as affected in their utility by a change in MD as patients with advanced glaucoma, because early glaucomatous loss often occurs without notice. Evidence on this issue in literature is limited, but two authors have reported similar observations with EQ-5D utilities.^{42, 43}

The costs associated with care for visually impaired and blind patients had a considerable impact on the incremental costs. Uncertainty surrounding the magnitude of such costs was assessed in the probabilistic sensitivity analyses and was shown not to affect the overall direction of the base-case outcomes. However, there is not only uncertainty about the magnitude of the costs but also about the moment such costs are incurred. In our base case model we used a gradual increase of resource consumption with deteriorating visual fields based on our own observational research. However, in previous cost-effectiveness studies in glaucoma, costs associated with blindness have been included only when a patient was completely blind. We have repeated our analyses with that assumption (Table 4, D). The absolute values for incremental costs and effects were different from the base case model, but the conclusions drawn from them would not change if ICER's below € 35,000/QALY gained are acceptable and QALY loss is not acceptable. In addition, there may be a limited amount of evidence on the subject but it seems unlikely that poor vision would only incur costs when a patient reaches a stage of legal blindness and not in all preceding stages of impaired vision.

ANCOVA indicated a modest impact of the value of the 'safe IOP' on incremental costs and effects. However, alternative values for 'safe IOP' within a reasonable range of the base case estimate did not lead to different directions of the outcomes in the PSA's. It is unknown from literature whether something like a 'safe IOP' actually

exists, although some authors report that the rate of glaucomatous progression might decrease to near zero if the intra-ocular pressure is low enough.^{44, 45} With the univariate sensitivity analysis (E) we showed that the direction of the base case outcomes did not change when the threshold value for the safe IOP was removed from the model.

In addition to the points above, there are additional aspects of the model structure that were not explicitly tested in sensitivity analyses, but that one must keep in mind with regard to the model results. First: we did not take into account any effect of cataract extraction on the intraocular pressure. Although the degree and duration of IOP reduction due to cataract surgery in patients with primary open-angle glaucoma is inconsistent in literature, reviews indicate that cataract surgery may indeed have a modest effect on IOP in primary-open angle glaucoma.^{46, 47} Had we accounted for this effect, it would have lead to slightly better outcomes for the strategy with immediate low target pressure strategies (as it had more cataract extractions), and therefore not have changed the direction of the outcomes. Second: we did not explicitly account for non-compliance and non-persistence to pressure-lowering medication. However, it should be realized that non-compliance was in fact included in the model implicitly. After all, we have derived estimates for the distribution of drug effectiveness and disease progression from clinical studies, and although compliance in a clinical trial will be higher than in real life, it is unlikely that trial patients have been perfectly compliant. In fact, an observational study on real-life drug-lowering effectiveness found averages that were comparable to those found in systematic reviews of clinical studies, indicating that non-compliance in clinical studies may be comparable to that in clinical practice.⁴⁸ An important draw-back of the implicit account of non-compliance, is that it cannot be manipulated in the model. This means that we could not, for example, define a positive relationship between the frequency of visual field testing and compliance, whereas it is not unlikely that such a relationship exists.

The criterion for progression in our model was an absolute loss of 2 dB. In clinical practice, factors such as the length of time in which the loss occurred, the life-expectancy of the patient and the sensitivity and specificity of the measurement method play a role in the assessment of progression and the need to change treatment. In the model we have chosen to keep the assessment of progression uncomplicated, because although it is likely that absolute outcomes of the treatment strategies change when the assessment of progression is modeled in more detail, the incremental cost-effectiveness ratios probably will not. The latter was also indicated in the ANCOVA's of the PSA results, where variation in the progression criterion did not account for any of the variation in incremental outcomes.

Taking a modeling approach is a way to explicitly aggregate the current understanding of glaucoma progression and the effectiveness of treatment, and to inform decisions about treatment strategies in the presence of uncertainty.

In this paper we have investigated the cost-effectiveness of glaucoma treatment and interpreted the results from an efficiency point of view. However, cost-effectiveness is not the only factor to be considered in decisions regarding the organization and funding of health care. For example, research has shown that decision makers also take account of factors like disease severity, individual health gain and constraints in the overall budget or logistical possibilities.⁴⁹ Still, from a cost-effectiveness point of view the results presented in this paper indicate that current care for glaucoma is very cost-effective, and that the efficiency of care could be further improved by aiming for the lowest medically achievable and tolerable intraocular pressure directly at treatment initiation. The implication of this strategy for clinical practice is that there is less need for titration towards a conservative target pressure, and therefore less need for intensive monitoring to check if the target pressure should be lowered. However, it also implies that surgery may be indicated at an earlier stage and hence more patients will need to be operated. If this consequence meets with resistance in practice, it will be important to explicate this resistance and check its validity. For example, there may be shortage of staff and facilities that make more surgery a daunting prospect. However, there may also be evidence of surgery risks or patient discomfort that was not sufficiently accounted for in this model. In that case, the model could be updated and rerun. The efficiency of the treatment strategy with a low initial target pressure has some implications for further cost-effectiveness research too. As long as a stepwise reduction in target pressure is used in the comparator strategy, any alternative strategy that leads to a lower target IOP faster, is likely to be the most cost-effective. Indeed, a treatment component like monitoring for progression loses its relevance in a strategy with a low initial target IOP, because its outcome does not affect adjustment of the target pressure anymore. As a consequence, an issue like the comparative accuracy of different monitoring techniques loses its relevance too. Therefore, the feasibility of implementing a low initial target IOP for all POAG patients should be investigated as a real possibility, and the outcomes of this investigation must be considered in future cost-effectiveness analyses of glaucoma treatment.

References

- McKinnon S, Goldberg L, Peeples P, Walt J, Bramley T. Current management of glaucoma and the need for complete therapy. *Am J Manag Care* 2008; 14:S20-S27.
- American Academy of Ophthalmology Glaucoma Panel. Primary open-angle glaucoma. Preferred practice pattern. San Francisco: American Academy of Ophthalmology, 2005.
- Rein D, Wittenborn J, Lee P, Wirth K, Sorensen S, Hoerger T, Saaddine J. The cost-effectiveness of routine office-based identification and subsequent medical treatment of primary open-angle glaucoma in the United States. *Ophthalmology* 2009; 116:823-832.
- European Glaucoma Society. Terminology and guidelines for glaucoma (third edition). Dogma: Savona, Italy; 2008.
- Walker W, Harremoës P, Rotmans J, Van der Sluijs J, Van Asselt M, Janssen P, Krayen von Krauss M. Defining uncertainty: A conceptual basis for uncertainty management in model-based decision support. *Integrated Assessment* 2003; 4:5-17.
- Groot Koerkamp B, Weinstein MC, Stijnen T, Heijnenbroek Kal MH, Hunink MG. Uncertainty and patient heterogeneity in medical decision models. *Med Decis Making* 2010; 30:194-205.
- Rodenburg-Van Dielen H. Guidelines for pharmacoeconomic research (version 2006). Diemen, The Netherlands: Health Insurance Board, 2005.
- Van Gestel A, Severens J, Webers C, Beckers H, Janssen N, Schouten J. Modeling complex treatment strategies: construction and validation of a discrete event simulation model for glaucoma. *Value Health* 2010; 13:358-367.
- Stahl JE. Modelling methods for pharmacoeconomics and health technology assessment: an overview and guide. *Pharmacoeconomics* 2008; 26:131-148.
- Heijl A, Leske C, Bengtsson B, Hyman L, Bengtsson B, Hussein M, for the Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression; results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002; 120:1268-1279.
- Lichter P, Musch D, Gillespie B, Guire K, Janz N, Wren P, Mills R, Group TC. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001; 108:1943-1953.
- European Glaucoma Society. Terminology and guidelines for glaucoma (second edition). Dogma: Savona, Italy; 2003.
- Poos M, Gijzen R. Visual disorders by age and sex [Gezichtsstoornissen naar leeftijd en geslacht]. National Compass of Public Health; Explorations of the future [Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid]. Bilthoven, The Netherlands: RIVM, 2010.
- Burr J, Azuara-Blanco A, Avenell A. Medical versus surgical interventions for open angle glaucoma. *The Cochrane Database of Systematic Reviews* 2004; Issue 2. Art.No.: CD004399.pub004392. DOI: 004310.001002/14651858. CD14004399.pub14651852.
- Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. *J Health Econ* 1995; 14:171-189.
- Van Gestel A, Webers C, Beckers H, Van Dongen C, Severens J, Hendrikse F, Schouten J. The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye* 2010; 24:1759-1769.
- Mangione C, Lee P, Gutierrez P, Spritzer K, Berry S, Hays R, for the National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* 2001; 119:1050-1058.
- Van der Sterre G, Van de Graaf E, Verezen C, Meulendijks C, Schouten J, Saxena R, Polling J, Van Rijn L, Hoyng C, Essink-Bot M, Simonsz H. National Eye Institute Visual Functioning Questionnaire-25: Dutch consensus translation (VFQ-25/NL). Rotterdam: Erasmus Medical Center Rotterdam, department of Ophthalmology, 2001.
- Torrance GW, Furlong W, Feeny D, Boyle M. Multi-attribute preference functions. *Health Utilities Index. Pharmacoeconomics* 1995; 7:503-520.

20. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation, First ed. Oxford University Press: Oxford, UK; 2006.
21. Gafni A, Birch S. Incremental cost-effectiveness ratios (ICERs): the silence of the lambda. *Soc Sci Med* 2006; 62:2091-2100.
22. Raad voor Volksgezondheid en Zorg (Council for Public Health and Health Care). Zinnige en duurzame zorg (Sensible and sustainable care). Zoetermeer: RVZ, 2006.
23. Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for cost-effectiveness in health care Health Technology Assessment (HTA). KCE reports 100C (D/2008/10273/96). Brussels, Belgium: Belgian Health Care Knowledge Centre (KCE), 2008.
24. Traverso CE, Walt JG, Kelly SP, Hommer AH, Bron AM, Denis P, Nordmann JP, Renard JP, Bayer A, Grehn F, Pfeiffer N, Cedrone C, Gandolfi S, Orzalesi N, Nucci C, Rossetti L, Azuara Blanco A, Bagnis A, Hitchings R, Salmon JF, Bricola G, Buchholz PM, Kotak SV, Katz LM, Siegartel LR, Doyle JJ. Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilisation in Europe. *Br J Ophthalmol* 2005; 89:1245-1249.
25. Lee PP, Walt JG, Doyle JJ, Kotak SV, Evans SJ, Budenz DL, Chen PP, Coleman AL, Feldman RM, Jampel HD, Katz LJ, Mills RP, Myers JS, Noecker RJ, Piltz-Seymour JR, Ritch RR, Schacknow PN, Serle JB, Trick GL. A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. *Arch Ophthalmol* 2006; 124:12-19.
26. Peeters A, Schouten JS, Severens JL, Hendrikse F, Prins MH, Webers CA. Latanoprost versus timolol as first choice therapy in patients with ocular hypertension; A cost-effectiveness analysis. *Acta Ophthalmol* 2010; . Epub ahead of print. PMID: 20731623.
27. Felli JC, Hazen GB. Sensitivity analysis and the expected value of perfect information. *Med Decis Making* 1998; 18:95-109.
28. Jansonius N. Towards an optimal perimetric strategy for progression detection in glaucoma: from fixed-space to adaptive inter-test intervals. *Graefes Arch Clin Exp Ophthalmol* 2006; 244:390-393.
29. Chauhan BC, Garway Heath DF, Goni FJ, Rossetti L, Bengtsson B, Viswanathan AC, Heijl A. Practical recommendations for measuring rates of visual field change in glaucoma. *Br J Ophthalmol* 2008; 92:569-573.
30. O'Brien B, Gertsen K, Willan A, Faulkner L. Is there a kink in consumer's threshold value for cost-effectiveness in health care? *Health Econ* 2002; 11:175-180.
31. Severens J, Brunenberg D, Fenwick E, O'Brien B, Joore M. Cost-effectiveness acceptability curves and a reluctance to lose. *Pharmacoeconomics* 2005; 23:1207-1214.
32. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, Reed SD, Rutten F, Sculpher M, Severens J. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. *Value Health* 2009; 12:409-418.
33. Goeree R, Burke N, O'Reilly D, Manca A, Blackhouse G, Tarride JE. Transferability of economic evaluations: approaches and factors to consider when using results from one geographic area for another. *Curr Med Res Opin* 2007; 23:671-682.
34. Pharmacoeconomic guidelines around the world. Available at: <http://www.ispor.org/PEguidelines/index.asp>. Accessed: 10-06-2011
35. Heijl A, Bengtsson B, Hyman L, Leske MC. Natural history of open-angle glaucoma. *Ophthalmology* 2009; 116:2271-2276.
36. Bengtsson B, Patella VM, Heijl A. Prediction of glaucomatous visual field loss by extrapolation of linear trends. *Arch Ophthalmol* 2009; 127:1610-1615.
37. Kwon Y, Kim C, Zimmerman B, Alward W, Hayreh S. Rate of visual field loss and long-term visual outcome in primary open-angle glaucoma. *Am J Ophthalmol* 2001; 132:47-56.
38. Mikelberg FS, Schulzer M, Drance SM, Lau W. The rate of progression of scotomas in glaucoma. *Am J Ophthalmol* 1986; 101:1-6.
39. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of long-term progression in the Early Manifest Glaucoma Trial. *Ophthalmology* 2007; 114:1965-1972.
40. Nouri-Mahdavi K, Hoffman D, Coleman A, Liu G, Li G, Gaasterland D, Caprioli J. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology* 2004; 111:1627-1635.
41. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Surv Ophthalmol* 2008; 53 Suppl1:S3-10.
42. Kobelt G, Jonsson B, Bergstrom A, Chen E, Linden C, Alm A. Cost-effectiveness analysis in glaucoma: what drives utility? Results from a pilot study in Sweden. *Acta Ophthalmol Scand* 2006; 84:363-371.
43. Burr J, Kilonzo M, Vale L, Ryan M. Developing a preference-based glaucoma utility index using a discrete choice experiment. *Optom Vis Sci* 2007; 84:797-808.
44. The AGIS investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000; 130:429-440.
45. Shirakashi M, Iwata K, Sawaguchi S, Abe H, Nanba K. Intraocular pressure-dependent progression of visual field loss in advanced primary open-angle glaucoma: a 15-year follow-up. *Ophthalmologica* 1993; 207:1-5.
46. Vizzeri G, Weinreb RN. Cataract surgery and glaucoma. *Curr Opin Ophthalmol* 2010; 21:20-24.
47. Shrivastava A, Singh K. The effect of cataract extraction on intraocular pressure. *Curr Opin Ophthalmol* 2010; 21:118-122.
48. van der Valk R, Webers CA, Hendrikse F, de Vogel SC, Prins MH, Schouten JS. Predicting intraocular pressure change before initiating therapy: timolol versus latanoprost. *Acta Ophthalmol* 2008; 86:415-418.
49. Koopmanschap M, Stolk E, Koolman X. Dear policy maker: Have you made up your mind? A discrete choice experiment among policy makers and other health professionals. *Int J Technol Assess Health Care* 2010; 26:198-204.

**The long term outcomes of four
alternative treatment strategies for
primary open-angle glaucoma**

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Introduction

In the manuscript “The long term outcomes of four alternative treatment strategies for primary open-angle glaucoma” we have reported the forecasted long-term health and cost outcomes of four different treatment strategies for glaucoma. The data underlying the forecasts were generated with a discrete event simulation model that simulated the lifelong treatment and disease progression of individual glaucoma patients. The construction and validation of the model have been reported elsewhere.¹ In this appendix we present an overview of the most important structural relationships, the base-case values of the main parameters in the model, the parameters of the patient-level distributions of patient attributes, the parameters of the population-level distributions used in the probabilistic sensitivity analysis, and a collection of additional results not reported in the main article.

Discrete Event Simulation model for glaucoma

Discrete event simulation

The typical elements of a discrete event simulation (DES) model are entities, attributes, events, relationships and outcomes. In order to simulate glaucoma and its treatment with a DES model, we have conceptualized knowledge of the underlying pathogenetic and therapeutic processes into these DES model elements. This paragraph provides some information on the DES model elements themselves, while the next paragraphs explain how these elements were combined to create a glaucoma disease progression model.

The entities in the model consisted only of individual patients (further referred to in the masculine form). Attributes are patient-level characteristics that pertain to the individual patient or to his better eye. Attributes are either fixed throughout the simulation (e.g. sex), or change in time (e.g. age). Relevant moments in time are represented by events, and at the occurrence of an event the attributes of the entity are reevaluated and (if needs be) adjusted. Relationships are the model elements that link entities, attributes, events and outcomes together with mathematical and/or logical terms. Outcomes are the model element that aggregate information needed to draw conclusions from the simulations. An outcome is expressed by a relationship involving any of the model elements or a combination of elements. Examples of outcomes are 1) the average lifetime IOP, which is an outcome based on an attribute, 2) the occurrence of conversion, which is an outcome based on an event, 3) the age at conversion, which is an outcome based on both an attribute and an event, and 4) discounted lifetime costs, which is an outcome based on attributes (e.g. medication), events (e.g. visit), discount rates and time.

Modeling glaucomatous disease progression

We have conceptualized glaucoma and its treatment from a clinical perspective (Figure 1), and have therefore not simulated the actual pathogenetic processes themselves, but rather how they manifest in clinical practice. In the full model we discerned two disease stadia: 1) ocular hypertension (OHT), which is characterized by an elevated intra-ocular pressure (IOP) without signs of retinal nerve fiber loss, and 2) primary open-angle glaucoma (POAG) which is characterized by a level of nerve fiber loss that causes optic nerve cupping and/or visual field loss. The transition from OHT to POAG was marked as 'conversion', and continuation of nerve fiber loss was termed 'progression'. In a natural disease progression (Figure 1A), a patient with OHT runs the risk of converting to POAG and progressing to blindness at a certain point in his life. A high intra-ocular pressure is the most important adaptable risk factor for both conversion and glaucomatous progression. The aim of pressure-lowering treatment is to prevent conversion and reduce the speed of progression to such a degree that the patient will not suffer visual disability from glaucoma during his lifetime.^{2,3} The main article "The long term outcomes of four alternative treatment strategies for primary open-angle glaucoma" only focused on glaucoma patients, so details about the model structure concerning treatment of OHT and mimicking the occurrence of conversion are not discussed in the remainder of this appendix.

Figure 1 Conceptualization of disease progression for DES model.

A) Natural course of disease. **B)** Disease progression under treatment: conversion is delayed, progression rate is reduced.

Figure 1 Continued.

A patient's conversion was modeled as an event, at which the attribute representing disease stadium changed from OHT to POAG. Visual field damage was modeled as a proxy for glaucoma severity and was expressed as Mean Deviation ranging from 0 (no damage) to -35 (severe damage) decibel (dB).⁴ The endpoint of glaucomatous progression is blindness. The clinical definition of blindness is actually based on the visual acuity and the restriction of the visual field to the central degrees rather than the MD, but these attributes were not simulated in the model. Therefore, we have made the assumption in the model that an MD value below -25 dB is comparable to blindness. Progression was modeled in each simulated patient by means of an individually determined speed of MD loss (dB/month) that changed with changes in the patient's IOP level.

Event-based time progression

Events in a discrete event simulation (DES) model represent relevant moments in time. At an event the attributes of the entity are reevaluated and (if needs be) adjusted (Figure 2). In the model, time-progression is event-based, which means that the model 'jumps' from one event to the next. The timing of future events may be conditional upon the new values of the attributes. For example, the time to the next scheduled visit is shorter after a switch in medication than when the same medication is continued.

Figure 2 Event-based time progression in discrete event simulation model and updating of attributes at each event.

Events and attributes

The events occurring in the model were: visits to the ophthalmologist, conversion from OHT to POAG, development of cataract, and death.

In the model we have used a large number of attributes to simulate the natural course of disease and the treated course of disease. Some attributes do not represent any physical characteristic of the patient but rather aid the model to keep track of the disease- or treatment history. An (non-exhaustive) overview of the main attributes used in the model is provided in Table 1.

Treatment

Scheme for treatment decisions

The choice for the various treatment options in the model is made based on the two flow-charts presented in Figure 3 (between treatment types) and Figure 4 (within the medication blocks shown in Figure 3).

Table 1 Overview of the most important attributes and relationships in the model.

Attributes	Values	Relationships	Updated at all events?
Age	Continuous number (>0)	$\text{Age} = F(\text{Age}_0, \text{time})$	Yes
Gender	Categorical: Male or female		No
IOP	Continuous number (>0)	$\text{IOP}_u = F(\text{IOP}_0, \text{surgery}, \text{time})$ $\text{IOP}_i = F(\text{IOP}_u, \text{Effect}(\%))$	Yes
Risk profile for progression	Number on a logarithmic scale		No
MD	Continuous number (<0)	$\text{MD} = F(\text{MD}_0, \text{MDR}, \text{time})$	Yes
MDR	Continuous number (>0)	$\text{MDR} = F(\text{MDR}_0, \text{IOP})$	Yes
Treatment type	Medication, LT, TE, implant		Only at 'visit'
Medication	Categorical: β -blocker, prostaglandin analogue, carbonic-anhydrase inhibitor (CAI), α -adrenergic agonist, or a combination of two or three of these.		Only at 'visit'
Effect (%)	Continuous number	$\text{Effect} = F(\text{medication}, \text{Effect}_0)$	Yes
Side-effects	Categorical: Yes or no	$\text{Side-effect} = F(\text{medication}, \text{Side-Effect}_0)$	Yes
Time-to-next-event	Continuous number or discrete number (visit)	$\text{Time-to-death} = F(\text{Age}, \text{gender})$ $\text{Time-to-conversion} = F(\text{IOP}, \text{Age}, \text{Risk}_0)$ $\text{Time-to-visit} = F(\text{treatment type}, \text{visit number})$	Yes
Target IOP	Discrete number	$\text{IOP}_{\text{target}} = F(\text{disease status}, \text{history of progression})$	Yes

$_0$ = baseline; IOP_u = IOP without medication or LT effect; IOP_i = current intraocular pressure; $F(x)$ = function of x ; MD = Mean Deviation; MDR = Mean Deviation Rate; TE = trabeculectomy; LT = laser trabeculoplasty.

Table 2 Example of a look-up table for target IOP depending on disease status and the history of glaucomatous progression.

Disease status	IOP _{target}
OHT	24 mmHg
POAG, without observed progression	21 mmHg
POAG, and one observed progression	18 mmHg
POAG, and two or more observed progressions	15 mmHg

IOP_{target} = target Intraocular Pressure; OHT= Ocular Hypertension; POAG= primary open-angle glaucoma

Treatment effectiveness

The effectiveness of each medication and surgical procedure in terms of pressure lowering (%) and the post-surgery IOP level respectively, was established for each simulated patient separately. To do so, the model made a random draw from population distributions that were defined on the basis of observations in clinical trials. Also the patient's proneness to side-effects and the presence of contra-indications for each of the medications were randomly drawn. Table 3 lists a summary of the parameters defining the distributions of treatment effectiveness in the patient population, and their primary sources. A detailed description of the derivation of these effectiveness estimates, as well as the estimated effectiveness of combination therapy, is provided elsewhere.¹ Table 4 shows an example of how the model randomly drew values for the effectiveness of each medication, LTP and surgery based on the distributions listed in Table 3 for eight consecutively simulated patients.

Briefly: Default estimates for drug effectiveness as monotherapy were derived from a meta-analysis of all commonly used glaucoma drugs in 2005.⁵ This meta-analysis included studies that compared pressure-lowering eye-drops monotherapy to placebo in POAG and/or OHT patients, and that used IOP as the primary endpoint of the study. A beta distribution was used to describe the medication effectiveness, because the beta distribution has the characteristics that it is limited to values between 0 and 1 (or in this case, 0 and 100% pressure lowering).

The prevalence of side-effects with each of the medications in the model was based on the results of the DURING study.⁶ In this study, previously untreated patients starting pressure lowering medication, and patients that switched medication, were followed for the next three visits. The estimate of the incidence of side-effects

Table 3 Base-case values of effectiveness parameters and their sources.

Parameter	Base-case value Medication Mean effect / Incidence of side-effects ^{a)}	Distribution	Source
Medication			
β-blocker	26 % / 8%	Beta	5, 6
Prostaglandin analogue	29.5 % / 8%	Beta	5, 6
Carbonic-anhydrase inhibitor	19.5 % / 14%	Beta	5, 6
α ₂ -adrenergic agonist	21 % / 23%	Beta	5, 6
Mean effect LT	34 %	Beta	7-12
Mean IOP after surgery (TE)	12.5 mmHg	Gamma	13-17
Mean IOP after surgery (tube implant)	15.0 mmHg	Gamma	14, 17, 18

IOP= Intraocular Pressure; MDR= Mean Deviation Rate; LT= Laser Trabeculoplasty; TE= Trabeculectomy.

^{a)} Side-effects that lead to a treatment switch.

was based on the proportion of patients on a certain treatment that stopped the medication due to side-effects (as judged by the ophthalmologist) within one or two follow-up visits. The effect of laser trabeculoplasty, trabeculectomy and tube implantation were based on literature reviews that we had conducted specifically to populate this model.

The effect of medication and laser treatment (LT) were simulated as a relative pressure lowering (%) of the IOP. In contrast, the effect of surgery was simulated by resetting the IOP altogether. Calculating the actual IOP under treatment was regulated by two sets of attributes. The first calculated an IOP (IOP_u), that indicated how high the IOP would be in the absence of medication or LT treatment. If a patient has not undergone surgery, the IOP_u was similar to the baseline IOP with a small annual increase (0.5%). When surgery occurred, IOP_u was reset. The second set of attributes calculated the total pressure lowering effect (in %) of all currently prescribed medications and previously performed LT treatment that act upon the IOP_u. The combination of IOP_u and the total pressure lowering effect yielded the actual IOP of the patient (IOP_a).

The model accounted for a gradual and linear decline in the pressure lowering effect of LT in ten years. For example, if the relative pressure lowering effect of LT in

Table 4 Example of randomly drawn effectiveness values for eight simulated patients.

	Pressure lowering effect					Side effects				IOP after TE	IOP after implant
	BB	PA	CAI	α_2 -AA	LTP	BB	PA	CAI	α_2 -AA		
Patient 1	22%	28%	45%	29%	38%	No	No	Yes	No	12.7	13.8
Patient 2	30%	12%	10%	12%	37%	No	No	No	No	11.6	18.3
Patient 3	22%	31%	12%	20%	26%	Yes	No	No	No	12.9	15.4
Patient 4	33%	28%	10%	18%	39%	No	No	No	No	11.0	18.2
Patient 5	28%	38%	15%	15%	24%	No	Yes	No	No	11.6	13.8
Patient 6	31%	29%	23%	7%	31%	No	No	No	No	10.9	13.3
Patient 7	17%	31%	12%	26%	15%	No	No	No	No	12.4	9.9
Patient 8	20%	23%	5%	41%	37%	Yes	No	No	No	13.7	16.7

BB= β -blocker; PA= Prostaglandin analogue; CAI= Carbonic-anhydrase inhibitor;
 α_2 -AA= α_2 -adrenergic agonist

a particular patient was drawn at 30%, the patient's IOP was lowered by 30% in the first year after LT, by 27% in the second year after LT, by 24% in the third year after LT etc.

The model considered three possible responses to trabeculectomy:

- 1) the newly established IOP_u is maintained lifelong (never failure)
- 2) the IOP_u remains at the pre-surgical level (immediate failure)
- 3) the IOP_u gradually increases to the pre-surgical level in ten years (long term failure)

The reaction that was applicable to the simulated patient was established by a random draw from a discrete probability distribution with probabilities 0.40, 0.12 and 0.48 respectively. Therefore, the IOP after trabeculectomy in a simulated patient depended on the outcome of two random draws: 1) the type of response, and 2) the height of the IOP after surgery. The latter was only relevant if the type of response was 'never failure' or 'long term failure'. If the response type was 'immediate failure', the IOP level of the patient remained at the pre-surgical unmedicated level.

Criterion for progression in the model

The disease progression of POAG patients was modeled via the gradual decrease of MD in time. Whether or not a simulated patient experienced 'clinical progression' in the sense that it called for a treatment adjustment therefore depended on the definition of progression in any particular analysis. The observation of progression in a simulated patient could trigger adjustment of the target pressure may be adjusted, and a consequential treatment change.

In the model employed to generate the results described in the article "The long term outcomes of four alternative treatment strategies for primary open-angle glaucoma", an absolute MD decrease of 2 dB was set as the criterion for progression, irrespective of the time-frame and life-expectancy of the patient. The threshold of 2 dB was based on the literature reports by Wesselink *et al.* and Heijl *et al.*, where POAG patients with confirmed progression had an average MD decrease of 2.4 dB and 2.3 dB respectively.^{9, 19} In real clinical practice the establishment of progression is a process that involves multiple measurements and clinical judgment. It is not only important to establish objectively whether the optic nerve or the visual field has worsened, but also whether this worsening calls for a treatment change. Not only the absolute change may play a role, but also the time-frame in which this absolute change was observed relative to the life-expectancy of the patient. The criterion for progression in this base case model may therefore be considered rather stringent compared to clinical practice.

It is important to note that the base case model did not directly take inter-test variability of visual field measurements into account. The modeled MD value represented the 'real' MD value, and it was assumed that the ophthalmologist can measure this value with a 100% sensitivity and specificity. In that context, the progression criterion of 2 dB defines the threshold for the absolute reduction in MD that will, in the model, call for a treatment change, given that it has been established that the real MD decrease is indeed more than 2 dB. The 2 dB threshold should not be confused with the threshold that will in clinical practice trigger a suspicion of progression and call for extra visual field measurements to confirm or invalidate this suspicion.¹⁹ However, the model added the costs of an extra visual field measurement to a visit in which progression is observed, to account for of the extra visual field measurement that would be performed in clinical practice to confirm a suspected progression.

In the model, the absolute MD decrease was calculated as the difference in the measured MD relative to either the first MD measurement in the model, or the MD value at the moment the previous progression was observed during a visit event.

Visits and visual field measurements

Visits

We used a lookup table in the model to determine the time to the next scheduled visit (Table 5). The length of the time interval between two visits depended on two factors: 1) whether or not there had been a treatment change, and 2) the type of new treatment. The number of visits since that last treatment change is counted in the leftmost column of Table 5, while the new treatments are listed in the top row. For example, a patient that is not treated at all will visit the ophthalmologist every 1000 months (i.e. never). In treated patients the first visit after a change in medication will take place 3 months after the change, but subsequent visits occur every 6 months as long as the treatment remains unaltered. After LT or surgery a series of short visit intervals follows to be able to monitor the patient closely. The visit frequency gradually returns back to the normal interval length.

Table 5 Example of randomly drawn effectiveness values for eight simulated patients.

Visit number	No treatment	Medication	LT	Surgery
1	36 months	3 months	1 week	3 days
2	36 months	6 months	5 weeks	3 days
3	36 months	6 months	6 months	3 days
4	36 months	6 months	6 months	3 days
5	36 months	6 months	6 months	1 week
6	36 months	6 months	6 months	1 week
7	36 months	6 months	6 months	1 week
8	36 months	6 months	6 months	2 weeks
9	36 months	6 months	6 months	2 weeks
10	36 months	6 months	6 months	1 month
> 10	36 months	6 months	6 months	6 months

Visual field measurements

The model recalculated the MD value of a simulated patient at each event, in order to simulate disease progression and calculate utilities. However, it used a second MD attribute to simulate treatment decisions during the visit events. This second MD attribute represented the *MD as measured*. The value of the MD as measured can only be recalculated during a visit event if the occurrence of a visual field measurement was simulated. Whether or not a visual field measurement was

performed during a visit event, was controlled by a fixed attribute that defined the normal interval between visual field measurements in patients. For example, if the treatment strategy used a visual field measurement frequency of twice a year, the interval was 6 months. If the frequency of visual field measurements was once every two years, the interval was set at 2 years.

The model tracked the occurrence of visual field measurements (each simulation by default starts with a visit in which the visual field is measured), and checked at each visit whether the time since the previous measurement was longer than the set interval. If this was the case, a visual field measurement was modeled to occur during the visit.

Summary of cost estimates

Table 6 presents a summary of resource costs used in the model and their primary sources. A detailed description of the derivation of these parameter values is provided elsewhere.¹ The cost year was 2006. Cost prices from sources earlier than 2006 were indexed with the health-care specific consumer price index.²⁰

Parameters for probabilistic sensitivity analysis

Table 7 contains an overview of the parameter distributions reflecting the uncertainty surrounding the population-level parameters, as used in the probabilistic sensitivity analyses.

Populations in this study

The simulated population in this study represented POAG patients at their first encounter with an ophthalmologist. The following paragraphs describe the distributions that were used to sample the initial values of the main patient level attributes for each simulated patient, and a short description of their sources.

Initial age

The age distribution of the average population of POAG patients was based on the study population in the Early Manifest Glaucoma Trial.⁹ The average age was 68 ± 5 years and the distribution was slightly skewed to the left. In the disease progression model we used a normal distribution with average 68 and standard deviation 5 (Figure 5).

Table 6 Costs (in 2006 Euro's) associated with attributes and events in the simulation model.

Resource	Costs	Source
β-blocker	€ 6.00/month	21, 22
Prostaglandin analogue	€ 20.20/month	21, 22
Carbonic-anhydrase inhibitor	€ 13.90/ month	21, 22
α ₂ -adrenergic agonist	€ 14.00/month	21, 22
Ophthalmologist consultation	€ 65	23, 24
Visual field measurement	€ 133 (€ 266 in case of progression)	23, 24
LT	€ 75	24, 25
Trabeculectomy	€ 1,214 (+ 1 ophthalmologist consultation)	23, 24
Tube implantation	€ 1,714 (+ 1 ophthalmologist consultation)	23, 24
Cataract surgery	€ 1,400	23, HA
Paid household help	€ 37 / month (if MD < -10 dB)	1, 23
Homecare nursing	€ 159 / month (if MD < -10 dB)	1, 23
Family help	€ 56 / month (if MD < -15 dB)	1, 23
Homecare grooming	€ 103 / month (if MD < -15 dB)	1, 23
Retirement home	€ 80 / month (if MD < -20 dB)	1, 23
Nursing home	€ 130 / month (if MD < -20 dB)	1, 23
Informal care	€ 20 / month (if MD < -5dB)	1, 23
Low-vision services	€ 1-5 /month	1, 26
Transport to ophthalmologist	€ 4.90 / visit (if MD > -10 dB) € 8.90 / visit (if MD < -10 dB)	1, 23
Transport to pharmacy	€ 1.50 / visit (if MD > -10 dB) € 2.60 / visit (if MD < -10 dB)	1, 23
Low-vision aids	€ 325 (once) if MD moves below -15 dB	1, 27
Productivity loss	€ 3,029 (once) if MD moves below -15 dB while the patients is younger than 65 years.*	1, 24

Costs for LT (Laser Trabeculoplasty) and surgery were doubled to account for the same procedure in the other (i.e. worse) eye. Costs for visual field measurement were doubled if progression was observed to account for a confirmatory test. Transport costs to the pharmacy were incurred once in three months if the patient received medication, and transport costs to the ophthalmologist/hospital were added for each visit and for each procedure (LT, surgery). *Friction costs. HA= Hospital Administration.

Figure 5 Histogram of initial age in simulated patients based on normal distribution with average 68 years, standard deviation 4 years.

Gender

The gender distribution of the average POAG population in the model was based on the EMGT population.⁹ In this population, 34% were men.

Initial IOP

The value of the initial IOP in the average (newly diagnosed) POAG population in the disease progression model was based on the IOP of the participants in the Early Manifest Glaucoma Trial (EMGT), the Collaborative Interventional Glaucoma Treatment Study (CIGTS), and the Groningen Longitudinal Glaucoma Study.^{9, 19, 28} In all three trials, new glaucoma patients were included. In the EMGT population the average intra-ocular pressure at baseline was 21 ± 4 mmHg, whereas the CIGTS population had an average intra-ocular pressure of 28 ± 6 at baseline.^{9, 28} The unselected POAG population (including normal tension glaucoma patients) in the Groningen longitudinal glaucoma study had a baseline IOP of 30.3 ± 9.5 mmHg. The differences were likely to be caused by the eligibility criteria of the trials: the EMGT excluded patients with an average IOP (in both eyes) higher than 30 mmHg, while the CIGTS excluded patients with an IOP lower than 20 mmHg. In the model, the baseline IOP in the POAG population was described by a normal distribution with mean 28 mmHg and standard deviation 3 mmHg, truncated on the left at 22 mmHg. The resulting distribution has an average of 29 ± 3 mmHg (Figure 6).

Table 7 Distributions representing uncertainty surrounding basecase (default) population parameter estimates in probabilistic sensitivity analysis.

Variable	Distribution	Mean	SD	Minimum	Maximum	Most likely (default)	Alpha	Beta
Timolol pressure lowering, monotherapy	Beta					0.27	511	1381
Latanoprost pressure lowering effect, monotherapy	Beta					0.30	589	1407
Dorzolamide pressure lowering effect, monotherapy	Beta					0.20	294	1213
Brimonidine pressure lowering effect, monotherapy	Beta					0.21	148	559
Pressure lowering after surgery	Triangular			1.5	2.5	2		
LT monotherapy	Beta					0.34	763	1480
LT added to medication	Triangular			0.12	0.34	0.18		
Incidence of timolol contraindications	Beta					0.10	123	1396
Side-effects with timolol	Beta					0.08	10	109
Side-effects with latanoprost	Beta					0.08	22	258
Side-effects with dorzolamide	Beta					0.14	2	12
Side-effects with brimonidine	Beta					0.23	5	17
IOP after TE	Normal	12.5	0.3			12.5		
IOP after tube implant	Normal	15	0.37			15		
Rate of visual field loss	Normal	0.028	0.0021			0.028		
Relative Risk of visual field loss rate by IOP (per mmHg higher)	Normal	1.13	0.03			1.13		
Progression criterion	Uniform	2	4			2		
Relative risk for cataract from trabeculectomy	Triangular			1.5	4.9	2.7		
Cost price Medications (factor)*	Triangular			0.75	1.25	1		
Costs Hospital (factor)*	Triangular			0.5	1.5	1		
Costs Care (factor)*	Triangular			0	2	1		
VFQ: coefficient for MD (per dB)	Normal	0.0155	0.0018	0				
VFQ: coefficient for side-effects	Normal	-0.097	0.017		0			
VFQ: coefficient for cataract	Normal	-0.092	0.043		0			
HUI: coefficient for MD (per dB)	Normal	0.010	0.0036	0				
HUI: coefficient for side-effects	Normal	-0.1	0.05		0			
HUI: coefficient for cataract	Normal	-0.059	0.074		0			
IOP below which no progression	Triangular			12	14	13		

*Factor indicates that all parameter estimates are multiplied by a factor in the probabilistic sensitivity analyses. In the base case model the factor is 1.

SD= standard deviation; LT= laser trabeculoplasty; IOP= intraocular pressure;

TE= trabeculectomy; VFQ= visual functioning questionnaire; MD= mean deviation; dB= decibel;

HUI= Health Utilities Index.

Figure 6 Histogram of initial IOP in simulated patients based on normal distribution with average 28 mmHg, standard deviation 3 mmHg, truncated at 22 mmHg.

MD at baseline

Similarly to the initial IOP, the value of the initial MD in the average (newly diagnosed) POAG population in the disease progression model was based on the IOP of the participants in the Early Manifest Glaucoma Trial (EMGT), the Collaborative Interventional Glaucoma Treatment Study (CIGTS), and the Groningen Longitudinal Glaucoma Study.^{9, 19, 28} The average baseline MD in the EMGT study was -4.7 ± 3.5 dB, in the CIGTS -5.5 ± 4.2 dB, and the distributions were skewed to the left. In the Groningen study, the baseline MD was -9.4 ± 7.6 . Considering that the distribution of MD values was skewed to the left, and the fact that the MD in a converted patient cannot take on a positive value, the population distribution of MD in the average population of POAG patients in the model was based on a (negative) gamma distribution. The distribution was truncated at -3 dB because patient with POAG at the first presentation to an ophthalmologist will generally not have MD values higher than -3 dB. The base case distribution (- Gamma (2, 2.5, truncated at 3 dB) has an average of -6.7 ± 3.4 dB and has 99% of its values between -3 and -17 dB (Figure 7).

Intrinsic MD deterioration

In the model, each individual patient was 'assigned' a reference rate of MD loss (MDR_{ref}) that represented the rate with which MD would decrease annually if IOP and additional risk were as in the referent POAG population (i.e. the population on which the estimates of the MDR_{ref} distribution was based). Literature does not

Figure 7 Histogram of initial Mean Deviation based on a negative gamma distribution with alpha 2 and beta 2.5, truncated at -3 dB.

provide data on the actual distribution of the rate of MD progression in the POAG population. For the sake of the model consistency, it was assumed that the decrease in the Mean Deviation in glaucoma patients is always larger than zero (i.e. there are no patients with an improving visual field). We therefore chose to use a gamma distribution, because values in the Gamma distribution are always higher than zero while the distribution is flexible in its shape through the shape parameter. The estimate of the distribution of progression rates in the POAG population was based on the treated patient population in a meta-analysis of five studies.^{9, 29-32} This meta-analysis is described in the appendix of an earlier report about the simulation model.¹ The average progression rate in the meta-analysis was 0.33 dB/year (which corresponds to 0.028 dB/month), and the standard deviation was derived from the individual studies and estimated at 0.63 dB/year (which corresponds to 0.053 dB/month). This average and standard deviation were used to estimate the parameters of the Gamma distribution, which were then fine-tuned to match survival curves for progression as observed in practice. The derivation of the final parameters for the Gamma distribution is described in more detail elsewhere.¹ In the model, the rate of visual field loss in an individual patient was drawn from a gamma distribution with an average of 0.34 dB/year (99% between 0.02 and 1.12 dB/year). The resulting distribution is drawn in Figure 8. The IOP and additional risk (relative risk) of the referent population were 15.5 mmHg and 1 (i.e. neutral) respectively.

Figure 8 Histogram of the individual deterioration of the Mean Deviation of simulated patients at IOP 15.5 mmHg, based on a gamma distribution with alpha 2 and beta 0.014.

Relative risks

Relative risk of IOP on rate of MD deterioration

Lowering intra-ocular pressure reduces the risk of progression in POAG patients.^{9, 28, 33} However, the magnitude of risk reduction per unit of pressure lowering has not been established in systematic reviews or meta-analyses. The only source for an estimate of the relative risk of the intra-ocular pressure on progression is the EMGT study.

The EMGT authors have performed a multivariate Cox proportional hazards models and found a hazard ratio of 1.13 (95% CI: 1.07; 1.19) per mmHg higher during a median follow-up of 6 years, corrected for age, baseline IOP, exfoliation, number of eligible eyes and MD.⁹ The reference value of the intra-ocular pressure in the model is the average value of the intra-ocular pressure in the treated EMGT group (15.5 mmHg).

The model recalculated the current loss in MD for a simulated patient throughout the simulation, using information on the MDR_{ref} , the relative risk of IOP on the MDR, and the current IOP of the patient according to the equation below.

For example: a male patient from a neutral risk patient population could, by random draw from the distribution, be assigned an MDR_{ref} of 0.3 dB/year. If this patient has an IOP of 15.5 mmHg, his MD would deteriorate by 0.3 dB per year. However, if his IOP were 14 mmHg, his MD would deteriorate by 0.25 dB per year, and if his IOP were 20 mmHg, his MD would deteriorate by 0.52 dB per year. If his IOP were lower than 13 mmHg, his MD would not deteriorate at all.

Calculation of current MDR of individual i

*When $IOP \geq IOP_{no\ progression}$

$$MDR = MDR_{ref} \cdot HR_i = MDR_{ref} \cdot e^{\ln(HR_{IOP}) \cdot (IOP_A - IOP_{av})} \cdot HR_{other}$$

*When $IOP < IOP_{no\ progression}$

$$MDR = 0$$

MDR = Mean Deviation Rate of individual i at current event

MDR_{ref} = Mean Deviation Rate of individual i if IOP and HR_{other} were as the average in the reference POAG population.

HR_i = Total hazard ratio of individual i at current event

HR_{IOP} = Hazard ratio of IOP (per 1 mmHg higher than average IOP in the reference POAG population)

HR_{other} = Hazard ratio of other risk factors (<progression risk>_A)

IOP_A = IOP at current event (mmHg)

IOP_{av} = average IOP (mmHg) in the reference POAG population (15.5 mmHg)

$IOP_{no\ progression}$ = IOP threshold for disease progression.

Derivation of relative risk of glaucomatous damage on rate of MD deterioration

The structure of the default model includes a constant rate of MD deterioration in the natural course of disease given that the IOP remains constant, and as a result the expected MD deterioration in untreated patients is linear in time. However, some studies have indicated that baseline visual field damage may be a prognostic factor for faster progression. This may be a horse racing effect, but it may also indicate a true relationship between existing damage and the speed of deterioration of the visual field. The impact of such a relationship on the results reported in the main paper were investigated in a structural sensitivity analysis, in which we wanted to assess 1) whether the model outcomes in terms of absolute incremental costs and effects would change, and 2) whether the conclusion drawn from the cost-effectiveness would change. If the answer to this latter question would be yes, we would want to know that the assumption made in the sensitivity analysis is plausible. When it's not, we still don't know if the assumption of a linear MD decrease in time will relevantly impact the results of the cost-effectiveness analyses. So we needed

to design a plausible non-linear relationship between MD and time in the natural course of disease.

In the basecase model, the rate of MD loss is affected by IOP. In the sensitivity analysis, the rate of MD loss in time is not only affected by IOP, but also by MD.

Basecase model:

$$MDR = MDR_{ref} \cdot HR_i = MDR_{ref} \cdot HR_{IOP} e^{((IOP)_A - IOP_{av})} \cdot HR_{other}$$

Sensitivity analysis model:

$$MDR = MDR_{ref} \cdot HR_i = MDR_{ref} \cdot HR_{IOP} e^{((IOP)_A - IOP_{av})} \cdot HR_{MD}^{|MD|} \cdot HR_{other}$$

The problem is that we cannot readily quantify HR_{MD} because there are no reports in literature from which it can be derived. Therefore, we have collected information from the Early Manifest Glaucoma Trial (because the reported results from that trial included the observed changes in MD over time), and mimicked the relationships described above.⁹

From the EMGT data we derived the following data: $MDR_{ref} = -0.36$ dB/year, $HR_{IOP} = 1.13$ per mmHg higher, $IOP_{av} = 15$ mmHg, MD baseline: -5 dB, Follow-up: 6 years.

In the untreated group, the average IOP was 21 mmHg and the MD-change 0.05 dB/month (which is 3.6 dB in 6 years). In the treated group, the average IOP was 15 mmHg and the MD-change 0.03 dB/month (which is 2.2 dB in 6 years).

The relative risk of progression associated with $MD < -4$ dB was 1.38 in a multivariate model. The MD of -4 dB was the median, whereas the average MD of the whole population was -5 dB. The lowest MD was -16 dB (eligibility criterion). If we estimate the average MD in the group 'MD < -4 dB' at -8 dB and the MD in the group 'MD > -4 dB' at -2 dB, the difference in average MD would be -6 dB. This difference should then be associated with an 1.38 HR. The simplest calculation renders an estimate of 1.06 ($1.06^6 = 1.42$), but this does not take account of the fact that MD decreases in time and therefore impacts the progression speed within the 6 years of follow-up more profoundly in the group that already started with a lower MD. So a plausible

estimate of HR_{MD} should be lower than 1.06. Also, HR_{MD} must be higher than 1.0, because a value of 1.0 indicates not additional risk. For the structural sensitivity analysis we have therefore chosen to use an estimated relative risk of 1.03. This number at least renders a relationship that is different from the basecase model (too small difference does not bring out the impact of the change), whereas it is not such an extreme estimate that it is implausible. To check the face validity of the estimate, we have drawn the expected course of MD in time in patients with IOP levels of 15 mmHg and 21 mmHg at HR_{MD} values of 1.00, 1.06 and 1.03 in Figure 9 to Figure 11 respectively.

Figure 9 Expected Mean Deviation over time when HR_{MD} is 1.0 in patients with a constant IOP of 15 mmHg (black) or 21 mmHg (gray). MD loss in 6 years: 3.8 dB (IOP 21 mmHg) and 2.2 dB (IOP 15 mmHg).

Figure 10 Expected Mean Deviation over time when HR_{MD} is 1.06 in patients with a constant IOP of 15 mmHg (black) or 21 mmHg (gray). MD loss in 6 years: 7.0 dB (IOP 21 mmHg) and 3.4 dB (IOP 15 mmHg).

Figure 11 Expected Mean Deviation over time when HR_{MD} is 1.03 in patients with a constant IOP of 15 mmHg (black) or 21 mmHg (gray). MD loss in 6 years: 5.0 dB (IOP 21 mmHg) and 2.7 dB (IOP 15 mmHg).

Additional results

Cost-effectiveness acceptability curves

This section contains four figures that display the cost-effectiveness acceptability curves of the four investigated alternative treatment strategies for primary open-angle glaucoma. A cost-effectiveness acceptability curve is a helpful tool to obtain insight in the acceptability of the expected incremental cost-effectiveness ratio (ICER) when the willingness-to-pay threshold is not exactly known.³⁴

The cost-effectiveness acceptability curves were created with the outputs from the probabilistic sensitivity analysis (PSA), in which we have assessed how the expected ICER changes when the population-level input parameters simultaneously vary within their confidence intervals. For each unique set of population parameter values, a new ICER was calculated. Ultimately, the PSA renders a collection of estimated ICER's scattered over the cost-effectiveness plane (Figure 1 in the main article). With this collection of data, we can establish in how many cases the ICER indicated an acceptable cost-effectiveness of the alternative treatment strategy. For example, we can count in how many cases the ICER indicated dominance, or in how many cases the ICER was below a certain threshold value. The number of acceptable ICER's relative to the total number of ICER's in the PSA analysis indicates the probability that the real ICER is acceptable at a particular threshold value for willingness-to-pay. The cost-effectiveness acceptability curve shown below, plot the probability of an acceptable ICER against a range of possible willingness-to-pay thresholds.

A related method to obtain insight in the impact of uncertainty in the ICER, is the expected value of perfect information (EVPI). The EVPI quantifies the loss in health and resources that could potentially arise as a result of decision making in uncertainty.³⁵ The EVPI therefore represents the value of eliminating all uncertainty, for example by performing additional research. When the EVPI is zero, it means that there is no value in additional research, because a reduction in uncertainty would not lead to better decision making.

Figure 12 Cost-effectiveness acceptability curve (black solid line) and expected value of perfect information (gray dashed line) of a treatment strategy with initial latanoprost compared to 'usual care' for increasing values of willingness-to-pay.

Figure 13 Cost-effectiveness acceptability curve (black solid line) and expected value of perfect information (gray dashed line) of a treatment strategy with initial target pressure 15 mmHg compared to 'usual care' for increasing values of willingness-to-pay.

Figure 14 Cost-effectiveness acceptability curve (black solid line) and expected value of perfect information (gray dashed line) of a treatment strategy with visual field measurements every 6 months compared to 'usual care' for increasing values of willingness-to-pay.

Figure 15 Cost-effectiveness acceptability curve (black solid line) and expected value of perfect information (gray dashed line) of a treatment strategy with visual field measurements every 24 months compared to 'usual care' for increasing values of willingness-to-pay.

Breakdown of cost outcomes

Table 8 Breakdown of cost outcomes in each of the simulated treatment strategies.

	Usual care	No care	Strategy 1 Initial medication	Strategy 2 Target pressure	Strategy 3a VF 6 months	Strategy 3b VF 24 months
Total Costs	€ 37,328	€ 67,002	€ 37,401	€ 34,026	€ 38,765	€ 37,040
Visits	€ 4,946	€ 396	€ 5,072	€ 4,919	€ 6,829	€ 3,937
Medication	€ 3,948	€ 0	€ 4,745	€ 4,257	€ 3,923	€ 4,007
Surgery	€ 2,407	€ 938	€ 3,208	€ 2,348	€ 2,457	€ 2,295
Care	€ 21,814	€ 61,398	€ 16,980	€ 21,678	€ 21,332	€ 22,620
Informal care	€ 3,391	€ 3,578	€ 3,242	€ 3,382	€ 3,388	€ 3,392
Low-vision services and aids	€ 407	€ 517	€ 377	€ 404	€ 404	€ 413
Transport	€ 395	€ 20	€ 390	€ 393	€ 395	€ 396
Production loss	€ 20	€ 155	€ 12	€ 19	€ 20	€ 21
Total costs, discounted	€ 23,892	€ 42,099	€ 23,982	€ 22,343	€ 24,956	€ 23,573
Visits	€ 3,566	€ 396	€ 3,685	€ 3,545	€ 4,879	€ 2,854
Medication	€ 2,670	€ 0	€ 3,405	€ 2,937	€ 2,660	€ 2,697
Surgery	€ 1,716	€ 747	€ 2,342	€ 1,666	€ 1,753	€ 1,625
Care	€ 13,063	€ 37,938	€ 10,167	€ 12,968	€ 12,790	€ 13,516
Informal care	€ 2,312	€ 2,467	€ 2,203	€ 2,305	€ 2,312	€ 2,312
Low-vision services and aids	€ 273	€ 395	€ 252	€ 272	€ 271	€ 277
Transport	€ 275	€ 18	€ 278	€ 272	€ 274	€ 274
Production loss	€ 17	€ 138	€ 10	€ 16	€ 17	€ 18
Incremental costs, discounted¹						
Societal perspective	Comparator	€ 18,207	-€ 1,550	€ 90	€ 1,063	-€ 319
Healthcare perspective²	Comparator	€ 18,066	-€ 1,416	€ 101	€ 1,065	-€ 324

VFQALY= life years adjusted for VFQ-25 score; QALY= quality-adjusted life years;

ICER= incremental cost-effectiveness ratio.

¹ Incremental versus 'Usual Care'. ² Including only costs for visits, medication, surgery and care.

Subgroup analyses

The following tables show the model outcomes of the four alternative treatment strategies compared to usual care in terms of discounted costs and discounted QALY's in subgroups of primary open-angle glaucoma patients. The subgroups were created by separate analyses of cohorts of 3000 patients that were heterogeneous in all patient-level attributes, except for the attribute of interest, i.e. either the initial IOP or the initial Mean Deviation. An exception to this was made in the comparison between the treatment strategy with an initial target pressure of 15 mmHg versus usual care (Table 10): an initial simulation run in the mildest subgroup of patients (with an initial IOP between 22 and 24 mmHg and an initial MD of -3 to -5 dB) produced outcomes that already indicated in a very favorable cost-effectiveness ratio for the treatment strategy with a low initial target pressure strategy. In patient subgroups with higher IOP and/or more severe initial visual field damage, the cost-effectiveness of the more intensive treatment can only be expected to be more favorable. Additional analyses were therefore not performed.

Table 9 shows that the expected incremental cost-effectiveness ratio (ICER) of initial latanoprost versus usual care (with initial timolol) appears to vary dramatically between the subgroups. However, one must keep in mind that the ICER is calculated as the incremental costs divided by the incremental QALY's. The expected incremental QALY's of initial latanoprost are near zero in all subgroups (and in the heterogeneous population), and small variations in the denominator of a fraction result in very large variations in the outcome of the quotient. This is the reason why the ICER ranges from € 1,947 to € 98,647 between the subgroups. In fact, from the results for the incremental costs and incremental QALY's separately we can see that the differences between the subgroups are not nearly as variable as the ICER's suggest. The expected incremental costs for initial latanoprost are higher in subgroups with lower initial IOP, and also higher in subgroups with more advanced glaucomatous damage. Overall, the most favorable cost-effectiveness of initial latanoprost, with ICER's well below € 10,000/QALY can be expected in patients with either a high initial IOP (higher than 28 mmHg) or mild to moderate glaucomatous damage (MD below -10 dB).

Table 11 shows that the expected incremental costs and the incremental health gain of an increased frequency of visual field testing hardly differs between and within the heterogeneous population and the subgroups.

Table 12 shows that a decrease in the frequency of visual field testing can be expected to lead to cost savings and health losses in all subgroups, similar to the results in the heterogeneous population. If health losses are not acceptable, the

results of all subgroup analyses lead to the same conclusion as the results in the heterogeneous population, which is that a reduction in the frequency of visual field testing is not preferable. However, if one does want to consider the ratio between health losses and cost savings in the decision, the subgroup analyses indicate that the largest cost savings per lost QALY can be expected in patients with a low initial IOP (below 26 mmHg).

Alternative strategies when usual care entails a low initial target IOP

In view of the dominance of the treatment strategy with a low initial target IOP, we have rerun the simulations of the other treatment strategies, but this time in the context of a low initial target IOP. This means that the target IOP was 15 mmHg in all treatment strategies, including the comparator strategy 'usual care' (see Table 13). Table 14 shows the results of these analyses.

Table 14 shows that initial latanoprost was expected to be slightly dominant over initial timolol. Compared to the outcomes of initial latanoprost in the context of a stepwise reduction of target IOP, both the incremental costs and the incremental health benefits changed in favor of initial latanoprost. In fact, the incremental costs of latanoprost changed sign, indicating that initial latanoprost may save costs rather than come at some additional costs. This is probably the result of the slightly higher average effectiveness of latanoprost. It can be expected that with initial latanoprost, more patients can reach the low target IOP with monotherapy, which saves some costs on medication. Still, the absolute differences with the outcomes in the main paper are small.

With regard to the treatment strategies with alternative frequencies of visual field testing, the outcomes were also somewhat different in the context of a single target pressure (15 mmHg) than in the context of a stepwise reduction in target IOP, particularly with respect to the incremental QALY's. Two VF tests per year cost € 1,247 more and rendered 0.001 QALY's compared with one VF test, which results in an ICER of € 945,449 per QALY gained. On the other hand, a VF test frequency of once per two years was expected to save € 554 at the loss of 0.006 QALY's compared with a VF test every year. Although this strategy is associated with a net loss in health, the health effect may be small enough and the compensation large enough (€ 91,063 per QALY lost) to make this latter strategy worth considering.

Table 9 Initial latanoprost versus usual care in subgroups of patients based on initial IOP and initial Mean Deviation (MD).

	Usual care		Initial latanoprost		Incremental medication		Incremental	
	Costs	QALY's	Costs	QALY's	Costs	QALY's	Incremental Costs	Incremental QALY's
Heterogeneous population	€ 23,015	10.32	€ 23,105	10.32			€ 90	0.01
Initial IOP 22 to 24 mmHg	€ 19,490	10.30	€ 19,879	10.31			€ 389	0.01
Initial IOP 24 to 26 mmHg	€ 21,210	10.36	€ 21,570	10.36			€ 359	0.00
Initial IOP 26 to 28 mmHg	€ 21,925	10.06	€ 22,068	10.06			€ 143	0.00
Initial IOP 28 to 30 mmHg	€ 23,592	10.19	€ 23,604	10.19			€ 13	0.01
Initial MD -3 to -5 dB	€ 14,003	10.55	€ 14,020	10.56			€ 17	0.01
Initial MD -5 to -10 dB	€ 23,263	10.23	€ 23,309	10.24			€ 46	0.01
Initial MD -10 to -15 dB	€ 46,658	9.65	€ 46,747	9.65			€ 89	0.00

MD = Mean Deviation; dB = decibel; QALY = Quality-adjusted life year; ICER = Incremental cost-effectiveness ratio.

Table 10 Initial target pressure of 15 mmHg versus usual care in subgroups of patients based on initial IOP and initial Mean Deviation (MD).

	Usual care		Target IOP 15 mmHg		Incremental	
	Costs	QALY's	Costs	QALY's	Incremental Costs	Incremental QALY's
Heterogeneous population	€ 23,016	10.21	€ 21,466	10.32	-€ 1,550	0.115
						Dominant
Initial IOP 22 to 24 mmHg and initial MD -3 to -5 dB	€ 11,503	10.65	€ 11,609	10.75	106	0.10
						€ 1,081

MD = Mean Deviation; dB= decibel; QALY= Quality-adjusted life year; ICER= Incremental cost-effectiveness ratio.

Table 11 Visual field tests every 6 months versus usual care in subgroups of patients based on initial IOP and initial Mean Deviation (MD).

	Usual care		VF every 6 months		Incremental	
	Costs	QALY's	Costs	QALY's	Incremental Costs	Incremental QALY's
Heterogeneous population	€ 23,356	10.40	€ 24,419	10.41	€ 1,063	0.01
						€ 173,486
Initial IOP 22 to 24 mmHg	€ 20,053	10.43	€ 21,263	10.44	€ 1,210	0.01
						€ 108,457
Initial IOP 24 to 26 mmHg	€ 21,576	10.39	€ 22,722	10.40	€ 1,147	0.00
						€ 1,332,097
Initial IOP 26 to 28 mmHg	€ 22,783	10.34	€ 23,906	10.34	€ 1,123	0.01
						€ 190,220
Initial IOP 28 to 30 mmHg	€ 24,182	10.39	€ 25,241	10.40	€ 1,059	0.01
						€ 109,959

Initial MD -3 to -5 dB	€ 14,188	10.64	€ 15,280	10.65	€ 1,092	0.01	€ 121,586
Initial MD -5 to -10 dB	€ 23,274	10.37	€ 24,369	10.38	€ 1,095	0.01	€ 196,554
Initial MD -10 to -15 dB	€ 46,695	9.56	€ 47,755	9.57	€ 1,060	0.01	€ 89,703

MD = Mean Deviation; dB= decibel; QALY= Quality-adjusted life year; ICER= Incremental cost-effectiveness ratio.

Table 12 Visual field tests every 24 months versus usual care in subgroups of patients based on initial IOP and initial Mean Deviation (MD).

	Usual care		VF every 24 months		Incremental	
	Costs	QALY's	Costs	QALY's	Incremental Costs	Incremental QALY's
Heterogeneous population	€ 22,785	10.26	€ 22,466	10.24	-€ 319	-0.01
						€ 21,516
Initial IOP 22 to 24 mmHg	€ 20,022	10.39	€ 19,537	10.39	-€ 485	-0.00
						€ 109,166
Initial IOP 24 to 26 mmHg	€ 21,535	10.30	€ 21,044	10.29	-€ 490	-0.01
						€ 45,377
Initial IOP 26 to 28 mmHg	€ 22,480	10.34	€ 22,097	10.32	-€ 382	-0.02
						€ 23,700
Initial IOP 28 to 30 mmHg	€ 23,831	10.41	€ 23,514	10.39	-€ 317	-0.02
						€ 15,668
Initial MD -3 to -5 dB	€ 14,237	10.70	€ 13,918	10.69	-€ 319	-0.02
						€ 19,763
Initial MD -5 to -10 dB	€ 23,805	10.35	€ 23,499	10.34	-€ 306	-0.01
						€ 20,959
Initial MD -10 to -15 dB	€ 46,295	9.50	€ 45,945	9.49	-€ 350	-0.01
						€ 27,590

MD = Mean Deviation; dB= decibel; QALY= Quality-adjusted life year; ICER= Incremental cost-effectiveness ratio.

Table 13 Features of the comparator strategy 'Usual care' and the alternative treatment strategies.

	Usual care	Strategy 1 Latanoprost	Strategy 3a VF 6 months	Strategy 3b VF 24 months
Start treatment	Always	Always	Always	Always
Target pressure (mmHg)				
initial	15	15	15	15
after first progression	15	15	15	15
after second progression	15	15	15	15
First choice medication	Timolol	Latanoprost	Timolol	Timolol
VF measurement interval	12 months	12 months	6 months	24 months

Table 14 Incremental cost-effectiveness outcomes of alternative treatment strategies with target IOP 15 mmHg in all strategies.

Compared to 'Current care', discounted	Strategy 1 Initial medication	Strategy 3a VF 6 months	Strategy 3b VF 24 months
Incremental Costs	- € 219	€ 1,247	- € 554
Incremental QALY's	0.011	0.001	-0.006
Incremental ICER (/QALY)	Dominant	€ 945,449	€ 91,063

VFQALY= life years adjusted for VFQ-25 score; QALY= quality-adjusted life years;
ICER= incremental cost-effectiveness ratio

References

1. Van Gestel A, Severens J, Webers C, Beckers H, Jansonius N, Schouten J. Modeling complex treatment strategies: construction and validation of a discrete event simulation model for glaucoma. *Value Health* 2010; 13:358-367.
2. Maier P, Funk J, Schwarzer G, Antes G, Falck-Ytter Y. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ* 2005; 331:134.
3. Peeters A, Webers C, Prins M, Zeegers M, Hendrikse F, Schouten J. Quantifying the effect of intra-ocular pressure reduction on the occurrence of glaucoma. *Acta Ophthalmol* 2010; 88:5-11.
4. Heijl A, Patella V. *Essential perimetry; The field analyzer primer*, Third ed. Carl Zeiss Meditec: Dublin, California, USA; 2002.
5. Van der Valk R, Webers C, Schouten J, Zeegers M, Hendrikse F, Prins M. Intraocular pressure-lowering effects of all commonly used glaucoma drugs - a meta-analysis of randomized clinical trials. *Ophthalmology* 2005; 112:1177-1185.
6. Beckers HJ, Schouten JS, Webers CA, van der Valk R, Hendrikse F. Side effects of commonly used glaucoma medications: comparison of tolerability, chance of discontinuation, and patient satisfaction. *Graefes Arch Clin Exp Ophthalmol* 2008; 246:1485-1490.
7. McIlraith I, Strasfeld M, Colev G, Hitnik C. Selective laser trabeculoplasty as initial and adjunctive treatment for open-angle glaucoma. *J Glaucoma* 2006; 15:124-130.
8. Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT) and Glaucoma Laser Trial Follow-up Study: 7. Results. *Am J Ophthalmol* 1995; 120:718-731.
9. Heijl A, Leske C, Bengtsson B, Hyman L, Bengtsson B, Hussein M, for the Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression; results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002; 120:1268-1279.
10. Chung P, Schuman J, Netland P, Lloyd-Muhammad R, Jacobs D. Five-year results of a randomized, prospective, clinical trial of diode vs argon laser trabeculoplasty for open-angle glaucoma. *Am J Ophthalmol* 1998; 126:185-190.
11. Damji K, Shah K, Rock W, Bains H, Hodge W. Selective laser trabeculoplasty versus argon laser trabeculoplasty: a prospective randomised clinical trial. *British Journal of Ophthalmology* 1999; 83:718-722.
12. Juzych M, Chopra V, Banitt M, Hughes B, Kim CS, Goulas M, Shin D. Comparison of long-term outcomes of selective laser trabeculoplasty versus argon laser trabeculoplasty in open-angle glaucoma. *Ophthalmology* 2004; 111:1853-1859.
13. Beckers H, Kinders K, Webers C. Five-year results of trabeculectomy with mitomycin C. *Graefes Arch Clin Exp Ophthalmol* 2003; 241:106-110.
14. Wilson M, Mendis U, Paliwal A, Haynatzka V. Long-term follow-up of primary glaucoma surgery with Ahmed glaucoma valve implant versus trabeculectomy. *Am J Ophthalmol* 2003; 136:464-470.
15. Singh K, Mehta K, Shaikh N, Tsai J, Moster M, Budenz D, Greenfield D, Chen P, Cohen J, GS B, Shaikh S, Group tPTAS. Trabeculectomy with intraoperative mitomycin C versus 5-fluorouracil; prospective randomized clinical trial. *Ophthalmology* 2000; 107:2305-2309.
16. Wudunn D, Cantor L, Palanca-Capistrano A, Hoop J, Alvi N, Finley C, Lakhani V, Burnstein A, Knotts S. A prospective randomized trial comparing intraoperative 5-fluorouracil vs mitomycin C in primary trabeculectomy. *Am J Ophthalmol* 2002; 134:521-528.
17. Gedde S, Schiffman J, Feuer W, Herndon L, Brandt J, Budenz D, group tTvs. Treatment outcomes in the Tube Versus Trabeculectomy study after one year of follow-up. *Am J Ophthalmol* 2007; 143:9-22.
18. Goulet RJ, 3rd, Phan AD, Cantor LB, Wudunn D. Efficacy of the Ahmed S2 Glaucoma Valve Compared with the Baerveldt 250-mm² Glaucoma Implant. *Ophthalmology* 2007.
19. Wesselink C, Heeg G, Jansonius N. Glaucoma monitoring in a clinical setting: Glaucoma Progression Analysis versus Nonparametric Progression Analysis. *Arch Ophthalmol* 2009; 127:270-274.
20. Statline. Available at: <http://statline.cbs.nl/StatWeb/>. Accessed: 2010
21. Pharmacotherapeutic compass (Farmacotherapeutisch kompas). Available at: www.fk.cvz.nl. Accessed: December 2007

22. Foundation for pharmaceutical statistics (Stichting Farmaceutische Kengetallen). Data and facts 2007 (Data en feiten 2007).
23. Oostenbrink J, Bouwmans C, Koopmanschap M, Rutten F. Manual for costing research (Handleiding voor kostenonderzoek; Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg.). Diemen, The Netherlands: Health Care Insurance Board (CVZ); 2004:164.
24. Oostenbrink J, Rutten-van Mölken M, Opdenoordt T. The treatment of newly diagnosed patients with glaucoma or with ocular hypertension in the Netherlands: an observational study of costs and initial treatment success based on retrospective chart review. *Doc Ophthalmol* 1999; 98:285-299.
25. Peeters A, Schouten JS, Webers CA, Prins MH, Hendrikse F, Severens JL. Cost-effectiveness of early detection and treatment of ocular hypertension and primary open-angle glaucoma by the ophthalmologist. *Eye* 2008; 22:354-362.
26. Dutch Healthcare Authority (Nederlandse Zorgautoriteit). Maximum tariffs (Tariefbeschikking maximum-tarieven extramurale zorg in het tweede en derde compartiment). 2007.
27. GIP database. Available at: www.gipdatabank.nl. Accessed: 2006
28. Lichter P, Musch D, Gillespie B, Guire K, Janz N, Wren P, Mills R, Group TC. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001; 108:1943-1953.
29. Smith SD, Katz J, Quigley HA. Analysis of progressive change in automated visual fields in glaucoma. *Invest Ophthalmol Vis Sci* 1996; 37:1419-1428.
30. Katz J, Gilbert D, Quigley HA, Sommer A. Estimating progression of visual field loss in glaucoma. *Ophthalmology* 1997; 104:1017-1025.
31. Chen P, Bhandari A. Fellow eye prognosis in patients with severe visual field loss in 1 eye from chronic open-angle glaucoma. *Arch Ophthalmol* 2000; 118:473-478.
32. Chen PP. Correlation of visual field progression between eyes in patients with open-angle glaucoma. *Ophthalmology* 2002; 109:2093-2099.
33. The AGIS investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000; 130:429-440.
34. Van Hout BA, Al M, Gordon G, Rutten F. Costs, effects and C/E ratios alongside a clinical trial. *Health Econ* 1994; 3:309-319.
35. Claxton K. Exploring uncertainty in cost-effectiveness analysis. *Pharmacoeconomics* 2008; 26:781-798.

Chapter 6

The long term effectiveness and cost-effectiveness of initiating treatment for ocular hypertension

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Abstract

Objective: To investigate the long-term health and economic consequences of direct treatment initiation in ocular hypertension patients.

Methods: A cost-effectiveness analysis with a societal perspective and a lifelong horizon was performed. The primary outcomes were the incremental quality-adjusted life years (QALY's) and costs of direct pressure lowering treatment for ocular hypertension, compared to a strategy where treatment is postponed until conversion to glaucoma has been observed. We used a decision analytic model based on individual patient simulation to forecast disease progression and treatment decisions in both strategies in a representative heterogeneous patient population, and in eighteen patient subgroups stratified by initial IOP and additional risk factors for conversion.

Results: The incremental discounted health gain of direct treatment was 0.27 QALY's, whereas the incremental discounted costs were -€ 649 during an average lifetime of 26 years. In the simulations of patient subgroups, the model outcomes moved towards higher health gains and lower incremental costs with increasing risk of conversion in the patient population. The incremental cost-effectiveness ratio of direct treatment ranged from € 15,425 per QALY gained in the lowest-risk subgroup to dominance in the highest-risk subgroup. Probabilistic uncertainty analysis indicated that uncertainty surrounding the model input parameters did not affect the conclusions.

Conclusion: Direct pressure lowering treatment is a dominant treatment strategy for patients with ocular hypertension.

Introduction

An elevated intra-ocular pressure (IOP) is a well known risk factor for the development of primary open-angle glaucoma (POAG), and pressure lowering treatment has been shown to reduce the risk of glaucoma onset.¹⁻³ Still, the need to initiate treatment in every ocular hypertension (OHT) patient is subject of debate, since an appreciable proportion ($\pm$ 40%) of the OHT population does not develop glaucoma even if untreated, whereas treatment itself may cause discomfort and side-effects.³⁻⁵ To maximize health, caregivers will have to selectively initiate treatment in patients that are expected to benefit from it, and withhold it from patients in whom the harm from treatment is expected to surpass the benefits. Currently, the European Glaucoma Society recommends to consider treatment in OHT patients if the IOP is repeatedly in the high twenties, even without risk factors, and the UK guidelines provide an algorithm for treatment initiation based on central corneal thickness, IOP and age.^{6,7} These guidelines are mainly based on clinical studies of treatment effectiveness, but also consider the outcomes of economic analyses. Economic evaluations assess the question whether the resource allocations required to carry out a particular guideline are justified given the expected benefits, and are therefore useful sources of information in guideline development. Currently, the availability of economic evaluations of OHT treatment to substantiate decision rules about treatment initiation in literature is limited to one report, which presents a cost-effectiveness analysis based on data from the Ocular Hypertension Treatment Study (OHTS).⁸ The authors used a Markov model for glaucomatous disease progression, and concluded that it is likely cost-effective to initiate OHT treatment only in patients with an IOP $\geq$ 24 mmHg and an annual risk to develop glaucoma of 2% or more. The US perspective of the study has been noted as a minor limitation to its applicability in the UK treatment guidelines. Additional issues that may further limit the applicability of these study outcomes are the fact that the analysis was based entirely on the relatively low-risk OHTS population, and the limited possibility in a Markov model to account for patient characteristics, multiple treatment options and the gradual progression of glaucoma.^{2,9} The aim of this study was to generate additional data with a patient level simulation model to further inform (stratified) treatment guidelines for OHT by assessing the long-term effectiveness and efficiency of OHT treatment.

Methods

In order to make predictions of the long-term consequences of different treatment approaches to manage OHT, we have developed a computer model in which the disease progression of individual patients with OHT or POAG can be simulated.

The development and validation of the model itself has been described extensively elsewhere.¹⁰ In addition, a detailed description of the model structure and input sources has been provided in a previous publication concerning various treatment strategies for POAG in this journal.¹¹ Here we provide a brief summary of the simulation process and the outlines of the model structure. An additional appendix specifies the sources we used to describe the characteristics of individual OHT populations, and gives a brief account of the sources on which the input parameters of the base case model and their uncertainty distributions were based.

The model simulates the disease progression of an individual OHT patient and his/her contacts with healthcare providers through discrete event simulation. A simulated patient with ocular hypertension can develop a certain degree of visual field damage and thus convert to glaucoma. With the progression of time, the visual field damage deteriorates and may eventually drop below a degree that represents blindness. The risk of conversion and the rate of visual field progression is determined in part by the patient's predisposition, and in part by the intraocular pressure. The model simulates treatment decisions at ophthalmologist visits, as a result of which the intraocular pressure is lowered and the disease progression is delayed.

The benefit of the patient level modeling is that every relevant characteristic of a patient is accounted for and simulated in detail as it changes in time. Also, every single treatment choice is simulated and can be adapted according to a patient's status or history. The discrete event time lapse ensures that all relevant moments in time are acknowledged and that the time interval between events is adjustable to the situation.

Model structure

A single simulation started with establishing the initial characteristics (attributes) of a virtual patient by random draws from distributions representing the variation in the real OHT patient population. The parameters of these distributions are specified under 'simulated population' below. The simulation time-line started with an initial event representing the patient's first visit to an ophthalmologist, and the model subsequently advanced to time-points of relevant events. In addition to an ophthalmologist visit, the other events in the model were conversion from OHT to POAG and death. The patient attributes were recalculated at each event, and so were the time intervals to all possible future events. The latter were linked to changes in the patient's attributes. For example, the timing of the next ophthalmologist visit was shorter when a simulated patient received a new treatment than when treatment remained unaltered. The type and timing of the next event was governed by the

event with the shortest time interval. Table 1 shows the simulation process for a fictive patient. The table is only for illustrative purposes and is a simplification of the actual attributes considered in the model. The simulation ended with the death of the patient, after which all relevant outcomes from the patient's disease and treatment history were collected in a database. This process was repeated 3000 times to generate a heterogeneous cohort of patients. The cohort size of 3000 patients was chosen based on stability research of the outcomes with increasing cohort size. At cohort sizes higher than 3000 patients, the improvement in the stability of the outcomes flattened out while the computation time kept increasing proportionally to the cohort size.

Table 1 Excerpt of time progression and attribute recalculation in the model for an example patient. Time and intervals are in months.

Time	Event	Age	IOP	Glaucoma	Treatment	Interval to next visit	Interval to conversion	Interval to death
0	Visit	55	28	No	None	12	336	300
12	Visit	56	28	No	None	12	7	288
19	Conversion	56	28	Yes	None	5	n.a.	281
24	Visit	57	28	Yes	Timolol	3	n.a.	276
27	Visit	57	21	Yes	Timolol	6	n.a.	273
etc								

The time to the next visit was determined by a cross table, in which the appropriate intervals were defined according to the treatment status and the number of visits that passed since the last treatment change. The time of death was established by a random draw at the start of the simulation from a survival curve based on survival rates in the Dutch population and the patient's initial age. The time to conversion was randomly drawn from a distribution that was based on the patient's conversion risk, which was in turn recalculated at each event based on IOP, age and the presence of other risk factors for conversion. The rationale for using the latter is that various factors apart from IOP and age have been identified as potentially associated with the development of POAG, but the evidence regarding the associations is not always conclusive.^{12, 13} Since the risk from these factors is generally not amendable and stays constant during the simulation, the aggregate

magnitude of the risk is more important than the source. We chose to use one parameter to represent the additional risk (HR_{other_i}) of conversion attributable to factors other than IOP and age. The total conversion risk was calculated according to equation 1 and 2.

$$P = 1 - S = 1 - e^{-h_i \cdot t} \quad (1)$$

$$h_i = HR_i \cdot h = HR_{Age}^{\frac{(\langle Age \rangle_i - \langle Age \rangle_{av})}{10}} \cdot HR_{IOP}^{(\langle IOP \rangle_i - IOP_{av})} \cdot HR_{other_i} \cdot h \quad (2)$$

In which P= cumulative probability of conversion, S= Conversion free survival, h_i = current hazard rate of individual i at current event, t= time interval, HR_i = Total hazard ratio of individual i at current event, HR_{age} = Hazard ratio of age, HR_{IOP} = Hazard ratio of IOP, $\langle Age \rangle_i$ = Age of individual i at current event, $\langle Age \rangle_{av}$ = Average age of reference OHT population, $\langle IOP \rangle_i$ = IOP of individual i at current event, IOP_{av} = average IOP in the reference OHT population, HR_{other} = Hazard ratio of other risk factors, h= hazard rate in the reference OHT population.

In this equation, the hazard ratio of age was 1.26 per decade older, and the hazard ratio of IOP was 1.09 per mmHg higher.¹³ The hazard rate of conversion in the reference OHT population was based on the Kaplan-Meier estimate of conversion in the Ocular Hypertension Treatment Study, which was 9.5% in 5 years.¹⁴ The reference age and IOP in this population were 55 years and 24 mmHg respectively.

We quantified glaucomatous damage using standard automated perimetry global index Mean Deviation (MD). At a conversion event, the model assigned a degree of visual field loss to the converted patient by making a random draw from a distribution representing the variation in glaucomatous damage in early glaucoma patients (see 'simulated population'). Once a patient had visual field damage, the model simulated its deterioration in time based on the personal progression rate and IOP. The fact that conversion occurred did not affect the interval until the next ophthalmologist visit, as conversion usually does not trigger care seeking behavior. We simulated the possibility that the conversion would go undetected in an ophthalmologist visit depending on whether a visual field measurement was performed or not (see 'treatment strategies compared'). The probability to detect conversion was 65% without a visual field measurement, and 100% otherwise.¹⁴

Simulated populations

The derivations of the distribution parameters we used to characterize the heterogeneous OHT population are described in the appendix. The initial IOP of each new patient was randomly drawn from a normal distribution with mean 22 mmHg, standard deviation (SD) 4, and truncated at 22 mmHg which resulted in an average

of 25 mmHg.¹⁴⁻¹⁶ The natural logarithm of the conversion risk attributable to factors other than IOP and age was also randomly drawn from a normal distribution (mean 0.0, SD 0.7). We used a normal distribution for the age of OHT patients (mean 55, SD 10) and a gamma distribution for the Mean Deviation (MD) after conversion ($\alpha=6$, $\beta=0.5$) that resulted in skewed distribution with an average of -3 dB.¹⁴⁻¹⁶ The percentage of men in the population was 40%.¹⁴

We anticipated that direct treatment of OHT would be more beneficial in patients with a higher risk of conversion, so we repeated the analyses in eighteen subgroups each consisting of 3000 patients that were heterogeneous except for their initial IOP and their risk of conversion from factors other than IOP and age. We defined three levels of the latter: low, neutral and high with an HR_{other} of 0.5, 1.0 and 2.0 respectively. For example, an HR_{other} of 0.5 could be the result of a thicker central cornea (613 μ m rather than 573 μ m), and an HR_{other} of 2.0 could result from some disc cupping (cup/disc ratio 0.56 rather than 0.36) and a thinner cornea (545 μ m).¹⁷ A further distinction in patient subgroups was made based on the initial IOP, which was set at 22, 24, 26, 28, 30 or 32 mmHg. In the subgroups, the values of the initial IOP and HR_{other} were fixed to one value for all patients in the simulated cohort, but all other attributes were randomly drawn from distributions similar to the simulation of the heterogeneous cohort.

Treatment strategies compared

We investigated the cost-effectiveness of immediate pressure lowering treatment for OHT relative to the comparator strategy 'watchful waiting'. In both strategies the OHT patients were monitored with an annual follow-up visit, and a visual field (VF) measurement every three years. In the strategy 'direct treatment', patients immediately received pressure lowering therapy with a 21 mmHg target pressure. When treated OHT patients converted to POAG, the target pressure was adjusted to 18 mmHg and the patient was treated according to 'usual care' for POAG with two follow-up visits and one VF test per year.¹¹ The target pressure was further reduced to 15 mmHg in case of progression. In the comparator strategy, OHT patients did not receive treatment until conversion to POAG was seen at a follow-up visit, in which case treatment was initiated with a target pressure of 21 mmHg. As of that moment all settings for POAG treatment according to 'usual care' applied to the patient, and the target IOP was adjusted to 18 mmHg at the first occurrence of progression and to 15 mmHg at the second. Treatment consisted initially of medication (monotherapy and combination therapy up to triple therapy) and laser trabeculoplasty if maximal medication was insufficient to lower the IOP below target. Additional treatment options for POAG consisted of glaucoma surgery, with co-medication if necessary.¹¹

Cost input

All direct medical, direct non-medical and indirect non-medical costs were taken into account (societal perspective). This included costs for ophthalmologist visits, VF measurements, medication, surgery, home care (household, grooming and nursing), visual impairment rehabilitation and aids, retirement- and nursing home, transportation to healthcare providers, informal care, and production losses as a result of POAG based on the friction cost method. The latter entails that the period over which the production loss is calculated is limited to the time an employer needs to replace a sick employee.¹⁸ Costs were calculated as the product of cost prices and resource use. Cost prices were derived from a number of different sources, and are listed in table 2. A detailed description of the derivation of these parameter values is provided elsewhere.¹⁰ The cost year was 2006. Cost prices from sources earlier than 2006 were indexed with the health-care specific consumer price index.¹⁹ Resource use related to ophthalmologist care, such as visits, medication and surgery, was simulated directly by the model. On the other hand, resource use related to long term care, such as home-care and rehabilitation, was estimated by linking the degree of visual field loss of the simulated patient to the average resource use observed in a study with patients representing various stages of glaucoma severity.²⁰

Utility input

Quality-adjusted life-years (QALY's) are the preferred outcomes measure when improvement in quality-of-life is an important effect of the intervention under investigation.²¹ In order to calculate QALY's, the life-years of the simulated patients were multiplied by the utility during these life-years. Utility is an aggregate measure of health-related quality-of-life which values a health state on a scale from 0 (death) to 1 (best imaginable health state). In the calculation of the utility of a simulated patient during the intervals between events, the model took three attributes into account: the presence of side-effects from medication, the presence of cataract and the amount of visual field loss. The initial utility value was 0.88, which was lowered by 0.101 for side-effects, by 0.065 for cataract and by 0.011 for each dB loss in MD.²⁰

Outcomes

Each patient was simulated according to both direct treatment strategy and the watchful waiting strategy. From both strategies we collected the clinical outcomes for each simulated patient, like whether the patient converted to POAG, whether the patient progressed to blindness, which types of procedures were applied and what the average IOP was during the simulation. Additionally, we collected health economic outcomes, like the lifetime costs of treatment and care, and the QALY's. The latter

Table 2 Costs (in 2006 Euro's) associated with attributes and events in the simulation model.

Resource	Costs	Source
β-blocker	€ 6.00/month	1,2
Prostaglandin analogue	€ 20.20/month	1, 2
Carbonic-anhydrase inhibitor	€ 13.90/ month	1,2
α ₂ -adrenergic agonist	€ 14.00/month	1,2
Ophthalmologist consultation	€ 65	3,4
Visual field measurement	€ 133 (€ 266 in case of progression)	3,4
LT	€ 75	4,5
Trabeculectomy	€ 1,214 (+ 1 ophthalmologist consultation)	3,4
Tube implantation	€ 1,714 (+ 1 ophthalmologist consultation)	3,4
Cataract surgery	€ 1,400	3, HA
Paid household help	€ 37 / month (if MD < -10 dB)	3,6
Homecare nursing	€ 159 / month (if MD < -10 dB)	3,6
Family help	€ 56 / month (if MD < -15 dB)	3,6
Homecare grooming	€ 103 / month (if MD < -15 dB)	3,6
Retirement home	€ 80 / month (if MD < -20 dB)	3,6
Nursing home	€ 130 / month (if MD < -20 dB)	3,6
Informal care	€ 20 / month (if MD < -5dB)	3,6
Low-vision services	€ 1-5 /month	6,7
Transport to ophthalmologist	€ 4.90 / visit (if MD > -10 dB) € 8.90 / visit (if MD < -10 dB)	3,6
Transport to pharmacy	€ 1.50 / visit (if MD > -10 dB) € 2.60 / visit (if MD < -10 dB)	3,6
Low-vision aids	€ 325 (once) if MD progresses below -15 dB	6,8
Productivity loss	€ 3,029 (once) if MD progresses below -15 dB while the patients is younger than 65 years.*	4,6

Costs for LT (Laser Trabeculoplasty) and surgery were doubled to account for the same procedure in the other (i.e. worse) eye. Costs for visual field measurement were doubled if progression was observed to account for a confirmatory test. Transport costs to the pharmacy were incurred once in three months if the patient received medication, and transport costs to the ophthalmologist/hospital were added for each visit and for each procedure (LT, surgery). *Friction costs. HA= Hospital Administration. Sources: 1) Health Care Insurance Board (CVZ)³⁶, 2) Foundation for pharmaceutical statistics³⁷, 3) Oostenbrink *et al.*, 2004³⁸, 4) Oostenbrink *et al.*, 1999³⁹, 5) Peeters *et al.*, 2008³⁰, 6) Van Gestel *et al.*, 2010¹⁰, 7) Dutch Healthcare Authority⁴⁰, 8) Drug information stystem⁴¹

were calculated as a product of the length of each interval between events and the quality-of-life expressed in utility during that interval. The health economic outcomes were collected after ten years and after the patient died (i.e. lifelong). The future effects and costs were discounted with 1.5% and 4.0% respectively.²¹

Sensitivity analyses

The variation in the incremental outcomes due to uncertainty surrounding the input parameters was assessed with a probabilistic sensitivity analysis (PSA), in which the simulation of the heterogeneous cohort was repeated multiple times with different combinations of input parameter values that were varied within their limits of uncertainty. The values of the input parameters were drawn from probability distributions representing their uncertainty. The base case values, the uncertainty distributions and the sources of information used to estimate both are described in the appendix. We ran 150 cohort simulations in the PSA, which was enough to render stable outcomes. With the PSA outcomes we calculated the probability of an acceptable balance between effects and costs at increasing thresholds of willingness-to-pay for an extra QALY.²² Additionally, we calculated the expected value of perfect information (EVPI) in order to assess the value of further research to reduce uncertainty in any of the model parameters.²³

Results

The simulated lifetime of the patients in the heterogeneous cohort covered on average 25.7 ± 12.9 years. A comparison of the outcomes in both treatment strategies is presented in table 3. With watchful waiting, the occurrence of conversion from OHT to POAG was 14.6% within the first five years and 25.2% after ten years. Ultimately, 57.0% of the patients not treated for OHT conversed to POAG somewhere during their lifetime and 1.5% went blind. With direct treatment, the occurrence of conversion from OHT to POAG was 7.7% after five years, 14.7% after ten years and 36.5% in the patients' lifetime. Blindness occurred in 0.4% of the simulated patients. The lifetime use of medication was higher when OHT patients were treated directly, but the incidence of LT and surgery were lower.

The health economic outcomes are listed in Table 4. Within a time horizon of ten years, direct treatment of OHT resulted on average in slight health gains and additional costs at an incremental cost-effectiveness ratio (ICER) of € 30,597. However, over a lifelong horizon direct treatment resulted on average in 0.27 QALY's gained and cost reductions of € 649 per patient compared to watchful waiting.

Table 3 Average lifetime clinical outcomes of simulated patients in a heterogeneous cohort of OHT patients.

	Watchful waiting	Direct treatment
IOP in follow-up (mmHg)	23.6	17.7
Occurrence of POAG*	57%	37%
Occurrence of blindness*	1.5%	0.4%
Average number of medications	0.5	1.3
Occurrence of LT*	23%	23%
Occurrence of TE*	15%	12%
Occurrence of ReTE*	4.8%	3.2%
Occurrence of tube implant*	2.9%	2.3%
Occurrence of CE*	28%	28%
End-of-life MD (dB)	-5.5	-2.8

* Percentage of the cohort in which the event occurred during the simulated life time. LT= laser trabeculoplasty; TE= trabeculectomy; ReTE= second trabeculectomy; CE= cataract extraction; MD= Mean Deviation; dB= decibels

Table 4 Health-economic outcomes of simulated patients in a heterogeneous OHT cohort after ten years and after a lifelong horizon. Average per patient.

	Watchful waiting	Direct treatment	Incremental	ICER
10-year horizon				
Costs	€ 2,302	€ 3,415	€ 1,113	€ 35,573
QALY's	8.15	8.18	0.03	
Discounted costs	€ 1,891	€ 2,844	€ 957	€ 33,645
Discounted QALY's	7.62	7.65	0.03	
Lifetime (mean 26 years)				
Costs	€ 18,327	€ 14,343	- € 3,984	Dominant
QALY's	21.79	22.17	0.38	
Discounted costs	€ 7,722	€ 7,073	- € 649	Dominant
Discounted QALY's	17.55	17.81	0.27	

QALY= quality-adjusted life-years; OHT= ocular hypertension; ICER= incremental cost-effectiveness ratio.

A breakdown of the incremental costs is provided in Figure 1. Differences in costs between the two treatment strategies occurred mainly in two cost categories: medication and care. Direct treatment was associated with higher costs for medication, but lower costs for (informal) care. The figure also illustrates how costs further in the future are discounted more heavily. In particular, the relative contribution of costs for care is much larger in the undiscounted incremental costs than in the discounted incremental costs of direct treatment compared to watchful waiting. Figure 2 illustrates the uncertainty surrounding the ICER as a cloud of possible cost-effectiveness outcomes resulting from the probabilistic sensitivity analysis. The cost-effectiveness acceptability curve (figure 3) showed that at a willingness-to-pay threshold of € 0 per QALY, the probability that direct treatment is cost-effective was 83%. At thresholds of € 10,000 per QALY and higher, this probability had increased to 100%. Likewise, the expected value of perfect information decreased from € 96 per patient to € 0 per patient between the thresholds of € 0 and € 10,000 per QALY.

Figure 1 Distribution of the total costs in eight cost categories in both treatment scenarios (gray) and incremental (black) in a heterogeneous OHT population. The total height of the bars indicates the undiscounted costs; the solid bars indicate the discounted costs and the dotted portion indicates the amount that is discounted away.

The outcomes of the comparison of direct treatment versus watchful waiting in subgroups of OHT patients are listed in Table 5. Direct treatment resulted in health gains irrespective of the initial IOP and additional risk. The health gains were larger

Figure 2 Cost-effectiveness plane showing the average incremental cost-effectiveness ratio (ICER) of direct treatment in all patients compared to watchful waiting in a heterogeneous OHT population, both in the base case model as in each of the cohort simulations in the probabilistic sensitivity analysis. The grey line represents an incremental cost-effectiveness ratio of € 30,000/QALY

Figure 3 Cost-effectiveness acceptability curve of direct treatment compared to watchful waiting in ocular hypertension patients (solid black line), and the expected value of perfect information (EVPI, dashed gray line) at increasing acceptability thresholds for the incremental cost-effectiveness ratio.

Table 5 Incremental discounted cost-effectiveness outcomes of direct treatment versus watchful waiting in subgroups of OHT patients based on initial IOP and additional risk of conversion (HR_{other}).

	Average 5-year risk of conversion ^{a)}	Incremental costs (€)	Incremental QALY's	ICER (€ per QALY)
Low risk ($HR_{other} = 0.5$)				
22 mmHg	4%	€ 1,259	0.082	€ 15,425
24 mmHg	5%	€ 851	0.122	€ 6,954
26 mmHg	6%	€ 624	0.175	€ 3,563
28 mmHg	7%	€ 1,127	0.221	€ 5,088
30 mmHg	8%	€ 807	0.303	€ 2,660
32 mmHg	10%	€ 49	0.403	€ 121
Neutral risk ($HR_{other} = 1.0$)				
22 mmHg	8%	€ 541	0.149	€ 3,629
24 mmHg	10%	-€ 193	0.214	Dominant
26 mmHg	11%	-€ 765	0.293	Dominant
28 mmHg	13%	-€ 1,085	0.374	Dominant
30 mmHg	16%	-€ 1,788	0.469	Dominant
32 mmHg	18%	-€ 2,826	0.571	Dominant
High risk ($HR_{other} = 2.0$)				
22 mmHg	16%	-€ 327	0.231	Dominant
24 mmHg	18%	-€ 1,276	0.300	Dominant
26 mmHg	22%	-€ 1,995	0.370	Dominant
28 mmHg	25%	-€ 3,168	0.497	Dominant
30 mmHg	29%	-€ 4,045	0.583	Dominant
32 mmHg	33%	-€ 6,046	0.728	Dominant

QALY= quality-adjusted life-years; ICER= incremental cost-effectiveness ratio.

^{a)} Calculated from age, IOP and HR_{other} of the simulated patient population.

as the total risk of conversion in the subgroup increased. The health gains came at additional cost in the subgroups with low additional risk of conversion and in the subgroup with neutral additional risk and an initial IOP of 22 mmHg. In the other subgroups direct treatment resulted in cost savings.

Discussion

In this study we have used a patient-level simulation model of OHT and POAG to simulate the disease progression of patients with ocular hypertension, and used its output to estimate the additional health and costs that can be expected from direct pressure lowering treatment compared to watchful waiting. The modeling approach provides an efficient method to generate new information from available evidence, without the need to conduct clinical studies. Direct treatment turned out to be a dominant strategy over watchful waiting in a heterogeneous population of OHT patients over the lifetime horizon. Over a shorter time horizon, the cost-effectiveness of direct treatment was less favorable, with a discounted ICER of € 30,597. Although this amount may still be acceptable, it is clear that the time horizon plays an important role in the cost-effectiveness of OHT treatment. Pressure lowering treatment in OHT is a preventative measure involving short term investments to prevent long term health loss. The time-horizon should therefore be long enough to capture future effects, or the ICER will overstate the contribution of short term investments.

Direct treatment resulted in better health outcomes in all simulated subgroups. The general tendency across the subgroups was that incremental costs decreased as the initial IOP in the subgroup increased. An exception to this tendency was seen in the subgroups with a low additional risk of conversion (table 5), which showed a local 'peak' of incremental costs in the 28 mmHg subgroup. This observation can be explained by a shift in the balance between the short term costs of treatment and long term savings in low vision related care. Up to an initial IOP of 26 mmHg, monotherapy is sufficient to get most patients below the target pressure of 21 mmHg, but higher initial IOP's will mostly require combination therapy. The marginal costs of extra medication cause a sudden increase in overall treatment costs, which is reflected in the total incremental costs. In the subgroups with neutral and high additional risk a small deviation from the tendency was observed due to the same effect, but it was far less pronounced because the contribution of treatment costs to the overall costs was smaller in these subgroups. Direct treatment was dominant in all subgroups, except for the subgroups with a conversion risk lower than 10% in five years. The latter had ICER's in the range of € 100 to € 15,500 per QALY. The implications of these ICER's for decisions regarding the desirability of direct treatment in low-risk subgroups depends on the way ICER's are used to aid decision making. In the net monetary benefit calculations we have assumed an acceptability threshold of € 30,000 per QALY based on ranges mentioned in literature and authority reports, although the threshold may be lower (€ 20,000 per QALY) for preventive care.²⁴⁻²⁶ The method of comparing the ICER to an acceptability threshold

in order to gauge the relative value-for-money of the intervention has been criticized though, and if it were employed, it is very likely that the acceptability threshold varies between jurisdictions, between disease severities, and in time.^{24, 27} We can therefore only report the value of the ICER of direct treatment in low-risk OHT patients, and not speculate on its acceptability.

The outcomes of the probabilistic sensitivity analysis showed that even if the input parameter values are randomly varied within their uncertainty margins, the outcome of the analysis shows dominance for direct treatment initiation in the majority of cases. This implies that even though there is uncertainty about the exact value of the model's input parameters, this does not result in decision uncertainty. In addition, the EVPI dropped to zero at willingness-to-pay thresholds higher than € 10,000 per QALY, which suggests that there is no value in further research to reduce uncertainty surrounding any of the population parameters in the model. In addition to parameter uncertainty, we have considered the impact of structural uncertainty. An issue of structural uncertainty in our model is the way both eyes of the patient are handled. In the base case model we have simulated *patients* rather than individual eyes, and simulated that both eyes underwent similar treatment and disease progression. This structural choice involves uncertainty, as not all patients in clinical practice will present with symmetrically affected eyes. In order to assess the impact of this assumption we have performed an additional analysis in which we modeled only the worse eye of the patient and assumed that the other eye remained completely unaffected. The lifetime discounted outcomes with watchful waiting in a heterogeneous OHT population were 18.04 QALY's and € 4,580, whereas the strategy with direct treatment resulted in 18.15 QALY's and € 5,830. The ICER of direct treatment was therefore € 11,523 per QALY gained. The outcomes of the base case model (dominance) and this univariate sensitivity analysis represent the two boundaries of the uncertainty spectrum regarding the symmetry of disease progression in both eyes, and all realistic scenarios encountered in clinical practice will fall within these boundaries. Structural uncertainty also played a role in the way costs related to visual impairment were accounted for. The results of our analyses showed that low-vision related costs played an important role in the overall cost-effectiveness of treatment, while there is a considerable degree of uncertainty about the size of these costs and how they increase with progressing disease. Previously, authors investigating health economics of ocular hypertension and glaucoma treatment have not included such costs in the analysis,²⁸ considered only nursing home costs,²⁹ or assumed resource use in this category only in case of blindness.^{8, 30, 31} In our study, we have assumed a gradual increase in low vision related costs with increasing loss of visual field, which was based on measurements in our study in 531 patients representing all

levels of OHT and POAG severity and MD values ranging from 0 dB to -32 dB in the better eye.²⁰ The probabilistic sensitivity analysis showed that even when the low vision related costs were varied between a factor 0 (i.e. no costs) and 2, the dominance of direct treatment was not affected. On the same note, the EVPI analysis indicated that, despite the uncertainty about low vision related costs, there is no value in additional research to reduce that uncertainty in the context of the currently investigated treatment decision. This example illustrates how the fact that some model input is quite uncertain does not invalidate the entire model, and that it is more important to acknowledge uncertainty and assess its impact than negate the informative power of the aggregated evidence. It also demonstrates that the model input with the highest degree of uncertainty is not necessarily the one with the largest impact on the outcome, and is therefore not the most likely candidate for future research. In fact, we have conducted analysis of variance with the PSA input and outcomes, and found that uncertainty about the relative risk of IOP on conversion had the largest impact (see appendix).

The dominance that we found for direct treatment relative to watchful waiting differs considerably from the \$144,780 per QALY that has been reported by Kymes *et al.* for the United States of America (2004 € 1 ≈ \$ 1.25).^{8, 32} The difference is caused by lower incremental costs (-€ 649 versus \$ 7,239) and higher incremental QALY's (0.27 versus 0.05) in our study. We compared the methodology of both studies and identified several issues that might explain the differences. First, the setting of the studies affected the estimates for the cost price of medication, cataract surgery and POAG surgery, as cost prices in the United States are generally higher than those reported for European countries.³³⁻³⁵ Second, Kymes *et al.* attributed resource use associated with visual impairment only in case of blindness, and not in preceding stages. These two factors are probably the main reason why treatment in the study by Kymes *et al.* was associated with incremental costs rather than cost savings. Additionally, four issues may contribute to the differences in incremental effects. First, the estimated utility loss as a result of disease progression was smaller in the study by Kymes *et al.* than in our study, particularly in advanced stages. Second, the horizon was much shorter. Kymes *et al.* do not report the actual duration of follow-up in their study, but considering the total QALY's reported (13.6) and the utility in early and moderate glaucoma (0.97 and 0.89) it is likely to be around 15 years, whereas the horizon was 26 years in our study. As the results of our study have shown, the length of the time horizon has a considerable impact on the ICER of OHT treatment. Third, the risk of conversion in the study by Kymes *et al.* was distributed towards lower values than in our simulated population. The authors reported that 70% of the patients had an annual conversion risk lower than 2%, whereas this was 44% in our simulated population. Since the incremental effects of

direct treatment are smaller with decreasing conversion risk (Table 5), a population with more low-risk patients will result in smaller average incremental effects of direct treatment. Finally, the future QALY gains in the study by Kymes *et al.* were more heavily discounted which reduces the net present value of future health gains (3% versus 1.5%). The combination of all factors may have resulted in the difference in outcomes of our study compared to those reported earlier. These issues do not necessarily concern 'wrong' choices in either of the studies but rather reflect the different decision making contexts targeted by the two studies.

In conclusion, we found that direct pressure lowering treatment is a dominant strategy compared to watchful waiting in a heterogeneous population of ocular hypertension patients, and that the efficiency of direct treatment increases with increasing initial IOP and the presence of additional risk factors for conversion.

References

1. Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. *N Engl J Med* 2009; 360:1113-1124.
2. Peeters A, Webers C, Prins M, Zeegers M, Hendrikse F, Schouten J. Quantifying the effect of intra-ocular pressure reduction on the occurrence of glaucoma. *Acta Ophthalmol* 2010; 88:5-11.
3. Maier P, Funk J, Schwarzer G, Antes G, Falck-Ytter Y. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ* 2005; 331:134.
4. Beckers HJ, Schouten JS, Webers CA, van der Valk R, Hendrikse F. Side effects of commonly used glaucoma medications: comparison of tolerability, chance of discontinuation, and patient satisfaction. *Graefes Arch Clin Exp Ophthalmol* 2008; 246:1485-1490.
5. Heijl A, Bengtsson B. Long-term effects of timolol therapy in ocular hypertension: a double-masked randomised trial. *Graefes Arch Clin Exp Ophthalmol* 2000; 238:877-883.
6. National Collaborating Centre for Acute Care. Glaucoma: diagnosis and management of chronic open-angle glaucoma and ocular hypertension. London: National Collaborating Centre for Acute Care, 2009.
7. European Glaucoma Society. Terminology and guidelines for glaucoma (third edition). Dogma: Savona, Italy; 2008.
8. Kymes SM, Kass MA, Anderson DR, Miller JP, Gordon MO. Management of ocular hypertension: a cost-effectiveness approach from the Ocular Hypertension Treatment Study. *Am J Ophthalmol* 2006; 141:997-1008.
9. Caro JJ, Moller J, Getsios D. Discrete event simulation: the preferred technique for health economic evaluations? *Value Health* 2010; 13:1056-1060.
10. Van Gestel A, Severens J, Webers C, Beckers H, Jansonius N, Schouten J. Modeling complex treatment strategies: construction and validation of a discrete event simulation model for glaucoma. *Value Health* 2010; 13:358-367.
11. Van Gestel A, Webers C, Beckers H, Severens J, Jansonius N, Hendrikse F, Schouten J. The cost-effectiveness of four strategies to treat primary open-angle glaucoma. *Acta Ophthalmol* 2012; 90:20-31.
12. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Surv Ophthalmol* 2008; 53 Suppl1:S3-10.
13. Gordon MO, Torri V, Miglior S, Beiser JA, Floriani I, Miller JP, Gao F, Adamsons I, Poli D, D'Agostino RB, Kass MA. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. *Ophthalmology* 2007; 114:10-19.
14. Kass M, Heuer D, Higginbotham E, Johnson C, Keltner J, Miller J, Parrish R, Wilson R, Gordon M, the Ocular Hypertension Treatment Study Group. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002; 120:701-713.
15. Miglior S, Zeyen T, Pfeiffer N, Cunha-Vaz J, Torri V, Adamsons I, The European Glaucoma Prevention Study (EGPS) Group. Results of the European Glaucoma Prevention Study. *Ophthalmology* 2005; 112:366-375.
16. Heeg GP, Jansonius NM. The Groningen longitudinal glaucoma study III. The predictive value of frequency-doubling perimetry and GDx nerve fibre analyser test results for the development of glaucomatous visual field loss. *Eye* 2008.
17. Gordon M, Beiser J, Brandt J, Heuer D, Higginbotham E, Johnson C, Keltner J, Miller J, Parrish R, Wilson M, Kass M. The Ocular Hypertension Treatment Study: Baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002; 120:714-720.
18. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. *J Health Econ* 1995; 14:171-189.
19. Statline. Available at: <http://statline.cbs.nl/StatWeb/>. Accessed: 2010
20. Van Gestel A, Webers C, Beckers H, Van Dongen C, Severens J, Hendrikse F, Schouten J. The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye* 2010; 24:1759-1769.
21. Rodenburg-Van Dielen H. Guidelines for pharmacoeconomic research (version 2006). Diemen, The Netherlands: Health Insurance Board, 2005.

22. Van Hout BA, Al M, Gordon G, Rutten F. Costs, effects and C/E ratios alongside a clinical trial. *Health Econ* 1994; 3:309-319.
23. Felli JC, Hazen GB. Sensitivity analysis and the expected value of perfect information. *Med Decis Making* 1998; 18:95-109.
24. Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for cost-effectiveness in health care Health Technology Assessment (HTA). KCE reports 100C (D/2008/10273/96). Brussels, Belgium: Belgian Health Care Knowledge Centre (KCE), 2008.
25. Raad voor Volksgezondheid en Zorg (Council for Public Health and Health Care). Zinnige en duurzame zorg (Sensible and sustainable care). Zoetermeer: RVZ, 2006.
26. Verweij A, Barnhoorn M, Van den Berg M. Wat is de kosteneffectiviteit van preventie? (What is the cost-effectiveness of prevention). *Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid* (Exploration of future public health National compass of public health). Bilthoven: Rijksinstituut voor volksgezondheid en milieu (Research for man and environment), 2008.
27. Gafni A, Birch S. Incremental cost-effectiveness ratios (ICERs): the silence of the lambda. *Soc Sci Med* 2006; 62:2091-2100.
28. Stewart WC, Stewart JA, Nassar QJ, Mychaskiw MA. Cost-effectiveness of treating ocular hypertension. *Ophthalmology* 2008; 115:94-98.
29. Rein D, Wittenborn J, Lee P, Wirth K, Sorensen S, Hoerger T, Saaddine J. The cost-effectiveness of routine office-based identification and subsequent medical treatment of primary open-angle glaucoma in the United States. *Ophthalmology* 2009; 116:823-832.
30. Peeters A, Schouten JS, Webers CA, Prins MH, Hendrikse F, Severens JL. Cost-effectiveness of early detection and treatment of ocular hypertension and primary open-angle glaucoma by the ophthalmologist. *Eye* 2008; 22:354-362.
31. Burr J, Mowatt G, Hernández R, Siddiqui M, Cook J, Lourenco T, Ramsay C, Vale L, Fraser C, Azuara-Blanco A, Deeks J, Cairns J, Wormald R, McPherson S, Rabindranath K, Grant A. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007; 11.
32. The European Central Bank, Euro foreign exchange reference rates. Available at: <http://www.ecb.europa.eu/stats/eurofxref/eurofxref-hist.xml>. Accessed: November 2011
33. Oostenbrink J, Rutten-van Mölken M, Sluyter-Opdenoordt T. Resource use and costs of patients with glaucoma or ocular hypertension: a one-year study based on retrospective chart review in the Netherlands. *J Glaucoma* 2001; 10:184-191.
34. Kobelt G, Jönsson L. Modeling cost of treatment with new topical treatments for glaucoma. *Int J Technol Assess Health Care* 1999; 15:207-219.
35. Traverso CE, Walt JG, Kelly SP, Hommer AH, Bron AM, Denis P, Nordmann JP, Renard JP, Bayer A, Grehn F, Pfeiffer N, Cedrone C, Gandolfi S, Orzalesi N, Nucci C, Rossetti L, Azuara Blanco A, Bagnis A, Hitchings R, Salmon JF, Bricola G, Buchholz PM, Kotak SV, Katz LM, Siegartel LR, Doyle JJ. Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilisation in Europe. *Br J Ophthalmol* 2005; 89:1245-1249.
36. Pharmacotherapeutic compass (Farmacotherapeutisch kompas). Available at: www.fk.cvz.nl. Accessed: December 2007
37. Foundation for pharmaceutical statistics (Stichting Farmaceutische Kengetallen). Data and facts 2007 (Data en feiten 2007).
38. Oostenbrink J, Bouwmans C, Koopmanschap M, Rutten F. Manual for costing research (Handleiding voor kostenonderzoek; Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg). Diemen, The Netherlands: Health Care Insurance Board (CVZ), 2004.
39. Oostenbrink J, Rutten-van Mölken M, Opdenoordt T. The treatment of newly diagnosed patients with glaucoma or with ocular hypertension in the Netherlands: an observational study of costs and initial treatment success based on retrospective chart review. *Doc Ophthalmol* 1999; 98:285-299.
40. Dutch Healthcare Authority (Nederlandse Zorgautoriteit). Maximum tariffs (Tariefbeschikking maximumtarieven extramurale zorg in het tweede en derde compartiment). 2007.
41. GIP database. Available at: www.gipdatabank.nl. Accessed: 2006

**The long term effectiveness and
cost-effectiveness of initiating
treatment for ocular hypertension**

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Introduction

In the manuscript “The long term effectiveness and cost-effectiveness of initiating treatment for ocular hypertension” we have reported the forecasted long-term health and cost outcomes of direct treatment initiation in patients with ocular hypertension compared to a watchful waiting strategy. The data underlying the forecasts were generated with a discrete event simulation model that simulated the lifelong treatment and disease progression of individual ocular hypertension patients. The construction and validation of the model itself have been reported elsewhere.¹ An overview of the structural relationships, the way treatment was simulated, and the sources of the base-case values of the main parameters in the model have been presented in an article and its supplemental material in *Acta Ophthalmologica* recently.² The current appendix lists model structure elements and input parameter that differ from or are additional to those previously reported. This appendix also provides the derivation of parameters for the population-level distributions used in the probabilistic sensitivity analysis, and a collection of additional results not reported in the main article.

Visit schedule

We used a lookup table in the model to determine the time to the next scheduled visit (Table 6). The length of the time interval between two visits depended on two factors: 1) whether or not there had been a treatment change, and 2) the type of new treatment. The number of visits since that last treatment change is counted in the leftmost column of Table 6, while the new treatments are listed in the top row. For example, a patient that is not treated at all will visit the ophthalmologist every 12 months. In OHT patients, the first visit after a change in medication will take place 3 months after the change, but subsequent visits occur every 12 months as long as the treatment remains unaltered. After LT or surgery a series of short visit intervals follows to be able to monitor the patient closely. The visit frequency gradually returns back to the normal interval length.

Distribution of patient-level attributes

The gender of each simulated patient, the initial age and IOP, and the degree of MD loss after conversion was determined by a random draw from distributions that had the characteristics described below. The derivation of the distribution parameters as reported below was reprinted from an earlier publication.¹

Table 6 Periods between visits in base case model.

Visit number	No treatment	After change of medication OHT	After change of medication POAG	LT	Surgery
1	12 months	3 months	3 months	1 week	3 days
2	12 months	12 months	6 months	5 weeks	3 days
3	12 months	12 months	6 months	6 months	3 days
4	12 months	12 months	6 months	6 months	3 days
5	12 months	12 months	6 months	6 months	1 week
6	12 months	12 months	6 months	6 months	1 week
7	12 months	12 months	6 months	6 months	1 week
8	12 months	12 months	6 months	6 months	2 weeks
9	12 months	12 months	6 months	6 months	2 weeks
10	12 months	12 months	6 months	6 months	1 month
> 10	12 months	12 months	6 months	6 months	6 months

Age

The age distribution of patients with OHT in the disease progression model was derived from the Ocular Hypertension Treatment Study and the European Glaucoma Prevention Study.^{3,4} The average age of the patients with OHT in those studies was 55 ± 12 years (skewed to the right) and 57 ± 10 (skewed to the left) respectively. In the disease progression model the age distribution of OHT patients was assumed to be normal with average 55 and standard deviation 10.

Gender

The gender distribution of patients with OHT in the disease progression model was derived from the Ocular Hypertension Treatment Study and the European Glaucoma Prevention Study.^{3,4} The percentage of men in these studies was 43% and 46% respectively. In the disease progression model the gender distribution of OHT patients was assumed to be dichotomous with a 40% probability of the male gender.

Baseline IOP

The distribution of intra-ocular pressure of new patients in the model was based on the average intraocular pressure found in the OHTS (25 mmHg), the EGPS (24 mmHg) and the Groningen longitudinal glaucoma study (27 mmHg), and on the reported

distribution of IOP's in the patient population in the European Glaucoma Prevention Study (EGPS).³⁻⁶ The average IOP in the EGPS population was 23.6 ± 1.7 mmHg, but the distribution was strongly skewed to the right and truncated at 29 mmHg. In the disease progression model the distribution of intraocular pressure at baseline in the average population of OHT patients was assumed to be a normal distribution with average of 22 mmHg and standard deviation 4, but truncated on the left at 22 mmHg. The resulting distribution has an average IOP of 25 mmHg is skewed to the right, and includes intra-ocular pressures up to the high thirties.

MD after conversion

The value of the Mean Deviation after conversion in the disease progression model was based on the Groningen longitudinal glaucoma study, where the average MD in recently converted patients was -3.6 dB with a range of -0.8 dB to -7.6 dB (personal communication).⁶

The OHT population distribution of MD after conversion in the model was represented by a (negative) gamma distribution, which cannot take a value higher than zero. The latter restriction was built into the model because it was precluded that POAG patients can have MD values higher than zero. The parameters of the distribution were iterated to obtain a gamma distribution with an average of 3 dB and a standard deviation of 1 dB. The parameters of the final distribution were – Gamma (6, 0.5), which has an average of -3 dB and a range of -0.5 to -7.5 dB.

Note: the MD value in an OHT patient only becomes relevant at (and after) a conversion event. This does not mean that the model assumes that the establishment of conversion was based on the visual field only. Rather, conversion is modeled as an event, as a given fact, that is not necessarily observed by the ophthalmologist. The model's determination of the MD value in the converted patient is a consequence of the fact that the patient has converted, because the model needs an MD value to be able to further simulate the disease progression. The chosen distribution of MD values in newly converted patients includes MD values that are close to zero, which represent the patients with glaucomatous changes in optic disc but without apparent defects in their visual field.

Other prognostic factors

The presence of risk factors for conversion other than IOP and age in the model was aggregated in a single variable. The average of this value is 1, since the average population of the OHTS and the EGPS studies (on which the relative risk of IOP and age were based) has the average risk of conversion, i.e. no additional risk (or risk reduction). The distribution of the value of this variable however could not be derived from the OHTS or the EGPS studies, because the conversion risk model constructed

from the OHTS and EGPS study results has never been applied to the actual study populations themselves.⁷ The OHTS investigators have however used a cohort of patients from the “Diagnostic innovations in glaucoma study” (DIGS) to validate their predication model for the development of POAG.⁸ We have used the risk distribution in the DIGS cohort to deduct the distribution of additional risk in an OHT population. The distribution of the natural logarithm of the additional risk was assumed to be normal with an average 0 (since $e^0 = 1$). A population was simulated with an age and IOP distribution similar to that reported for the DIGS population, and hazard ratio's for age and IOP as reported by the OHTS/EGPS investigators.⁷ Subsequently we used a normal distribution to simulate the additional risk, and the standard deviation of this distribution was fine-tuned in such a way that the resulting distribution of risk in the population resembled the distribution reported for the DIGS population. With a standard deviation of 0.7, the resulting distribution of predicted risk of conversion resembled the DIGS cohort best.

Base case estimates and probabilistic sensitivity analysis

The derivation of all the parameter inputs in the model have been described extensively before.¹ Table 7 lists the values that were the result of those derivations, and that were used as the base case parameter inputs in the model. In the probabilistic sensitivity analysis reported in the main article, we have assessed how uncertainty about these base case parameter values might influence the incremental cost-effectiveness outcomes of the model. The distributions that were used to characterize the uncertainty in the base case parameters are listed in Table 7 too.

We have not previously described how we have arrived at the particular distributions listed in Table 7 to describe the uncertainty surrounding the base case model input. Therefore, what follows is a concise account of the sources we have consulted and the considerations we have made in this regard. This account is an addition to the previously published technical appendix about the model, and is therefore best read in conjunction with that.¹

In order to acknowledge the uncertainty in the actual conversion risk in the average population with ocular hypertension that reports to the ophthalmologist, we have used a triangular distribution of the risk with a minimum of 9% (stemming from the Kaplan-Meier estimate in the OHTS study), a most likely value of 10 and a maximum of 17% (stemming from the total cumulative risk after an average of 60 months of follow-up (median 55 months) in the EGPS study).⁵ The OHTS and the EGPS are both recent and large randomized placebo controlled trials and are therefore the

best sources for the estimation of the baseline risk of conversion in an untreated population.

Default estimates for drug effectiveness as monotherapy were derived from a meta-analysis of ‘all commonly used glaucoma drugs’ in 2005.⁹ This meta-analysis included studies that compared pressure-lowering eye-drops monotherapy to placebo in POAG and/or OH patients, and that used IOP as the primary endpoint of the study. It reported the point estimates of the average pressure lowering effectiveness, and also the 95% confidence limits of these estimates, which represent the point estimate $\pm$ 1.96 times the standard error of the mean. From this we derived that the standard error of the mean was typically around 1% with all medication. We used a beta distribution to describe the uncertainty surrounding the drug effectiveness estimates, and the method of moments with the most most likely value and the standard error of the mean lead to the alpha and beta parameters listed in Table 7.

The average effectiveness of medication after surgery was based on expert opinion.¹ We used a triangular distribution between 1.5 and 2.5 mmHg, with the most likely value at 2.0 mmHg to describe the uncertainty surrounding this estimate.

The effectiveness of LTP as monotherapy and added to concurrent medications were based on a literature review, but this review did not allow for a characterization of the uncertainty surrounding the base case effectiveness parameters. The uncertainty surrounding the effectiveness of LTP as monotherapy was characterized with a beta distribution and a 1% standard error, analogous to the effectiveness estimates of latanoprost. The uncertainty surrounding the effectiveness of LTP added to concurrent medication was characterized by a triangular distribution between 12% and 34%, derived from the lowest value found in literature and the default estimate for the effectiveness of LTP monotherapy.¹⁰⁻¹⁵

Timolol contraindications are asthma and severe chronic obstructive pulmonary disease, sinusbradycardia, second- or third degree atrioventricular block, and latent or uncontrolled heartfailure. In the DURING study, the prevalence of respiratory contraindications (which is the most evident and directive contraindication in clinical practice) was 123/1273.¹⁶ This was rounded up to a default estimate of 10%, and the absolute numbers were directly inserted in a beta distribution to reflect the uncertainty.

The prevalence of side-effects with each of the medications in the model was based on the results of the DURING study.¹⁷ Patients that were previously untreated and started pressure lowering medication, and patients that switched medication, were followed for the next three visits. When the initiated treatment was stopped due to side-effects this was registered. In the model, the occurrence of side-effects

means that the patient suffers from side-effects that are always a reason to switch to another therapy. There are a number of randomized controlled trials that investigate pressure lowering monotherapies and that report on the occurrence of adverse events, but from these number we cannot derive the occurrence of side-effects that warrant a treatment switch. Therefore we have based our estimates and the surrounding uncertainty solely on our observational data. We have used the original data from this research as an input to beta distributions. Alpha is the number of patients stopping treatment, and beta is the number of patients not stopping treatment.

The effect of surgery in the model was based on a literature review.¹⁸⁻²² In order to estimate the uncertainty in the estimate of the average IOP after trabeculectomy, we performed a quick meta-analysis of the data from these trials using Review Manager 4.2.9. We included all the studies that reported the mean postoperative IOP and a parameter of variance (standard deviation in all cases, $n=3$). The overall estimate of the postoperative IOP was 12.0 (95% CI 11.41; 12.65). In the probabilistic analyses we therefore used a normal distribution (12.5, 0.3) for the average IOP after trabeculectomy.

The point estimate of the IOP after a Baerveldt implantation was based on expert opinion and literature.^{19, 22, 23} In the probabilistic analyses we used a normal distribution (15, 0.37) for the average IOP after trabeculectomy. The estimate of the standard deviation for this distribution was derived by transforming the standard deviation reported by Gedde *et al* to the standard error of the mean.

The point-estimate for the relative risk of IOP for conversion to POAG was 1.09 for each mmHg higher than 23.9 mmHg, based on the results of the pooled OHTS/EGPS risk model and a meta-analysis performed in the University Eye Clinic Maastricht.^{7, 24} In the probabilistic analysis, the value of the relative risk of IOP per mmHg was drawn from a normal distribution with a mean of 1.09 and a standard deviation of 0.03, truncated at the value 1.00, based on the 95% confidence interval reported by Gordon *et al*.

The point-estimate for the relative risk of age for conversion to POAG was 1.26 per decade higher than 54.9 years, based on the results of the pooled OHTS/EGPS risk model.⁷ In the probabilistic analysis, the value of the relative risk of age per decade was drawn from a normal distribution with a mean of 1.26 and a standard deviation of 0.1, truncated at the value 1.00, based on the 95% confidence interval of the estimate by Gordon *et al*.

The base case estimate of the average rate of MD progression was based on a meta-analysis of studies reporting the annual MD change in treated patients.^{12, 25-28}

The literature review and method for the meta-analysis have been described elsewhere.¹ The average rate of MD change per year in treated patients was -0.33 dB/year with a 95% confidence interval of -0.38 to -0.28 . This equals 0.025 dB/month, with a 95% confidence interval of -0.032 to -0.023 . The standard error of the mean derived from this confidence interval is 0.0021 dB/month. In the probabilistic analyses, the mean MD change per month was therefore drawn from a normal distribution with mean = 0.028 and standard deviation = 0.0021.

The relative risk of IOP on the MD progression rate was derived from the results of the Early Manifest Glaucoma Study, where a multivariate Cox proportional hazards model correcting for age, baseline IOP, exfoliation, number of eligible eyes and MD found a hazard ratio of 1.13 (95% CI: 1.07; 1.19) per mmHg higher for IOP during follow-up.¹² We calculated the standard error of the mean from the reported confidence interval (i.e. 0.03), and used it as the standard deviation of the normal distribution that was used in the probabilistic sensitivity analysis.

The 'progression criterion' in the current model structure is a composite parameter that represents multiple clinical and statistical processes, and is therefore not measurable in clinical studies. In the definition of the base case value of the progression criterion, we took account of the fact that the model does not simulate intra-test variation but only simulates the 'real' MD value. We also considered the fact that in reality the intra-test variability in visual field tests is typically around 2 dB, and that it is common in clinical practice to perform a confirmatory visual field test after a routine test suggests deterioration of the visual field. If a visual field test is performed twice in a short term, and the Mean Deviation in both tests differs by more than 2 dB from the previous tests, than the chance that the difference is caused by intra-test variation rather than progression is small enough to substantiate adjustment of therapy or target pressure.²⁹ We felt that a statistically confirmed deterioration of the Mean Deviation by 2 dB is the lower boundary of the deterioration that warrants a treatment change in POAG patients, whereas a deterioration larger than 4 dB is the upper boundary, and it is not possible to define a most likely value. Therefore, the progression criterion was varied uniformly between 2 and 4 dB in the probabilistic sensitivity analysis.

The relative risk for cataract formation due to trabeculectomy was derived from a Cochrane systematic review.³⁰ The authors reported a relative risk of cataract extraction after surgery of 2.7 at up to three years follow-up, and a 95% confidence interval of 1.5 to 4.9. The uncertainty distribution for the relative risk for cataract from trabeculectomy was based on this outcome.

Table 7 Population parameters sampled in the probabilistic sensitivity analysis and their distributions representing the uncertainty surrounding the best estimate in the base case model.

Variable	Distribution	Mean	SD	Minimum	Maximum	Most likely (base case)	Alpha	Beta
Baseline conversion risk at 24 mmHg	Triangular			0.090	0.170	0.095		
	Source: ^{3, 5}							
Timolol pressure lowering, monotherapy (fraction)	Beta					0.27	511	1381
	Source: ⁹							
Latanoprost pressure lowering effect, monotherapy (fraction)	Beta					0.30	589	1407
	Source: ⁹							
Dorzolamide pressure lowering effect, monotherapy (fraction)	Beta					0.20	294	1213
	Source: ⁹							
Brimonidine pressure lowering effect, monotherapy (fraction)	Beta					0.21	148	559
	Source: ⁹							
Pressure lowering after surgery (mmHg)	Triangular			1.5	2.5	2		
	Source: (Expert opinion)							
LTP monotherapy (fraction)	Beta					0.34	763	1480
	Source: ¹⁰⁻¹⁵							
LTP added to medication (fraction)	Triangular			0.12	0.34	0.18		
	Source: ¹⁰⁻¹⁵							
Prevalence of Timolol contraindications	Beta					0.10	123	1396
	Source: ³²							
Side-effects with Timolol (prevalence)	Beta					0.08	10	109
	Beta					0.08	22	258
	Beta					0.14	2	12
	Beta					0.23	5	17
	Source: ¹⁷							
IOP after TE (mmHg)	Normal	12.5	0.3			12.5		
	Source: ¹⁰⁻¹⁵							
IOP after Implant (mmHg)	Normal	15	0.37			15		
	Source: ^{19, 22-23}							
Relative Risk of conversion by IOP (per mmHg higher)	Normal	1.09	0.03	1	100	1.09		
	Source: ^{7, 24}							
Relative Risk of conversion by age (per decade higher)	Normal	1.26	0.1	1	100	1.26		
	Source: ⁷							
Rate of visual field loss (dB/month)	Normal	0.028	0.0021			0.028		
	Source: ^{12, 25-28}							
Relative Risk of visual field loss rate by IOP (per mmHg higher)	Normal	1.13	0.03			1.13		
	Source: ¹²							
Progression criterion (dB lost)	Uniform	2	4			2		
	Source: Expert opinion							
Relative risk for cataract from trabeculectomy	Triangular			1.5	4.9	2.7		
	Source: ³⁰							
Costprice medication (factor)*	Triangular			0.75	1.25	1		
	Triangular			0.5	2	1		
	Triangular			0.5	2	1		
	Triangular			0.5	2	1		
	Triangular			0	2	1		
Costs care (factor)*	Triangular			0	2	1		
	Source: Expert opinion							
HUI: Beta for MD (per dB)	Normal	0.01	0.002	0	100	0.01		
	Normal	-0.1	0.05	-100	0	-0.1		
	Normal	-0.059	0.0743	-100	0	-0.059		
IOP below which no progression (mmHg)	Triangular			12	14	13		
	Source: Expert opinion, ^{33, 34}							

*Factor indicates that all parameter estimates are multiplied by a factor in the probabilistic sensitivity analyses. In the base case model the factor is 1.

The uncertainty surrounding the cost prices used as model input was captured in triangular distributions between half their base case estimate and double their base case estimate. These distributions reflect the fact that we cannot precisely quantify the degree of uncertainty around the cost-price estimates. The lower and upper boundaries of the distributions are arbitrary, but not unrealistic, and they are based on the actual differences in cost-price estimates that we found in all the sources that we consulted.¹ The uncertainty surrounding medication cost prices was smaller than the uncertainty surrounding the cost price of surgery, and the highest degree of uncertainty surrounded the cost price of low-vision related care.

The base case parameters for the Health Utilities Index were based on linear regression analyses with data from an observational study in OHT and POAG patients conducted in our own institution.³¹ The distributions of the uncertainty surrounding these parameters were based on the standard error of the mean of the regression coefficients in the same regression analyses.

Additional results

The outcomes of the probabilistic sensitivity analysis indicated that uncertainty in population parameters did not contribute to decision uncertainty regarding the initiation of treatment in a heterogeneous OHT population (Figure 2, main article). The EVPI dropped to zero at willingness-to-pay thresholds higher than € 10,000 per QALY, which suggests that there is little value in further research to reduce uncertainty surrounding any of the population parameters in the model (Figure 3, main article). Nevertheless, we have performed analysis of covariance to assess the impact of the uncertain population parameters on the cost-effectiveness outcomes. We used the incremental net monetary benefit (INMB) framework to do so. The INMB is calculated from a reformulation of the equation to assess the acceptability of the ICER: $\Delta C/\Delta E \leq \lambda$ becomes $\Delta E * \lambda - \Delta C \geq 0$ (λ is the acceptability threshold). A positive INMB indicates an acceptable ICER, and a higher number indicates more value for money. We have used an acceptability threshold of € 30,000 per QALY based on ranges mentioned in literature and authority reports, although in the Netherlands the threshold may be lower at € 20,000 per QALY for preventive care.³⁵⁻³⁷ The total variance in INMB explained was 95%. The most influential parameters in terms of contribution to the total sum of squares were the relative risk of IOP for conversion, the utility loss due to visual field deterioration, the contribution of IOP to the rate of visual field deterioration, the population risk of conversion, and the costs of low-vision related care (Figure 4). Despite their impact on the cost-effectiveness outcomes, variation in these parameters within uncertainty

Figure 4 Results from analysis of covariance with probabilistic sensitivity analysis outcomes. The bars represent the proportion of the sum of squares in the total incremental net monetary benefit (at an acceptability threshold of 30,000 euro per QALY) explained by the population parameter. Only the six parameters with the highest proportions are shown.

HR= hazard ratio; dB= decibels lost in the visual field's mean deviation.

limits did not lead to negative INMB outcomes at the chosen acceptability threshold and did therefore not affect the direction of the conclusion.

We have studied the cost-effectiveness of direct treatment versus watchful waiting in subgroups of ocular hypertension patients based on initial IOP and risk factors for conversion other than age and IOP separately. However, both factors contribute to the total risk of conversion. The total conversion risk of the investigated subgroups is listed in table 3 in the main article. We have used the outcomes of the subgroup analyses to investigate the option to base the decision to initiate treatment solely on the total conversion risk, rather than on IOP and additional risk factors separately. We plotted the INMB of direct treatment in each of the subgroups against the average total conversion risk in that subgroup. Figure 5 shows that all subgroups had a positive INMB, which is in agreement with the observation that the ICER of direct treatment was below € 30,000 per QALY in all subgroups. If the cost-effectiveness of direct treatment would depend solely on the total risk of conversion, the INMB outcomes of the subgroups would have overlapped in the graph and would have blended together to one line. The fact that they did not do that suggests that IOP has an extra effect on the cost-effectiveness outcomes apart from its contribution to the total conversion risk. For example, consider the two points drawn in figure 5 at a total conversion risk of 10% in 5 years. The INMB of direct treatment was much higher in patients with an initial IOP of 32 mmHg than in patient with an initial IOP of 24 mmHg, even though the average total conversion risk was similar in both populations (10%).

Figure 5 Incremental net monetary benefit of direct treatment compared to watchful waiting in 18 subgroups of OHT patients based on additional risk (marker series) and IOP. The points within the marker series represent increasing IOP: from left to right 22, 24, 26, 28, 30 and 32 mmHg.

Two conclusions can be drawn from Figure 5. One is based on the positive slope of the dots, which indicates that the total risk of conversion affects the long-term cost-effectiveness of treatment. All risk factors for conversion should therefore be taken into consideration in the decision to initiate pressure-lowering treatment. The other conclusion is based on the incongruence of the dots, which indicates that IOP has an extra impact on the long-term cost-effectiveness of treatment in addition to its impact via the total conversion risk. This would argue for a separate consideration of the IOP in decisions concerning treatment initiation in ocular hypertension. We must consider that this latter conclusion is made in the context of the application of a target pressure in current clinical practice, and indeed in the definition of successful treatment in the model. The cost-effectiveness outcomes as drawn in Figure 5 may have indeed blended together if all patients had been treated to achieve a target *risk* rather than a target *pressure*. The target pressure was defined as 21 mmHg in all subgroups, so the patients with an initial IOP of 32 mmHg received a much more intensive treatment than patients with an initial IOP of 24 mmHg. Likewise, their conversion risk would be lowered more profoundly by treatment, which probably explains the more beneficial cost-effectiveness outcome of direct treatment.

References

1. Van Gestel A, Severens J, Webers C, Beckers H, Jansonius N, Schouten J. Modeling complex treatment strategies: construction and validation of a discrete event simulation model for glaucoma. *Value Health* 2010; 13:358-367.
2. Van Gestel A, Webers C, Beckers H, Severens J, Jansonius N, Hendrikse F, Schouten J. The cost-effectiveness of four strategies to treat primary open-angle glaucoma. *Acta Ophthalmol* 2012; 90:20-31.
3. Kass M, Heuer D, Higginbotham E, Johnson C, Keltner J, Miller J, Parrish R, Wilson R, Gordon M, the Ocular Hypertension Treatment Study Group. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002; 120:701-713.
4. The European Glaucoma Prevention Study (EGPS) Group. The European Glaucoma Prevention Study design and baseline description of the participants. *Ophthalmology* 2002; 109:1612-1621.
5. Miglior S, Zeyen T, Pfeiffer N, Cunha-Vaz J, Torri V, Adamsons I, The European Glaucoma Prevention Study (EGPS) Group. Results of the European Glaucoma Prevention Study. *Ophthalmology* 2005; 112:366-375.
6. Heeg GP, Jansonius NM. The Groningen longitudinal glaucoma study III. The predictive value of frequency-doubling perimetry and GDx nerve fibre analyser test results for the development of glaucomatous visual field loss. *Eye* 2008.
7. Gordon MO, Torri V, Miglior S, Beiser JA, Floriani I, Miller JP, Gao F, Adamsons I, Poli D, D'Agostino RB, Kass MA. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. *Ophthalmology* 2007; 114:10-19.
8. Medeiros F, Weinreb R, Sample P, Gomi C, Bowd C, Crowston J, Zangwill L. Validation of a predictive model to estimate the risk of conversion from ocular hypertension to glaucoma. *Arch Ophthalmol* 2005; 123:1351-1360.
9. Van der Valk R, Webers C, Schouten J, Zeegers M, Hendrikse F, Prins M. Intraocular pressure-lowering effects of all commonly used glaucoma drugs - a meta-analysis of randomized clinical trials. *Ophthalmology* 2005; 112:1177-1185.
10. McIlraith I, Strasfeld M, Colev G, Hitnik C. Selective laser trabeculoplasty as initial and adjunctive treatment for open-angle glaucoma. *J Glaucoma* 2006; 15:124-130.
11. Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT) and Glaucoma Laser Trial Follow-up Study: 7. Results. *Am J Ophthalmol* 1995; 120:718-731.
12. Heijl A, Leske C, Bengtsson B, Hyman L, Bengtsson B, Hussein M, for the Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression; results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002; 120:1268-1279.
13. Chung P, Schuman J, Netland P, Lloyd-Muhammad R, Jacobs D. Five-year results of a randomized, prospective, clinical trial of diode vs argon laser trabeculoplasty for open-angle glaucoma. *Am J Ophthalmol* 1998; 126:185-190.
14. Damji K, Shah K, Rock W, Bains H, Hodge W. Selective laser trabeculoplasty versus argon laser trabeculoplasty: a prospective randomised clinical trial. *Brit J of Ophthalmol* 1999; 83:718-722.
15. Juzych M, Chopra V, Banitt M, Hughes B, Kim CS, Goulas M, Shin D. Comparison of long-term outcomes of selective laser trabeculoplasty versus argon laser trabeculoplasty in open-angle glaucoma. *Ophthalmology* 2004; 111:1853-1859.
16. Van der Valk R. PhDThesis: Glaucoma medication; evidence from clinical trials and effects in practice. *University Eye Clinic*. Maastricht: University of Maastricht; 2005:125.
17. Beckers HJ, Schouten JS, Webers CA, van der Valk R, Hendrikse F. Side effects of commonly used glaucoma medications: comparison of tolerability, chance of discontinuation, and patient satisfaction. *Graefes Arch Clin Exp Ophthalmol* 2008; 246:1485-1490.
18. Beckers H, Kinders K, Webers C. Five-year results of trabeculectomy with mitomycin C. *Graefes Arch Clin Exp Ophthalmol* 2003; 241:106-110.
19. Wilson M, Mendis U, Paliwal A, Haynatzka V. Long-term follow-up of primary glaucoma surgery with Ahmed glaucoma valve implant versus trabeculectomy. *Am J Ophthalmol* 2003; 136:464-470.

20. Singh K, Mehta K, Shaikh N, Tsai J, Moster M, Budenz D, Greenfield D, Chen P, Cohen J, GS B, Shaikh S, Group tPTAS. Trabeculectomy with intraoperative mitomycin C versus 5-fluorouracil; prospective randomized clinical trial. *Ophthalmology* 2000; 107:2305-2309.
21. Wudunn D, Cantor L, Palanca-Capistrano A, Hoop J, Alvi N, Finley C, Lakhani V, Burnstein A, Knotts S. A prospective randomized trial comparing intraoperative 5-fluorouracil vs mitomycin C in primary trabeculectomy. *Am J Ophthalmol* 2002; 134:521-528.
22. Gedde S, Schiffman J, Feuer W, Herndon L, Brandt J, Budenz D, group tTvts. Treatment outcomes in the Tube Versus Trabeculectomy study after one year of follow-up. *Am J Ophthalmol* 2007; 143:9-22.
23. Goulet RJ, 3rd, Phan AD, Cantor LB, Wudunn D. Efficacy of the Ahmed S2 Glaucoma Valve Compared with the Baerveldt 250-mm² Glaucoma Implant. *Ophthalmology* 2007.
24. Peeters A, Webers C, Prins M, Zeegers M, Hendrikse F, Schouten J. Quantifying the effect of intra-ocular pressure reduction on the occurrence of glaucoma. *Acta Ophthalmol* 2010; 88:5-11.
25. Smith SD, Katz J, Quigley HA. Analysis of progressive change in automated visual fields in glaucoma. *Invest Ophthalmol Vis Sci* 1996; 37:1419-1428.
26. Katz J, Gilbert D, Quigley HA, Sommer A. Estimating progression of visual field loss in glaucoma. *Ophthalmology* 1997; 104:1017-1025.
27. Chen P, Bhandari A. Fellow eye prognosis in patients with severe visual field loss in 1 eye from chronic open-angle glaucoma. *Arch Ophthalmol* 2000; 118:473-478.
28. Chen PP. Correlation of visual field progression between eyes in patients with open-angle glaucoma. *Ophthalmology* 2002; 109:2093-2099.
29. Vesti E, Johnson C, Chauhan B. Comparison of different methods for detecting glaucomatous visual field progression. *Invest Ophthalmol Vis Sci* 2003; 44:3873-3879.
30. Burr J, Azuara-Blanco A, Avenell A. Medical versus surgical interventions for open angle glaucoma. *The Cochrane Database of Systematic Reviews* 2004; Issue 2. Art.No.: CD004399.pub004392. DOI: 004310.001002/14651858. CD14004399.pub14651852.
31. Van Gestel A, Webers C, Beckers H, Van Dongen C, Severens J, Hendrikse F, Schouten J. The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye* 2010; 24:1759-1769.
32. Van der Valk R, Webers C, Schouten J, De Vogel S, Hendrikse F, Prins M. PhD Thesis "Glaucoma medication; evidence from clinical trials and effects in practice". Chapter 5: Predicting IOP change before initiating therapy: timolol vs latanoprost (the DURING study). *Department of Epidemiology*. Maastricht, The Netherlands: Maastricht University; 2005.
33. The AGIS investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000; 130:429-440.
34. Shirakashi M, Iwata K, Sawaguchi S, Abe H, Nanba K. Intraocular pressure-dependent progression of visual field loss in advanced primary open-angle glaucoma: a 15-year follow-up. *Ophthalmologica* 1993; 207:1-5.
35. Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for cost-effectiveness in health care Health Technology Assessment (HTA). KCE reports 100C (D/2008/10273/96). Brussels, Belgium: Belgian Health Care Knowledge Centre (KCE), 2008.
36. Raad voor Volksgezondheid en Zorg (Council for Public Health and Health Care). Zinnige en duurzame zorg (Sensible and sustainable care). Zoetermeer: RVZ, 2006.
37. Verweij A, Barnhoorn M, Van den Berg M. Wat is de kosteneffectiviteit van preventie? (What is the cost-effectiveness of prevention). *Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid* (Exploration of future public health National compass of public health). Bilthoven: Rijksinstituut voor volksgezondheid en milieu (Research for man and environment), 2008.

Chapter 7

The role of the expected value of individualized care in cost-effectiveness analyses and decision making

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Abstract

Objective: To explore the feasibility and potential role of the expected value of individualized care (EVIC) framework.

Methods: The EVIC quantifies how much benefits are forgone when a treatment decision is based on the best expected outcomes in the population rather than in the individual patient. We have reviewed which types of patient-level attributes contribute to the EVIC, and how they affect the interpretation of the outcomes. Additionally, we have applied the EVIC framework to the outcomes of a microsimulation-based cost-effectiveness analysis for glaucoma treatment.

Results: In order for EVIC outcomes to inform decisions about clinical practice, we need to calculate parameter-specific EVIC of known or knowable patient-level attributes, and compare it with the real costs of implementing individualized care. In the case study, the total EVIC was € 580 per patient, but patient-level attributes known at treatment decision had minimal impact. A subgroup policy based on individual disease progression could be worthwhile, if a predictive test for glaucoma progression could be developed and implemented for less than €130 per patient.

Conclusions: The EVIC framework is feasible in cost-effectiveness analyses and can be informative for decision making. The EVIC outcomes are particularly informative when they are (close to) zero. When the EVIC has a high value, implications depend on the type of patient-level attribute. EVIC can be a useful tool to identify opportunities to improve efficiency in healthcare by individualization of care, and to quantify the maximal investment opportunities for implementing subgroup policy.

Introduction

Decisions about the use of health care technologies are made on a daily basis, both in a policy setting concerning the adoption of a technology for a population in general, and in the clinical setting concerning treatment choices for individual patients. Such decisions are often complex and made in the context of uncertainty. Scientific decision analysis that employs a model representing the care system and patients of interest can inform such decisions. It enables a rational and objective assessment of the options, and provides insight in the probability that they are optimal. Therefore, decision analysis provides a tool to handle the existence of uncertainty, but it does not negate it. Indeed, the outcomes of medical decision analyses are surrounded by uncertainty of two main types. The first is that we do not have a precise estimate of the mean expected outcomes in the population.¹ The second is that patients are unique and therefore differ in expected outcomes.²

Uncertainty surrounding the population mean expected outcomes has relevance for decisions that are made on a population level, like which strategy should be the standard approach and which treatment should be reimbursed. Arguments have been made that societal decision making should be based on the expected outcomes of economic analyses, not on their statistical significance.³ However, exploration of uncertainty can play an important role in adoption decisions and provide valuable information for decisions regarding future research.^{4, 5} Several methods have been developed to assess the impact of various types of uncertainty on the expected outcomes and to use the outcomes of uncertainty analysis to prioritise future research.^{6, 7} One of these methods is the value of information analysis (VOI), which integrates information on the probability of making the wrong decision with its consequences in terms of health effects and resources forgone.^{8, 9} VOI analysis is applicable to all uncertainty that can be expressed in probability distributions and is often used to assess uncertainty in population parameters. In the latter context it is predominantly referred to as expected value of perfect information (EVPI) analysis.¹⁰ The EVPI represents the value society is willing to pay to optimize decision making at the population level, and can inform decisions about additional research to reduce population parameter uncertainty.

However, even if we had absolute certainty about the mean expected outcomes in the population, we still know that individual patients differ from one another, and therefore have different expected outcomes due to heterogeneity and variability.¹¹ Variability is the variation in outcomes that is the result of randomness, or “the random chance that patients with the same underlying parameters will experience a different outcome”.¹¹ Variability has also been defined in this context as stochastic

uncertainty.⁷ Heterogeneity on the other hand relates to the variation in outcomes that can be explained by patient-level attributes, like e.g. age, disease stage and co-morbidity.¹¹ Patient-level uncertainty (i.e. heterogeneity and variability) may not affect population expected values and therefore not affect population-level decision making, but knowledge of the impact of heterogeneity could identify opportunities to improve health care by adopting subgroup policies or making individual treatment decisions. It is natural for health care providers to acknowledge heterogeneity, and aim for individualized care to optimize the welfare of their patients. The growing attention for individualized care is also reflected in formal decision analysis. For instance, models are being developed to predict the effect of different cancer treatment modalities on survival and side-effects in individual patients, based on the patient's attributes.¹²

In 2007, Basu and Meltzer introduced a theoretical framework for value of information analysis based on uncertainty about cost-effectiveness outcomes in individual patients.¹³ They termed it the expected value of individualizing care (EVIC) framework, and argued that the EVIC represents the potential value that society is willing to pay so that individually efficient decisions are made. In their example, individualization was based on patients' preferences, but they stated that the method would also be applicable to other individual-level attributes that might affect the costs and/or benefits of treatments.¹³ Since the EVIC framework could be a tool in the generation of decision support regarding individualized care, this paper aims to examine the feasibility of the EVIC framework when patient-level attributes other than preferences are considered, and how this affects the interpretation of the EVIC. Additionally, we aimed to explore the potential role of EVIC in decision making. The remainder of this paper is organised in three sections. The first provides a theoretical consideration of the EVIC framework and the interpretation of the outcomes. An empirical application of the framework is presented in the second section, and the final section provides a discussion of practical issues we encountered and suggests implications of the main findings of this paper.

Methods

Conceptual framework of EVIC

Within the expected value of individualized care framework, two approaches to patient management are compared.¹³ The first is the population-based approach, in which all patients receive the same treatment: the one that is optimal for the population outcomes. The second is the individualized approach, in which each patient receives the treatment that leads to optimal outcomes in that individual patient. We speak of

individualized care when any medical decision in the care cycle depends on a patient-level attribute. This can be as simple as a subgroup policy based on a single attribute (e.g. breast cancer screening based on age), or as complex as a custom made treatment plan for an individual patient based on a multitude of patient-level attributes like treatment history, biomarker profile and risk factors.

The expected value of individualized care quantifies the benefits forgone when a population-based approach is used rather than an individualized approach. The concept can be illustrated with the fictive results in Figure 1 (adapted from Basu and Meltzer, 2007).¹³ This figure shows the incremental cost-effectiveness of a hypothetical treatment relative to no treatment in three individual patients. Each cross represents the incremental costs and effects (in quality-adjusted life-years (QALY)) of treatment in each individual patient. The diamond represents the average incremental cost-effectiveness ratio (ICER) in the population, and indicates that treatment is expected to increase average health at some additional costs. The average ICER is lower than the maximum amount society is willing to pay for an extra QALY (λ) and would therefore justify a population-based approach to 'treat everybody'. However, the figure also shows that treatment is not effective (patient 3) nor cost-effective (patient 2 and 3) in all patients, and an individualized approach would render better overall outcomes.

Calculation of EVIC

The benefits forgone with a population-based approach may include both costs and effects and are expressed in either monetary units (net monetary benefit, NMB) or health units (net health benefit, NHB). In the present paper we use the NMB statistic, which is calculated by multiplying the health effects with the willingness-to-pay threshold λ , and subtracting the costs. A treatment is cost-effective when the incremental net monetary benefit (INMB) is positive. In this paper we use the prefix *i* (as in *i*NMB) to indicate individual patient outcomes rather than average population outcomes.

The EVIC is calculated as the average of the maximum net benefits of the treatments in each patient minus the maximum of the average net benefits of the treatments in all patients as denoted in equation 1,

$$EVIC = \int_{\theta \in \Theta} \{\max_j iNMB_j(\theta)\} p(\theta) d\theta - \max_j \int_{\theta \in \Theta} iNMB_j(\theta) p(\theta) d\theta \quad (1)$$

in which j represents the treatment options, θ is a vector of patient-level attributes that determine the net monetary benefits from any treatment j , and $p(\theta)$ is the joint distribution of θ in the population.¹³

The calculation of EVIC is analogous to the calculation of EVPI, but there are important differences too (Table 1). Equation 1 can be simplified to $EVIC = \text{Mean}_{\theta} \{ \text{Max}_j \text{iNMB}_j \} - \text{Max}_j \{ \text{Mean}_{\theta} \text{iNMB}_j \}$.¹⁴ An example of the calculation of EVIC based on fictive data for the patients in Figure 1 is listed in Table 2. Treatment results in the highest average iNMB per patient (€ 158,000), but the maximal achievable average iNMB (€ 178,000) would be obtained if only patient 1 were treated. Individualization of the treatment decision would therefore render € 20,000 per patient.

The results in the example show that it is most efficient to treat only patient 1, not patient 2 and 3. It also shows that treatment is beneficial for patient 1 while it harms patient 3. However, treatment is beneficial for patient 2, but this patient would not receive treatment in the individualized approach discussed above, due to the relatively high costs. This is the consequence of optimizing the decision with an efficiency goal, but it is questionable whether it is ethical to withhold treatment for patient 2. For this reason, Basu and Meltzer introduced the 'EVIC without cost internalization'.¹³ In this alternative approach, the optimal intervention for each individual

Table 1 Similarities and differences between EVIC and EVPI.

		EVIC	EVPI
Level	Captures the value of optimizing treatment decision on the level of the	Individual patient	Population
Source		Patient heterogeneity and variability	Population parameter uncertainty
Source	Magnitude depends on differences between	Individual ICERs	Average population ICERs
Source	Data generated by	Patient level simulation or individual comparative effectiveness research	Probabilistic sensitivity analysis of population parameters
Calculation	Total	$EVIC = \text{Mean}_{\theta} \{ \text{Max}_j \text{iNMB}_j \} - \text{Max}_j \{ \text{Mean}_{\theta} \text{iNMB}_j \}$	$EVPI = \text{Mean}_{\phi} \{ \text{Max}_j \text{NMB}_j \} - \text{Max}_j \{ \text{Mean}_{\phi} \text{NMB}_j \}$
Calculation	Parameter specific	$EVIC_{\theta_i} = EVIC - (\text{Mean}_{\theta_i} [\text{Mean}_{\theta_c} \{ \text{Max}_j \text{iNMB}_j (\theta_c \theta_i) \}] - \text{Mean}_{\theta_i} [\text{Max}_j \{ \text{Mean}_{\theta_c} \text{iNMB}_j (\theta_c \theta_i) \}])$	$EVPI_{\phi_i} = EVPI - (\text{Mean}_{\phi_i} [\text{Mean}_{\phi_c} \{ \text{Max}_j \text{NMB}_j (\phi_c \phi_i) \}] - \text{Mean}_{\phi_i} [\text{Max}_j \{ \text{Mean}_{\phi_c} \text{NMB}_j (\phi_c \phi_i) \}])$
Foundation		Many values for a patient-level attribute exist within a patient population, and the optimal treatment decision for an individual patient depends on the value of that attribute.	There is one true value for a parameter in the population, and the average optimal treatment decision for the patient population depends on the value of that parameter.
Interpretation	The magnitude indicates the	Maximal value of implementing individualized care	Maximal value of performing additional research into the population parameter
Interpretation		Total EVIC value is not informative, unless it is zero	Total EVPI value is not informative, unless it is zero
Interpretation		Parameter-specific EVIC is informative in combination with information on the actual costs of implementing individualized care	EVPI is informative in combination with information on the actual costs of additional research
Relationship		EVIC and EVPI are not correlated. The value of EVPI does not predict the value of EVIC, nor vice versa.	

EVIC= expected value of individualizing care; EVPI= expected value of perfect information; ICER= incremental cost-effectiveness ratio; EVPI= parameter-specific EVPI; θ = vector of patient-level attributes; θ_i = patient-level attribute of interest; θ_c = remaining patient-level attributes; j = treatment options; iNMB= individual net monetary benefit; ϕ = vector of population parameters; ϕ_i = parameter of interest; ϕ_c = remaining (uncertain) parameters.

Table 2 Calculation of EVIC based on fictive outcomes data for patient 1, 2 and 3 in Figure 1.

	No treatment			Treatment			iINMB in population based approach	Max iINMB in individualized care
	Costs	QALY's	iINMB	Costs	QALY's	iINMB		
Patient 1	€ 1,000	5	€ 149,000	€ 4,000	8	€ 236,000	€ 87,000	€ 236,000
Patient 2	€ 1,000	5	€ 149,000	€ 31,000	5.5	€ 134,000	-€ 15,000	€ 149,000
Patient 3	€ 1,000	5	€ 149,000	€ 31,000	4.5	€ 104,000	-€ 45,000	€ 149,000
Mean ₀ (iINMB)			€ 149,000			€ 158,000		
Max ₋₁ {Mean ₀ (iINMB)}						€ 158,000		
Mean ₀ {Max ₋₁ (iINMB)}								
EVIC	€ 178,000 - € 158,000 = € 20,000							€ 178,000

iINMB= individual net monetary benefit when $\lambda = € 30,000/QALY$

Figure 1 Cost-effectiveness plane with incremental outcomes of three individual patients (✱) and the population-based mean incremental cost-effectiveness ratio (◆), adapted from Basu and Meltzer 2007.¹³

patient is the one that produces the maximum expected health benefits. In the example this would lead to the decision to treat patient 1 and 2 (not 3), and the EVIC without cost internalization would be € 15,000 per patient (Table 3).

Calculation of EVIC requires data on the outcomes of each treatment option in each individual patient, so data from most (randomized) clinical studies are not suitable for EVIC analysis as they divide the study population into separate study arms. Patient data for EVIC analysis must therefore be retrieved from studies with special designs and analyzing techniques that allow for individualized comparative effectiveness research, or be generated in decision-analytic models based on individual patient simulation.^{15, 16}

Interpretation of EVIC

The EVIC quantifies the net benefit that can, in theory, be gained by making individualized rather than population-based decisions. It therefore indicates the maximal investment that can be made to implement individualized care. In order for individualized care to be worthwhile, the actual costs of implementation need

Table 3 Calculation of EVIC without cost internalization based on fictive outcomes data for patient 1, 2 and 3 in Figure 1.

	No treatment			Treatment			iNMB of most effective option
	Costs	QALY's	iNMB	Costs	QALY's	iNMB	
Patient 1	€ 1,000	5	€ 149,000	€ 4,000	8	€ 236,000	€ 236,000
Patient 2	€ 1,000	5	€ 149,000	€ 31,000	5.5	€ 134,000	€ 134,000
Patient 3	€ 1,000	5	€ 149,000	€ 31,000	4.5	€ 104,000	€ 149,000
Mean ₀ (effect)		5			6		
Most effective {Mean ₀ (iNMB)}						€ 158,000	
Mean ₀ {Most effective(iNMB)}							€ 173,000
EVIC	€ 173,000 - € 158,000 = € 15,000						

iNMB= individual net monetary benefit when $\lambda = € 30,000/\text{QALY}$

to be lower than the EVIC. This may be easily achieved when the implementation costs are low (e.g. introducing a contraindication for certain surgical procedures), but facilitating individualized care may also come at considerable costs, for example when it requires thorough genetic testing. However, there are several issues that need to be considered in the interpretation of the total EVIC.

EVIC arises as a consequence of variation in iNMB between patients; if there were no variation in outcomes, the EVIC would be zero. Alternatively however, the fact that iNMB's are different in the population does not necessarily result in a positive (i.e. non-zero) EVIC. The EVIC only has a positive value when there are patients in the population that have iNMB's on one side of the acceptability threshold, while the average population iNMB is on the other. Additionally, the magnitude of the EVIC is determined by the distance of those iNMB's to the threshold line; the larger the distance, the higher the EVIC.

Consider for example Figure 1. With a willingness-to-pay threshold of € 30,000/QALY, only patient 2 and 3 'contribute' to the total EVIC, which would be € 20,000 per patient. At a threshold of € 10,000/QALY, the population ICER would be above the threshold line, and only patient 1 would contribute to the total EVIC, which would be € 9,000. At a threshold of € 0/QALY, all individual outcomes would be on the same side as the population average (above threshold), and the EVIC would be € 0.

When the EVIC has a positive value, there may be value in individualizing care. The absolute magnitude of the total EVIC represents the profit of giving each individual patient the optimal treatment. In other words, the EVIC expressed as monetary units per patient quantifies how much we can maximally spend on performing a 'magic test' that would give us complete information (i.e. reduce all uncertainty) about the outcome of treatment in an individual patient. This theoretical interpretation is not very useful in practice though. First, the value of the total EVIC does not necessarily account for all relevant patient heterogeneity and variability, particularly when the patient data are generated by an individual patient simulation model. In the latter case, the EVIC only represents the variability and patient heterogeneity that was built into the model. Second, the interpretation as stated above assumes that the 'magic test' is readily available. In reality, the test may still need to be developed, which also costs money. Third, it is unlikely that *one* test will be able to reduce *all* uncertainty. It is more realistic that there will be a *series* of tests for separate patient-level attributes that together reduce *part* of the uncertainty. Whether it is worthwhile to pursue this reduction in uncertainty depends on the value of that reduction and the costs of developing and performing these tests, which can be investigated with the parameter-specific EVIC calculations discussed below.¹³ When the total EVIC per patient is already very low, i.e. lower than the cost

of any available or conceivable test, there is no need to proceed to parameter-specific EVIC calculations. In that case, the low EVIC does not justify further efforts to individualize care.

Calculation of parameter-specific EVIC

The magnitude of the total EVIC may be impacted by many different patient-level attributes. Some attributes may contribute more than others and are therefore more interesting to explore for individualized care. Additionally, some attributes may be more feasible for the implementation of individualized care than others (see below). Their impact can be assessed and quantified with the parameter-specific EVIC, which represents the average benefits that may be gained by choosing the optimal treatment for each individual patient based on the value of that particular attribute (e.g. severity of disease) rather than a population-based approach. The parameter-specific EVIC is calculated as the difference between the total EVIC in the population-based approach and the EVIC that remains when treatment is individualized to the attribute of interest, as formulated in equation 2,

$$EVIC_{\theta_i} = EVIC - \int_{x \in \Theta_i} p_i(x) EVIC(\theta_c | \theta_i = x) dx \quad (2)$$

in which θ_i is the specific attribute of interest among the vector of attributes θ , θ_c are the remaining attributes, and $p_i(x)$ is the marginal probability distribution of the attribute of interest.¹³

Equation 2 can be simplified to $EVIC_{\theta_i} = EVIC - (\text{Mean}_{\theta_i}[\text{Mean}_{\theta_c}\{\text{Max}_j \text{iNMB}_j(\theta_c | \theta_i)\}] - \text{Mean}_{\theta_i}[\text{Max}_j \{\text{Mean}_{\theta_c} \text{iNMB}_j(\theta_c | \theta_i)\}])$. The parameter-specific EVIC is calculated from a series of simulations consisting of inner loops and outer loops. In each inner loop a cohort of heterogeneous patients is simulated with a fixed value for patient-level attribute θ_i . All other attributes (θ_c) are randomly drawn for each individual patient. In each outer loop a new value for θ_i is drawn from $p_i(x)$. Parameter-specific EVIC calculations can be quite time-consuming. Therefore it might be prudent to perform some exploratory analyses with the basecase cohort data (e.g. AN(C)OVA or stratified EVIC calculation (see appendix)) to identify the most influential patient-level attributes, and perform parameter-specific EVIC calculations on the most meaningful attributes only.

Interpretation of parameter-specific EVIC

For the interpretation of the parameter-specific EVIC it is important to consider the nature of the patient-level attribute that is targeted. Therefore it may be helpful to

distinguish the following categories:²

- Patient-level attributes known when the treatment decision is made. These are attributes that are readily known or easily measured, such as age, weight, blood pressure etc. The parameter-specific EVIC of an attribute with a value known at the treatment decisions suggests that the efficiency of care can be improved if treatment decisions are based on this attribute. Since the value of the attribute is readily known, there is no need to allocate resources to retrieve its value with additional testing. However, the actual implementation of an individualized care policy may require extra investments like equipment to provide different types of care, extra housing and (training of) staff, or the development and diffusion of clinical guidelines. The parameter-specific EVIC therefore quantifies the maximum investment that can be made to implement individualized care (Table 4).
- Patient-level attributes not known but measurable when the treatment decision is made. These are attributes that are generally not readily known because they are not normally collected in everyday patient care, for example due to patient discomfort or high costs, but that could be retrieved by performing additional measurements. For example, when cancer turns out to be irresectable during surgery, the unnecessary operation may have been avoided if the irresectability of the tumour had been diagnosed with more extensive imaging. Parameter-specific EVIC analysis could indicate whether routine application of extended imaging would be worthwhile. Other examples include genetic tests, invasive diagnostic tests, or preference elicitation tests. The value of the parameter-specific EVIC of an attribute that is not readily known quantifies the maximum investment that can be made to implement individualized care. The maximum investment not only includes the potential costs of implementing the individualized care policy, but also the costs of retrieving the unknown attribute (Table 4).
- Patient-level attributes revealed over time. These are attributes that can be established in retrospect but that are neither known nor measurable at the moment the treatment decision is made. For example, a patient's response to medication in terms of effects or side-effects may be very important for the outcome of treatment, but it is impossible to tell in advance what the response will be. The parameter-specific EVIC of attributes that are revealed over time indicates how much net benefits could be gained if treatment decisions could be based on knowledge that can only be obtained further down the road. Since it is impossible to look into the future, these potential efficiency gains are unlikely to be effectuated, unless 1) its value can be evaluated in a short period of time, or 2) there is another attribute that predicts its value. In the first case, a treatment strategy might be devised that involves postponement of the

treatment decision until the value is known, or ‘stopping rules’ that dictate abortion of a treatment strategy. In the second case, individualized care may be based on the predicting attribute. Take for example the case of duration of life versus life-expectancy: the former is a retrospective outcome while the latter is a prospective predictor. Duration of life is likely to affect the outcomes of treatment in individual patients, but it can only be determined at the end of a patient’s life. In this case, life-expectancy based on age, gender and co-morbidities might be a suitable predictor. When there is no readily available knowledge regarding predictive attributes, a high parameter-specific EVIC may suggest that there is value in additional research to obtain such knowledge. However, the maximal investment that can be made for additional research is not equal to the parameter-specific EVIC, because some financial room may need to be reserved for the implementation of individualized care (Table 4).

Table 4 Activities that can be financed within the limits of the parameter-specific EVIC, depending on the type of parameter.

Type of parameter	Provide individualized care	Retrieve parameter value	Perform additional research into predictive attributes	Perform additional research into heterogeneity
Heterogeneity				
Known patient-level attribute	x			
Knowable patient-level attribute	x	x		
Patient-level attribute revealed over time	x	x	x	
Unexplained variability	x	x	(x)	x

In addition, differences in individual patient outcomes may not only arise from patient heterogeneity, but also from variability. Variability may therefore have a non-zero parameter-specific EVIC, but this number does not have practical relevance. It represents the inevitable loss of efficiency in health care as a result of coincidence. If EVIC and parameter-specific EVIC have been calculated based on actual patient data rather than a simulation model, part of what appears to be

unexplained variability in statistical analyses, may actually be attributable to (yet) unknown patient heterogeneity. In theory, a high parameter-specific EVIC for unexplained variability may therefore suggest that there is value in research to reveal those sources of patient heterogeneity. However, it may be difficult, if not impossible, to calculate the maximal room for investment for such research from the EVIC.

Application of EVIC framework to the case of glaucoma

To test the feasibility of the EVIC framework we have applied it to the empirical data of a cost-effectiveness analysis for the treatment of glaucoma. Primary open-angle glaucoma is a neurodegenerative disease of the optic nerve that can ultimately lead to loss of peripheral vision and blindness.¹⁷ Details of the analysis methods are provided in an appendix supplemental to this paper. Briefly: the cost-effectiveness data had a lifelong horizon and a societal perspective, and were generated with a discrete event simulation model of individual glaucoma patients. The construction and validation of the model have been reported elsewhere.¹⁸ We quantified severity of glaucoma by the Mean Deviation (MD). A decrease in MD indicated progression (i.e. worsening) of glaucoma. In the model, each patient was assigned an initial MD (decibels (dB)) and an intrinsic rate of progression (dB/month). We have compared the life-long outcomes in terms of societal costs and quality-adjusted life-years (QALYs) in two treatment strategies: high intensity versus low intensity (see appendix). We generated a heterogeneous cohort of 3000 patients and simulated their disease progression in each of the two treatment strategies. We calculated the EVIC from the outcomes of the individual patients in both strategies. Additionally, we investigated the impact of population parameter uncertainty with a probabilistic sensitivity analysis and EVPI calculation.⁶ In calculations of NMB, EVPI and EVIC we have used an arbitrary λ of € 30,000/QALY for illustrative purposes.¹⁹ The (parameter-specific) EVIC was calculated according to equation 1 and 2 with cost internalization, unless stated otherwise. The calculation of the parameter-specific EVIC was based on data from a two-level simulation. First, we sampled a value for the patient-level attribute of interest. Then we simulated a cohort of 3000 patients in which each patient had a unique set of patient-level attributes, except for the attribute of interest, which was fixed to the sampled value. This process was repeated with new values for the attribute of interest until we observed a stable estimate for the parameter-specific EVIC. This was the case after 120 repetitions.

Results

Cost-effectiveness and EVIC

High intensity treatment resulted in an average health gain of 0.12 QALYs and cost savings of € 1,527 per patient compared to low intensity treatment, and was therefore the dominant strategy at the population level. High intensity treatment was more expensive in terms of visits, medication and surgery, but this was compensated by cost savings in low-vision related care.

Figure 2A visualises the uncertainty in the population outcomes due to parameter uncertainty through the results of the probabilistic sensitivity analysis of parameter uncertainty. Figure 2B shows the population-level cost-effectiveness acceptability curves. The EVPI was € 0, indicating that there is no value in further research to improve decision making at the population level.

In Figure 2A we have also drawn the scatter of ICER outcomes (iICERs) of the individual patients in the simulated cohort. It shows that the uncertainty at the individual level due to patient heterogeneity and variability was much larger than the uncertainty at the population level due to parameter uncertainty. Each light grey dot in Figure 2A represents the incremental costs and effects of high intensity treatment compared to low intensity treatment in one individual patient in the simulated cohort. High intensity treatment was more effective than low intensity treatment in 91% of the patients, and the percentage of patients with an acceptable ICER was 68% (Figure 2C). The EVIC was € 580 per patient, suggesting that there is room for improvement in the efficiency of care by taking into account the expected outcomes of a patient in an individual treatment decision. The value of the EVIC without cost internalization was € 189.

Parameter-specific EVIC

In an analysis of (co)variance including all simulated patient-level attributes, 41% of all observed variance was explained. The proportion of the total sum of squares explained by each of the attributes is drawn in Figure 3. The first seven attributes are known at the moment the treatment decision is made, and the remaining attributes are revealed over time. The attributes known at treatment decision appeared to have a minimal contribution to the variability in individual cost-effectiveness outcomes. As a consequence, it cannot be expected that EVIC can be reduced by individualizing care based on any of these attributes, and therefore there is no opportunity to improve efficiency in care on the basis of readily available information about the patients.

Figure 2 Cost-effectiveness of high intensity treatment versus low intensity treatment in glaucoma patients.

A: individual ICER (iICER) in each simulated patient (light grey), the average ICER in the population (black) and the population ICERs from the probabilistic sensitivity analyses of parameter uncertainty (dark grey). **B:** Cost-effectiveness acceptability curve (CEAC)(solid line) including EVPI per patient (dotted line). **C:** Individual cost-effectiveness acceptability curve (iCEAC; solid line) indicating the percentage of patients in the population with a positive i-INMB, and the EVIC per patient (dotted line).

ICER = incremental cost-effectiveness ratio; WTP = willingness-to-pay.

Two attributes stand out in Figure 3: duration of life and progression rate. Duration of life is a patient-level attribute that is revealed when a patient dies and that can therefore never play a role in treatment decisions. In clinical practice, life-expectancy based on gender, age and health state could be a good predictor for duration of life and therefore be a candidate attribute for individualized care. However, in the model outcomes, life-expectancy had only a minor impact when we entered it into the ANCOVA instead of duration of life. The other attribute, progression rate, is in reality also revealed over time. However, for the sake of illustration let us hypothesize that its value may be predictable with a test that is yet to be developed. The parameter-specific EVIC of progression rate would indicate the value of that test, and therefore inform us whether it would be feasible to develop and implement it in clinical practice. The value of the parameter-specific EVIC for progression rate was € 130. This indicates that it would be worthwhile to spend € 130 per patient in order to implement a subgroup policy based on progression rate. The maximum investment to develop the measurement instrument may be aggregated over all patients to whom the treatment decision will apply. For example, with an annual number of new glaucoma patients of 10,000, and an assumed applicability period of ten years, the total number is 100,000 patients.²⁰ This indicates that the maximum investment for development and implementation of a 100% sensitive and specific progression prediction test is € 13 million.

Figure 3 Proportion of the total sum of squares explained by all patient-level attributes in the model.

Suppose that the above-mentioned figures give rise to a positive decision regarding a subgroup treatment policy, the next question would be *how* treatment decisions should be adjusted to individual progression rates. A solution can be found in the results from the parameter-specific EVIC simulations. If the rate of progression has an impact on the cost-effectiveness of glaucoma treatment, there should be a turning-point value for progression rate at which the preferred strategy switches from low intensity treatment to high intensity treatment. In Figure 4 we have plotted the fixed value for the progression rate in each of the outer loops from the parameter-specific EVIC simulations against the average INMB of high intensity treatment compared to low intensity treatment found in that particular patient population. Up to progression rates of 0.008 dB per month the average INMB of intensive treatment was negative, which implies that low intensity treatment is most efficient. At MD progression rate values higher than 0.008 dB per month the INMB of intensive treatment was positive, which implies that high intensity treatment is most efficient. Therefore, individualized care could consist of low intensity treatment in patients with an MD progression rate below 0.008 dB per month and high intensity treatment in everyone else.

Figure 4 Results from the simulations for the parameter-specific EVIC of MD progression rate. The graph plots the value of the fixed MD progression rate in the population against the average incremental monetary net benefit of high intensity treatment versus low intensity treatment in that population (black) and the EVIC in that population (grey).

Discussion

In this paper we have explored the EVIC framework and applied it to a real world example in order to assess the feasibility and potential role of EVIC analysis in decision making. The importance of patient heterogeneity is increasingly recognized in medical research and acknowledged in clinical practice, because it offers the opportunity to tailor medical decisions to the individual attributes of the patient. Previously, Hoch *et al.* have described the application of regression based analysis techniques to investigate the impact of patient heterogeneity on cost-effectiveness outcomes in a patient population and to identify the most influential patient-level attributes.²¹ However, a strong relationship between a patient-level attribute and treatment outcomes is not enough argument to pursue individualized care. The key advantage of the EVIC framework is that it puts a maximum value to the efforts to individualize care, which, in combination with knowledge about the costs of those efforts, enables us to judge whether individualized care is likely to be worthwhile.

In this exploration of the EVIC framework we encountered a number of methodological issues. First, since the derivation of the parameter-specific EVIC is similar to that of the partial EVPI, and since several methods have been described to calculate partial EVPI, it is likely that there are other (mathematically equivalent) methods to calculate the parameter-specific EVIC than the one we have followed.¹⁴ However, partial EVPI calculations based on the reduction in expected opportunity loss may lead to biased estimates.¹⁰ Whether this also applies to parameter-specific EVIC calculations as proposed by Basu and Meltzer remains to be resolved, and is a question that was outside the scope of the research in this paper. Second, the calculation of parameter-specific EVIC can be quite time-consuming. Generating data for a single cohort of patients in an individual patient sampling model requires many simulations. The simulation of inner and outer loops for each patient-level attribute of interest can add up considerably, so it may be worthwhile to consider methods to increase the efficiency of the analyses. These methods may include the grouping of attributes of interest into an aggregate parameter-specific EVIC, calculation using a one-level algorithm, or use of a meta-model.²² Third, in the empirical example in this paper we have used ANCOVA as a screening tool to select potential attributes of interest and limit the number of parameter-specific analyses. ANCOVA assumes a linear relationship between the parameters and the INMB, but linearity may be violated or interactions may play a role. This could be the reason why only 41% of all variance was explained in the example. If there are clear indications of non-linearity in the data, it may be better to use non-linear statistical models. Fourth, a simulation model can mimic real-life variability in outcomes by employing random draws. When a single patient is simulated in different treatment

strategies, the random draws in each strategy may not be similar. As a result, a simulated patient with a high risk of event X in the comparator strategy may remain event-free as a result of favourable random draws, while the same patient with a low risk of event X in the alternative strategy may experience it due to unfavourable random draws. It is questionable whether that impact is valid in this case, since it was not the result of an increased risk of event X. The occurrence of the event in only one of the scenarios could increase the magnitude of the individual incremental outcomes, which could in turn contribute to the magnitude of the EVIC; this model-induced variability could therefore create noise in the EVIC outcomes. We tested this with the glaucoma model, which by default used similar random draw values in both treatment strategies. Due to dissimilar random draws, the total EVIC grew from € 580 to € 881. However, the parameter-specific EVIC of progression rate was € 117, which is comparable to the € 130 found earlier. So although model-induced variability may cause an artificially high value for EVIC, it did not seem to affect the values of the parameter-specific EVIC in our case study. Lastly, the validity of EVIC is conditional upon the validity of all assumptions associated with cost-effectiveness analysis and the INMB framework, such as the validity of using utility estimates, the validity of the model structure, the assumption that we know the value of λ , and the assumption that willingness-to-pay is equal to willingness-to-accept.²³⁻²⁶ The value of EVIC is highly dependent on λ , not only in terms of its absolute value, but also in terms of the relative impact of the heterogeneous attributes. A different value of λ could thus impact the implications of the EVIC outcome.²⁵

There is a great deal of analogy between the EVPI and the EVIC framework (Table 1). Indeed, the impressive amount of work conducted to date on the development of the EVPI framework could greatly benefit the dissemination of the EVIC methodology. However, it is important to realise that both frameworks represent two essentially different concepts, and both analyses may be performed in cost-effectiveness research; they are complementary. The foundation of EVPI is that there is *one* true value for a parameter in the population, and that the optimal treatment decision for all patients in the population depends on the value of that parameter. With additional research we could remove all uncertainty so we would know the parameter value and could therefore make the optimal treatment decision on a population level. Alternatively, the foundation of EVIC is that *many* values for a patient-level attribute exist within a patient population, and that the optimal treatment decision for an individual patient depends on the value of that attribute. The EVIC represents the value of acquiring and acknowledging all relevant patient-level information in the treatment decision for an individual patient.

The aim of this paper was to explore the potential role of the EVIC framework in cost-effectiveness analysis and decision making. Basu and Meltzer stated that “EVIC can provide a guide as to when population-level decision making may be especially at risk of providing poor guidance for coverage decisions because of failure to account for the value of individualized decision making”.¹³ Based on the exploration of the EVIC framework described in this paper, we would argue that the reverse is true and that the EVIC can provide a guide as to when population-level decision making is *not* at risk of providing poor guidance, both for medical as for policy decisions. This statement is based on the finding that the outcomes of EVIC and parameter-specific EVIC calculations are most conclusive when they are zero. In addition, the outcomes of parameter-specific EVIC calculations are informative when the parameter in question relates to a patient-level attribute whose value is known or measurable at the time the treatment decision is made. From a policy perspective, this translates to a potential role for EVIC to confirm that an adoption decision can be made on a population level, or provide a basis for a partial adoption decision (i.e. implement a subgroup policy) on the basis of a measurable patient-level attribute. As policies are generally made to seek an efficient allocation of existing resources and a maximization of health benefit in society, cost-effectiveness is often explicitly considered in the policy context. The EVIC calculation with cost internalization is therefore likely the most suitable approach for the policy perspective. Decisions regarding the allocation of resources to additional research may also be in the domain of the policy maker. Based on the findings in this paper however, we would conclude that results from EVIC analyses are only informative regarding additional research, when they are zero and therefore indicate that there is no value in additional research.

For the perspective of a clinical decision maker, e.g. health care providers or health care organizations, roughly the same conclusions regarding the potential role of EVIC can be drawn. From the clinical perspective, the EVIC outcomes may be most relevant when they are calculated without cost internalization. The potential role for EVIC analysis without cost internalization is most evident when the outcome is zero, because it indicates that there is low risk of poor guidance from population-level decision making, e.g. in the context of treatment guidelines. Additionally, parameter-specific outcomes of known or measurable patient-level attributes can indicate whether it is worthwhile to implement individualized care in clinical practice.

Conclusion

Building on the EVIC framework developed by Basu and Meltzer in the context of heterogeneity in patient preferences, we have illustrated that it is feasible to apply

the EVIC framework to all other patient-level attributes that may affect the costs and/or benefits of treatment. EVIC can be a useful tool to identify opportunities to improve efficiency in healthcare by individualization of care, and to quantify the maximal investment opportunities for implementing subgroup policy. The EVIC outcomes can play a role in both policy and clinical decision making, particularly when they are zero or when they concern known or measurable patient attributes.

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References

1. Walker W, Harremoës P, Rotmans J, Van der Sluijs J, Van Asselt M, Janssen P, Krayen von Krauss M. Defining uncertainty; A conceptual basis for uncertainty management in model-based decision support. *Integrated Assessment* 2003; 4:5-17.
2. Sculpher M. Subgroups and heterogeneity in cost-effectiveness analysis. *Pharmacoeconomics* 2008; 26:799-806.
3. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Economics* 1999; 18:341-364.
4. Griffin SC, Claxton KP, Palmer SJ, Sculpher MJ. Dangerous omissions: the consequences of ignoring decision uncertainty. *Health Econ* 2010; 20:212-224.
5. Chalkidou K, Lord J, Fischer A, Littlejohns P. Evidence-based decision making: when should we wait for more information. *Health Aff (Millwood)* 2008; 27:1642-1653.
6. Claxton K. Exploring uncertainty in cost-effectiveness analysis. *Pharmacoeconomics* 2008; 26:781-798.
7. Groot Koerkamp B, Weinstein MC, Stijnen T, Heijnenbroek Kal MH, Hunink MG. Uncertainty and patient heterogeneity in medical decision models. *Med Decis Making* 2010; 30:194-205.
8. Felli JC, Hazen GB. Sensitivity analysis and the expected value of perfect information. *Med Decis Making* 1998; 18:95-109.
9. Ades AE, Lu G, Claxton K. Expected value of sample information calculations in medical decision modeling. *Med Decis Making* 2004; 24:207-227.
10. Groot Koerkamp B, Myriam Hunink MG, Stijnen T, Weinstein MC. Identifying key parameters in cost-effectiveness analysis using value of information: a comparison of methods. *Health Econ* 2006; 15:383-392.
11. Briggs A, Sculpher M, Claxton K. *Decision modelling for health economic evaluation*, First ed. Oxford University Press: Oxford, UK; 2006.
12. Diamandis M, White NM, Yousef GM. Personalized Medicine: Marking a New Epoch in Cancer Patient Management. *Mol Cancer Res* 2010; 8:1175-1187.
13. Basu A, Meltzer D. Value of information on preference heterogeneity and individualized care. *Med Decis Making* 2007; 27:112-127.
14. Oostenbrink J, Al M, Oppe M, Rutten-van Mölken M. Expected value of perfect information: An empirical example of reducing decision uncertainty by conducting additional research. *Value Health* 2008; 11:1070-1080.
15. Basu A. Individualization at the heart of comparative effectiveness research: the time for i-CER has come. *Med Decis Making* 2009; Nov-Dec:N9-N11.
16. Stahl JE. Modelling methods for pharmacoeconomics and health technology assessment: an overview and guide. *Pharmacoeconomics* 2008; 26:131-148.
17. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet* 2004; 363:1711-1720.
18. Van Gestel A, Severens J, Webers C, Beckers H, Jansonius N, Schouten J. Modeling complex treatment strategies: construction and validation of a discrete event simulation model for glaucoma. *Value Health* 2010; 13:358-367.
19. National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal*. London, 2008.
20. Gommer A, Poos M. Statistics of eye ailments (prevalence and incidence) (Cijfers gezichtsstoornissen (prevalentie en incidentie)). In: RIVM, ed. *National Public Health Compass (Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid)*. Bilthoven, 2010.
21. Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. *Health Econ* 2002; 11:415-430.
22. Tappenden P, Chilcott J, Eggington S, Oakley J, McCabe C. Methods for expected value of information analysis in complex health economic models: development on the health economics of interferon-beta and glatiramer acetate for multiple sclerosis. *Health Technol Assess* 2004; 8:iii, 1-78.
23. Gyrd-Hansen D. Willingness to pay for a QALY; Theoretical and methodological issues. *Pharmacoeconomics* 2005; 23:423.
24. Severens J, Brunenberg D, Fenwick E, O'Brien B, Joore M. Cost-effectiveness acceptability curves and a reluctance to lose. *Pharmacoeconomics* 2005; 23:1207-1214.
25. Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for cost-effectiveness in health care Health Technology Assessment (HTA). KCE reports 100C (D/2008/10273/96). Brussels, Belgium: Belgian Health Care Knowledge Centre (KCE), 2008.
26. Dolan P, Shaw R, Tsuchiya A, Williams A. QALY maximisation and people's preferences: a methodological review of the literature. *Health Econ* 2005; 14:197-208.

**The role of the expected value of
individualized care in cost-effectiveness
analyses and decision making**

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Glaucoma

Glaucoma is a neurodegenerative disease of the optic nerve that can ultimately lead to loss of peripheral vision and blindness.¹ The prevalence of glaucoma increases with age from virtually zero in people younger than 45 years to 5% in people over 80 years.² It is estimated that the current prevalence of diagnosed glaucoma in The Netherlands is 100,000 people in the total population.³ A high intraocular pressure (IOP) is the most important risk factor for progression of the disease, and all current glaucoma treatment is directed at bringing the intraocular pressure down. Treatment is usually initiated with topical medication (eye-drop, building up from monotherapy with one substance to combination therapy of up to three or four different substances, whichever is necessary to bring the intraocular pressure below the target pressure set by the ophthalmologist. If medication alone is not effective enough, the patient may receive laser treatment and/or surgery.⁴

Glaucoma treatment modelling

The cost-effectiveness data were generated with an individual patient sampling model that simulated the lifelong treatment and disease progression of glaucoma patients. The construction and validation of the model have been reported elsewhere.⁵ The model was based on discrete event simulation and simulated the disease progression of individual patients by establishing the value of relevant patient-level attributes at discrete points in time. Each simulation started with a series of random draws from preset distributions (based on literature) to establish the initial set of attributes of the simulated patient. Next, the model advanced to time-points of relevant events and recalculated all attributes. This way, the attributes were adjusted to changing conditions such as age, treatment and IOP. The calculation of the new attribute values was directed by the network of relationships. The model kept advancing in time and updating the attributes until the simulated patient 'died'. Then all relevant outcomes from the patient's disease and treatment history were collected. This process was repeated to generate a heterogeneous cohort.

We quantified the severity of glaucoma by the parameter Mean Deviation (MD). A change in MD value therefore indicates progression of glaucoma. In the model, each patient was assigned an initial MD (dB) and an intrinsic rate of MD progression (dB/month). The latter was linked to the IOP, which was calculated from the baseline IOP and the total pressure lowering effect of current treatment.

The model contained a network of relationships to link disease progression to treatment and vice versa. The model simulated the application of each of the usual treatment modalities separately by mimicking ophthalmology visits at which treatment decisions were made based on the condition of the patient, the effect of

current treatment and treatment history. The model included four monotherapies of different classes of eye-drops and made combinations up to triple therapy. When medication alone did not sufficient reduce the IOP, the model moved to laser treatment, surgery, and finally device implantation. For each simulated patient the model made random draws to establish the effectiveness of all eye-drops and procedures, the occurrence of side-effects with each medication and the presence of contraindications from one type of medication. A history of cataract and cataract surgery or their occurrence during the simulated lifetime was included in the model structure because of several relevant relationships between cataract and glaucoma treatment.

All direct medical, direct non-medical and indirect non-medical costs were taken into account. The patient's utility was calculated based on glaucoma severity (MD), the presence of medication side-effects and the presence of cataract.

Populations and treatment strategies in this study

The simulated population in this study represents POAG patients at their first encounter with an ophthalmologist. We assumed that all patients (aged 68 ± 4 years) had some degree of visual field loss, measurable by automatic perimetry.⁵ The baseline MD was drawn from a gamma distribution with an average of -7.2 dB (99% between -3 and -17 dB). The rate of visual field loss was drawn from a gamma distribution with an average of 0.34 dB/year (99% between 0.02 and 1.12 dB/year). The baseline IOP was drawn from a normal distribution with mean 28 and standard deviation 3 mmHg, truncated at 22 mmHg.

The comparator treatment strategy was 'low intensity treatment'. In the low intensity treatment strategy, the initial target IOP was 21 mmHg. This was adjusted to 18 mmHg after a first occurrence of progression, and to 15 mmHg after a second occurrence of progression. For each class of medication we chose one representative. They were, in the order in which they replaced or supplemented existing medication: initial timolol, followed by latanoprost, dorzolamide and brimonidine. The visit interval was 6 months for stable patients, which was temporarily reduced after each treatment adjustment (Table 4). The frequency of VF measurements was once a year. The alternative treatment strategy was 'high intensity treatment', in which the target pressure was directly fixed at 15 mmHg for all patients and was no longer adjusted upon progression.

Table 4 Visit schedule. Months until next visit.

# visits since ...	Medication initiation or change	LT	Surgery
1	3	0.23	0.1
2	6	1.15	0.1
3	6	6	0.1
4	6	6	0.1
5	6	6	0.23
6	6	6	0.23
7	6	6	0.23
8	6	6	0.5
9	6	6	0.5
10	6	6	1
> 10	6	6	6

LT = Laser trabeculoplasty

Stratified analysis of individual cost-effectiveness outcomes

It is possible to obtain a rough estimate of the outcomes of the parameters-specific EVIC analysis with the results from the single cohort that rendered the results in Figure 2 of the main paper.⁶ In order to do so we have sorted the patients in ascending order according to their MD progression rate. Next we have grouped the patients together based on MD progression rates rounded to a three digit number (0.001, 0.002 etc.) and calculated the EVIC in each of these subgroups. Finally we calculated the average EVIC weighted by the number of patients in each group. This resulted in an estimated EVIC of € 482 and a parameter-specific EVIC for MD progression speed (rounded to a three digit number) of € 98. Additionally, we explored the reduction in total EVIC if we divided the simulated population in two subgroups at varying cut-off points for MD progression speed and assume that all patients in the subgroup would receive the treatment with the highest average INMB in that subgroup. The result is drawn in Figure 5. The largest reduction in total EVIC is observed at cut-off points around 0.009 dB per month.

Figure 5 Reduction in EVIC in the population as a result of subgroup policy depending on the cut-off point creating the subgroups.

References

1. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet* 2004; 363:1711-1720.
2. Gezichtsstoornissen naar leeftijd en geslacht. In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Available at: <http://www.nationaalkompas.nl>> Gezondheid en ziekte\ Ziekten en aandoeningen\ Zenuwstelsel en zintuigen\ Gezichtsstoornissen. Accessed: 10 June, 2010
3. Eye diseases. Scope of the problem. How often do eye diseases occur? Available at: http://www.rivm.nl/vtv/object_document/o1143n17763.html. Accessed: 18 May, 2006
4. European Glaucoma Society. Terminology and guidelines for glaucoma (third edition). Dogma: Savona, Italy; 2008.
5. Van Gestel A, Severens J, Webers C, Beckers H, Jansonijs N, Schouten J. Modeling complex treatment strategies: construction and validation of a discrete event simulation model for glaucoma. *Value Health* 2010; 13:358-367.
6. Basu A, Meltzer D. Value of information on preference heterogeneity and individualized care. *Med Decis Making* 2007; 27:112-127.

Chapter 8

General discussion

Summary of findings

The aim of the research presented in this doctoral thesis was to investigate whether the long-term consequences of intensive treatment for ocular hypertension (OHT) and primary open-angle glaucoma (POAG) are more favorable than those of the usual approach in current clinical practice. The intensive treatment strategies differed from usual care in terms of the target intraocular pressure, first-choice medication and frequency of visual field testing. For this purpose, cost-effectiveness analyses were performed with data generated with a computer simulation model that was designed and built for this purpose. The model outputs were realistic reflections of glaucomatous disease progression under various treatment strategies.

The computer simulation model was designed and populated mainly with evidence from scientific literature, but quantitative information about the impact of glaucoma on quality of life was lacking, as was information on resource consumption related to visual impairment and blindness. The observational survey described in chapter two including 531 patients with ocular hypertension or primary open-angle glaucoma in the Netherlands was conducted to provide the lacking data. As expected, more damage to the visual field was associated with a lower quality-of-life score. The outcomes of the survey were integrated in the model via an equation for the utility of the health state of a simulated patient based on the amount of visual field loss, the presence of cataract and the presence of side-effects from glaucoma medication. Additionally, low-vision related resource use found in the survey was stratified to visual field loss, and used to quantify the costs of low-vision related care of simulated patients.

The basic Markov model described in chapter three, synthesizing current evidence on conversion to and progression of glaucoma to estimate the long-term risk of blindness from ocular hypertension in treated and untreated patients, resulted in more valid estimates than those previously reported in literature.¹ However, the Markov model structure did not allow for an extended synthesis and extrapolation of evidence, and resulted in outcomes with large uncertainty intervals. Chapter four describes additional reasons why a Markov model structure was not suitable to address the research questions formulated for this thesis, why a model structure based on patient-level simulation and discrete event modeling was a better alternative, and how such a model was built and validated. The developed model simulates the disease course of an individual patient by calculating the value of relevant attributes at discrete moment in time (events). Examples of such attributes are age, intraocular pressure, medication, and degree of visual field loss. The time intervals between events depended on the patient's attributes and (in some cases)

randomness. The discrete events usually represented follow-up visits, but the model also considered conversion to POAG and death. Progression of POAG was modeled through a dynamic patient attribute representing deterioration of the visual field. At a simulated follow-up visit, the patient's condition (defined by the combination of relevant attributes) was evaluated and treatment decisions were 'made' according to the rules that were defined within the model structure to represent a treatment strategy. Large cohorts of individual patients, all different in terms of their initial attributes (i.e. heterogeneous), were simulated according to two different treatment strategies, generating stable average population outcomes and enabling comparisons between the strategies. The model was tested for its internal and external consistency during its development by simulating familiar situations. After the test results lead to satisfying results, the model was employed to predict the outcomes of new treatment approaches in primary open-angle glaucoma and ocular hypertension.

The simulation data of a heterogeneous population of patients with POAG indicated that a treatment strategy according to usual care in current clinical practice generates more health (1.19 quality adjusted life-years (QALY)) and leads to cost savings (€ 18,000) compared to a situation without treatment (chapter five). Moreover, the cost-effectiveness analyses of alternative treatment strategies showed that a strategy with a low target intra-ocular pressure at treatment initiation was dominant over the more moderate approach involving a gradual decrease of target pressure. In contrast, initiating treatment with latanoprost rather than timolol (both in standard recommended dosages) had only a minor effect on health and cost outcomes, which both increased slightly leading to a positive incremental cost-effectiveness ratio (ICER) of € 12,931/QALY. An increase in the frequency of visual field testing led to small health gains at relatively high costs (€ 173,486/QALY), and a decrease in the frequency of visual field testing lead to losses in health at relatively low cost savings (€ 21,516/QALY).

In a heterogeneous population of patients with ocular hypertension, direct initiation of treatment generated more health (0.27 QALY) and was cost-saving (-€ 649) compared to a situation in which no treatment was initiated until conversion to glaucoma had been observed (chapter six). Subgroup analyses revealed that this outcome would apply to all patient populations with initial intra-ocular pressures above 21 mmHg, except those with a conversion risk effectively lower than 8 to 10% in five years. In the latter cases, direct pressure-lowering treatment still lead to better health outcomes, but also to some additional costs instead of cost-savings. The highest ICER found for direct treatment initiation in the investigated low-risk subgroups was € 15,425/QALY.

The main conclusions drawn from the analyses in chapter five and six were based on the differences between the *average* consequences of each treatment strategy in the whole patient population. The obvious question following those conclusions would be whether they are valid for all patients, or whether certain subgroups of patients with different consequences can be identified that could be relevant for decision making. In chapter five and six, subgroups of patients were defined ad hoc. However, the exploration of the expected value of individualized care framework in chapter seven showed that there is a more efficient approach to assess the potential relevance of subgroup analyses. The case of a low target pressure in all glaucoma patients versus a stepwise reduction was used as an example. The results indicated that, given the sources of heterogeneity between patients currently considered in the model, there was no value in differentiating target pressure strategies between patients.

Implications for health care practice

In order to reflect on the implications of the research results for health care practice, three different levels of decision making are discerned here: the micro level (health care professionals at patient level), the meso level (healthcare professions, healthcare organizations and institutions) and the macro level (national healthcare perspective).² Between these levels, the relative weight of each of the outcomes presented in this thesis is likely to differ. The health outcomes will be of primary interest to decision makers at each level, but the relative importance of the economic outcomes increases from the micro to the macro level as the aim of the decisions shifts from optimizing the outcome for a single patient to optimizing the decision for all patients under limited availability of financial and human resources.²⁻⁶ The cost-effectiveness criterion has been formally included in the procedures of many regulatory institutions. Recent research about the actual use and barriers to use of economic evaluations in Sweden also showed that the highest level of the use of health economic evaluations was seen at the macro level (Table 1).^{5, 7}

Accordingly, the discussion of the implications of the research in this thesis for decision making at the micro level below focuses on the health outcomes, whereas the discussion of the implications for decision making at the meso and macro level considers both the health and cost consequences. Although the discussion thus focusses on effectiveness and cost-effectiveness criteria, we recognize that the reality of decision making in actual practice is much more complex and involves additional criteria like e.g. the consequences in terms of total budget impact, the distribution of health, ethical integrity, access to care, the practical organization of

Table 1 The use of (or attitude towards) health economic evaluations (of cost-effectiveness criterion) in Swedish pharmaceutical priority setting,⁷

	Dissemination	Recognition	Understanding	Utilization
Pharmaceutical Benefits Board (macro)	X	X	X	X (directly)
Formulary committees (meso)	X	X	X	X (indirectly)
Prescribing physicians (micro)	X	X		

health care etcetera.⁸ The consequences in these domains were not investigated in this thesis, and are therefore not explicitly considered in this discussion.

Micro-level

Decisions at the micro level are made between physicians and their patients. The goal of the decision is to optimize the outcome for the individual, and the decision maker will consider expected outcomes of each option for that particular patient at that particular moment in time. There is no certainty about the future course of events in a patient's life in any one of the options, so the best decision will be the one that is based on an assessment of probabilities and a choice for the option with the highest probability to render optimal outcomes. Without any a priori information about the patient, the probabilities for the optimal outcomes are similar to those found for a heterogeneous population. In the case of a POAG patient therefore, the optimal health outcomes in terms of the occurrence of visual impairment, blindness and quality-of-life can be expected when medical treatment is aimed at reaching a low intraocular pressure right away. The subgroup analyses furthermore showed that even if a physician would take into account prior information about the patient's disease severity and consequential risk of blindness, this conclusion would hold true. This does not mean that all patients will turn out to be better off in the chosen strategy. Both in the heterogeneous population and in the subgroup simulations, approximately 14% of the patients turned out to have better health outcomes with usual care than with a low target pressure. The same is inevitable in clinical practice; in some patients a decision may turn out to be suboptimal. The analyses in this thesis did however not indicate that such a suboptimal treatment choices could be prevented based on patient factors that are known or knowable at the treatment decision. And there is of course no objection to stopping intensive medication once

it is clear that it is not benefiting the patient. In reference to the other alternative strategies for POAG, concerning latanoprost as first-choice medication and increasing the frequency of visual field testing, the population outcomes had the same implications as for the strategy with a low target pressure. However, the incremental health outcomes found for these strategies were so close to zero, that it is likely that other considerations will prevail in the treatment decision. For example, patients are generally not fond of taking visual field measurements because they take long and require much concentration, which is taken into account by many ophthalmologists.

For OHT treatment, a similar argumentation applies. The average benefits of direct treatment initiation in the heterogeneous population were considerable, and the best chances of optimal health outcomes in an individual patient are therefore with treatment rather than watchful waiting. The subgroup analyses further indicated that it is not necessary to consider intraocular pressure or additional risk of conversion in this treatment decision. Similar to the discussion about above though, there is a considerable likelihood in OHT patients that, in hindsight, treatment was not necessary. Indeed, 43% of the simulated patients in the watchful waiting strategy did not convert to POAG during their entire lifetime. The problem is that one cannot tell in advance who these patients are going to be, even if one calculates the risk of conversion with highly evidence based risk calculators.⁹ The best chance of optimal health outcomes in OHT patients is with direct treatment initiation. The implication of this finding is that the attitude towards treatment initiation in ocular hypertension could change from "do not treat, unless the risk of glaucoma is too high", which is basically up to the ophthalmologist's judgment, towards "treat, unless the burden of treatment is too high", which is much more up to the patient's judgment.

Meso level

This discussion of the potential implications of the research outcomes at the meso level takes the perspective of two types of decision makers: 1) representatives of the glaucoma profession responsible for the formulation of treatment guidelines, like the Dutch Glaucoma Group (Nederlandse Glaucom Groep), the European Glaucoma Society and the American Academy of Ophthalmology in the United States of America,¹⁰⁻¹² and 2) directors/coordinators of glaucoma treatment facilities, like the University Eye Clinic in Maastricht and the Rotterdam Eye hospital, where all caregivers involved in glaucoma care work closely together to provide a 'one stop shop' for glaucoma patients.¹³⁻¹⁶

Management of glaucoma

The model was employed to forecast the consequences of abstaining from glaucoma treatment altogether in order to establish a 'null point' against which the merits of current glaucoma care could be offset. It turned out that current glaucoma care is very effective in preserving health, and leads to large cost reductions compared to withholding pressure lowering treatment. Whether or not glaucoma treatment should be provided is not a point of debate, but these outcomes confirm that providing glaucoma care is a very efficient allocation of resources and should be merited for that. An advantage of having quantitative information about the incremental cost-effectiveness of glaucoma treatment compared to 'doing nothing' is that it enables a fair comparison between sectors within ophthalmology, because 'doing nothing' is a comparator strategy that is communal for all ophthalmic disease areas.

The main question was whether the current treatment guidelines and organization of glaucoma clinics could be improved in order to achieve better and more efficient glaucoma care. The development of treatment guidelines and the organization of glaucoma care are very closely related, as treatment guidelines must consider the feasibility of delivering the care as recommended in the guidelines, and the formulation of clear treatment guidelines will facilitate the imminent reorganization of glaucoma clinics.¹⁷ Due to the ageing population and the higher incidence of glaucoma in the elderly population, the absolute number of glaucoma patients will rise in the near future. For example, the total number of patients with open-angle glaucoma in Europe is expected to increase by 16% within the next ten years.¹⁸ The demand of care from those additional patients will lead to higher work loads for ophthalmologists,¹⁹ which has prompted research into alternative ways to provide care for glaucoma patients.²⁰⁻²² A key component in managing the workload for glaucoma care givers is to shift some of the responsibilities from the ophthalmologists to other healthcare providers like optometrists and nurses. Such a shift would be facilitated by treatment guidelines that formulate explicit guidance on treatment decisions, so that healthcare providers other than glaucoma specialists can make treatment decisions without the need to refer the patient back to the ophthalmologist. Currently, most glaucoma guidelines employ the concept of a target pressure, and give suggestions for the course of action when a patient fails to reach it.^{11, 12, 23} However, there is no guidance on how to set the value of the target pressure itself. The results of the analyses in this thesis indicate that the use of a target pressure of 15 mmHg in the medical phase of treatment in all patients leads to better health outcomes than tailoring the target pressure in the course of treatment, and that it is even cost-saving from a societal perspective. Also, the analyses of the expected value of individualized care in chapter 7 showed that there is no indication that a

subgroup policy would lead to better outcomes. This means that, from an effectiveness and cost-effectiveness point of view, a 15 mmHg low-target-pressure for the initial medical phase of treatment should be recommended for all new glaucoma patients.

Such guidance on the value of the target pressure within clinical guidelines, without the need to specify dynamic and individualized target pressure tailoring, would make it easier to transfer minor decisions about medication adjustments from ophthalmologists to other health care providers. Also, with more medication, patients are likely to become stable (i.e. show no disease progression) more quickly and could therefore be transferred to a shared care environment earlier.²⁴ The need to precariously monitor signs of progression during medical treatment would cease because the occurrence of progression would no longer be a trigger for adjustment of the target pressure, and this would further reduce the demand for caregivers' time. Indeed, the consequences of reducing the frequency of visual field testing when a 15 mmHg target pressure was set for all patients was run through the model, which resulted in small health losses that might be considered acceptable in view of the large associated cost-reductions.

There are some annotations to the argument above. The fact that clinical guidelines would include recommendations on target pressure values does not imply that treatment decisions will become straightforward and do not require a careful and individualized consideration of the expected benefits and risks of each of the options by a specialist. The model did not assume a rigid adherence to the target pressure either. Several limiting conditions for treatment changes that were triggered by an IOP level above the target were built into the structure. For example, patients were not prescribed medications that had caused side-effects in the past, were not operated when no visual field progression had been detected, and were not operated after they had reached a certain age. These conditions mimic the fact that physicians are indeed very likely to consider the risks of further treatment when the fact that the patient's IOP is above target 'dictates' that a treatment change is in order. A fear of rigid adherence to a target IOP and prioritization of achieving the target pressure over the patient's welfare has lead some authors to criticize the use of a target pressure altogether.^{25, 26} Instead, it was argued, physicians should base their treatment decisions solely on an implicit weighting of risks and benefits of subsequent treatment steps. An argumentation like this precludes the coexistence of guidelines for target pressures and sound clinical judgment. It seems hardly realistic though to assume that physicians would abandon their judgment of risks and benefits in a blind pursuit of a target pressure recommended in a guideline. It is more likely that all ophthalmologists that treat glaucoma and ocular hypertension, even in the absence of any treatment guideline, set some kind of target pressure for

each of their patients anyway, whether implicitly in their mind or explicitly in the patient's dossier, and whether it is a short term or a long term target. The intraocular pressure is, after all, still the only modifiable risk factor for glaucoma, and it can be monitored with easy, non-invasive and cheap measurements. It only makes sense that the IOP is a component of the treatment goal in OHT and POAG patients, and it therefore makes sense to make it explicit in treatment guidelines.

In retrospect, the comparison between a prostaglandin analogue and a β -blocker as the first-choice medication seems hardly relevant. It was part of the original research question because previous treatment guidelines in The Netherlands dictated the use of β -blockers as first choice, and prostaglandin analogues as second choice only if β -blockers were contraindicated or ineffective.²⁷ In the light of the research findings in this thesis, the comparison between monotherapy with β -blockers or prostaglandin analogues has become inconsequential. It turned out that the largest gain in efficiency can be acquired with a low initial target pressure, which required direct combination therapy in 72% of the patients. Both types of medication are therefore likely to be administered simultaneously. In addition, the long-term cost-effectiveness ratio of first-choice prostaglandin analogues compared to β -blockers in the base case scenario of a stepwise reduction in target pressure was more favorable than often cited acceptability thresholds, and their cost-consequences can only be expected to improve with the current expiration of patents and anticipated price reduction of prostaglandin analogues.

Management of ocular hypertension

In the Netherlands, the most recent treatment recommendations for glaucoma issued by the Dutch Glaucoma Group are based on the second edition of the 'Terminology and guidelines for glaucoma' by the European Glaucoma Society, in combination with several minor addenda.^{10, 28} Within these guidelines, the decision to start pressure lowering treatment is left to the ophthalmologist, and it is recommended that treatment is considered if the patient has a high risk to develop glaucoma, or if the IOP is consistently in the high twenties.²⁸ When patients are not initiated on pressure-lowering treatment, it is recommended that they are monitored regularly (e.g. once or twice a year) to check that the patient has not converted to POAG.

The research in this thesis showed that the direct initiation of pressure lowering medication in all patients with ocular hypertension was dominant over watchful waiting. This was also the result of the analyses in most of the patient subgroups stratified by the degree of risk for glaucoma development. Moreover, even in low-risk subgroups, the ICER had a value that might be considered acceptable.

Therefore, from a cost-effectiveness point of view, there would be no objection to recommending the initiation of pressure lowering medication in all patients with ocular hypertension. Similar to the discussion regarding the organization of care for glaucoma patients, the implementation of such a recommendation in treatment guidelines would facilitate a reorganization of care for patient with ocular hypertension for a number of reasons. First, the decision to initiate treatment would be simplified. Initiation of treatment is discouraged in current treatment guidelines unless the risk of conversion is too high. This places the responsibility to accurately assess that risk with the ophthalmologist. Alternatively, when the default is that each patient with ocular hypertension is initiated on treatment, the decision to initiate treatment can become more of a joint decision between ophthalmologist and patient, and it is more likely based on patient preferences than on risk assessment. Second, when pressure lowering treatment is initiated, there is a lower urgency to check for conversion to glaucoma and the demand for intensive monitoring is reduced. Conversely however, patients under treatment will initially require more visits to the eye clinic for assessment of their medication and for follow-up, which will increase the demand for healthcare resources. Initiating treatment may be perceived as bearing the danger of 'transforming' a regular person with an elevated intraocular pressure into 'a patient', which by itself could affect quality-of-life just by changing the person's perception of himself. Such an effect has not been reported for ocular hypertension or glaucoma in literature though. We have checked our own observational data from the quality-of-life survey described in chapter two for such a 'patient effect', by introducing a dummy for 'never treated' (0) and 'ever treated' (1) in the multiple regression analysis of the quality-of-life scores. The coefficient for this factor was small on all quality-of-life instruments ($\pm 2\%$ worsening of the score) and did not reach statistical significance in any instrument. So reservations against treatment initiation in OHT patients from a disinclination to turn someone into a patient are not supported by data at this moment.

Macro-level

In the Netherlands, all glaucoma medications considered in this research are reimbursed and indicated as first-line monotherapy in glaucoma and ocular hypertension patients.²⁹ In this respect, the current research outcomes do not have implications for decision makers on the macro level insofar as the reimbursement of glaucoma medication is concerned. However, new treatment modalities for ocular hypertension and glaucoma are in development, and will need to be considered for reimbursement in the future.^{30, 31} Some of these have the same mode of action as existing pressure lowering eye-drops, but there are several new approaches to the treatment of glaucoma, including neuroprotective agents, ocular

implants for drug delivery, and gene therapy.^{30, 31} In time, the glaucoma disease progression model that has been built for the analyses in this thesis could be adapted to future findings and be employed to assess the long-term consequences of new treatment strategies in order to inform reimbursement decisions at the macro level in the future.

In addition to reimbursement of medications, decision makers at the macro level are concerned with the allocation of the macro budget available for health care. The analyses in this thesis took a societal perspective aggregating all cost-consequences no matter who the payer was. This fits the macro level perspective, but does not in itself enable a direct translation of the long-term cost-effectiveness outcomes in this thesis to macro level budget allocation decisions. The analyses involved many different budgetary sectors (pharmaceutical vs. hospital vs. ambulatory care) and took a lifetime horizon. They indicated that short term investments can lead to long-term cost savings, but the savings are generated in the future and in different budgetary sectors than the ones that carry the investments. A lifetime horizon is relevant in economic evaluations of glaucoma care because of the chronic nature of both the disease and the treatment, but macro level decisions are much more focussed on short term investments and results.³² The long term projections of the need for low-vision related rehabilitation and care for glaucoma patients were based on the current situation. It is not unlikely though that this sector will undergo major changes in the next twenty years involving the use of technology and robotics, that will affect its resource use, cost and potentially also its health benefits. In addition, the cost-effectiveness analyses in this thesis presumed a complete flexibility of resources, i.e. no constrictions in redirecting resource use from watchful waiting to medical treatment, or from low-vision rehabilitation to surgery, whereas macro level budget allocation decisions have to take inflexibility in this area into account. Finally, macro level allocation of available resources must cover all healthcare and therefore consider the efficiency of health care technology in all disease areas.

Despite the fact that the outcomes of the economic analyses in this thesis are only one piece of the puzzle for macro level budget allocation, they do have some implications. They showed that current care for POAG is dominant over 'doing nothing' in that it saves sight, quality of life and money, which implies that reallocating budget away from current POAG treatment would likely lead to inefficiencies. Intensification of treatment for POAG and (most) OHT patients was a dominant strategy over current care, but did involve additional costs for medication, ophthalmologist visits and surgical procedures for which budget would need to be made available on the macro level.

Implications for research

The research presented in this thesis has answered the research questions formulated in the introduction, and has generated information for decision makers in the three levels of decision making. Nevertheless, no research question can ever be answered with complete determinism, as residual uncertainties in the research context, method, input and outcomes will always remain. Some of the uncertainties may be addressable by further research, while others are the inherent result of unpredictability or randomness.³³ The next paragraphs discuss the remaining uncertainties most relevant for the research questions and decision makers addressed in this thesis, and explore the opportunities to reduce the uncertainty with additional research. In 2003, Walker *et al.* have proposed a conceptual framework for a systematic approach to communicate uncertainty in decision support, in which they distinguish three dimensions of uncertainty.³³ The first pertains to the *location* of uncertainty, i.e. where the uncertainty manifests itself within the model complex. The second pertains to the *level* of uncertainty, i.e. where the uncertainty manifests itself along the spectrum between deterministic knowledge and total ignorance. And the third pertains to the *nature* of uncertainty, i.e. whether the uncertainty is due to the imperfection of our knowledge or is due to the inherent variability of the phenomena being described. The paragraphs below have been structured according to the location of the uncertainty within the glaucoma model complex. The last paragraph of this chapter looks beyond the specific research questions and methodologies of this thesis, and discuss several opportunities to improve future research in the general area of health technology assessment and glaucoma management.

Remaining uncertainties and opportunities for further research

Model structure

The structure of the glaucoma model was based on discrete event simulation, which some authors consider the preferred technique for health economic evaluations.³⁴ Most research that was consulted to inform the construction of the glaucoma model was not designed for this particular purpose, and usually did not provide the exact kind of information that was needed. This prompted several translations of the existing data into the model structure through extrapolations, assumptions and iterations. The influence of the choices made in these processes have been addressed in sensitivity analyses and have been presented in the chapters on the cost-effectiveness outcomes of the model. Two important choices in the model structure have not been addressed in sensitivity analyses though. It concerns the exclusion of explicit consideration of patient (non)compliance in the

model structure, and the simulation of only the better eye rather than both eyes of the patient. These were deliberate choices in the design of the model, based on the expectation that the alternative would greatly increase the complexity of the model whereas the impact on the outcomes would be small. The increased model complexity is also the reason why these issues have not been assessed in sensitivity analyses; the only way to do that would have been to build a vastly more complex model and run all analyses again, which was beyond the scope and feasibility of the project. However, the issues are discussed in some detail below as an acknowledgement of their potential importance in future research.

Include treatment adherence and persistence

Non-adherence and non-persistence to the subscribed medication is a common issue in glaucoma management. Reviews report that non-adherence to glaucoma medication is typically around 20-30% and non-persistence after one year is often higher than 50%.³⁵⁻³⁷ Non-adherence and non-persistence were however not explicitly incorporated in the base case model. The main reasons for this choice were the consideration that the effectiveness estimates for the topical medications derived from clinical studies already represent a degree of non-adherence, and that the effect of non-persistence would not impact the incremental cost-effectiveness outcomes of the analyses. Comparisons of treatment versus no treatment would lead to smaller differences if non-persistence to both treatment and follow-up were incorporated, because the non-persistent patients would have a similar course of disease as untreated patients and 'dilute' the average outcomes in the treated population. On the other hand, if non-adherence to medication would lead to an earlier transition to laser treatment or surgery, it might even lead to better overall health outcomes. In either case, the magnitude of the incremental outcomes would likely change, but the overall direction of the outcomes would remain similar. In the comparisons between different treatment strategies, explicit consideration of adherence and persistence would only affect the outcomes if the nature of the treatment strategy itself would affect these attributes. For example, it could be postulated that a high frequency of follow-up visits stimulates patients to better adhere to their medication through positive reinforcement by the caregiver or by proof from diagnostic test that their disease has not worsened. It is hard to find proof for this hypothesis from the literature though; on the contrary, practical factors like forgetfulness, unavailability of eye-drops and difficulties holding the bottle above the eye are more important barriers for adherence than a lack of understanding about glaucoma and the benefit of treatment.^{38, 39} In addition, the effect of improved adherence on the actual pressure lowering effectiveness of medication is not well documented.^{37, 40}

Still, there are reasons why it could be worthwhile to explicitly incorporate adherence and persistence in future simulation models of glaucoma. The face validity of the model would benefit from it, as the challenge to motivate patients to use their medication as prescribed and to persist in doing so is an important aspect of every ophthalmologist's daily practice. Additionally, it would enable the economic evaluation of interventions improving compliance and persistence, which is not possible with the current model structure. An obstacle to the incorporation of non-adherence and non-persistence in the model structure would be that it requires the explicit definition of relevant relationships, like the impact of each treatment strategy on adherence and persistence, the impact of non-adherence on medication effectiveness, and the potential relationship between patient characteristics and non-adherence and non-persistence (heterogeneity), while research data on these relationships are scarce. It would therefore be prudent to carefully consider whether extension of the model is relevant in the context of the research questions asked.

Micro-simulation of the other eye

The current model simulates one individual eye (the better) in one individual patient. This does not mean that the other eye is ignored altogether, as its treatment and the impact of its condition on quality of life are in fact considered. The other eye is not modeled as a separate entity with its own course of disease though, and in this respect it is not different from other published models on ocular hypertension and glaucoma.⁴¹⁻⁴⁷ This has advantages, as treatment strategies and guidelines are typically formulated for 'the eye' and 'the patient', and do not differentiate depending on the condition of the other eye either. However, the structure of the discrete event model does allow for the other eye to be modeled as a separate entity, and therefore it raises the question whether it should be. After all, treatment choices, and their long term (cost-)effectiveness, for any particular eye may depend on the status of the other eye. Health-related quality of life depends on the status of both the better eye and worse eye (chapter two), and so do the costs associated with low vision and blindness. This issue has been tackled partially by performing a sensitivity analysis in which only one eye was affected by glaucoma while the other eye remained healthy, but the base case model outcomes can be expected to be more accurate if the model accounts for disease progression and treatment in both eyes separately. The implication, as already mentioned, is that the model's complexity would increase to a large extent. Not only does it require micro-simulation of the other eye via attributes related to its condition and treatment status, but also consideration of interactions and correlations between the two eyes, and consideration of the status and current treatment of both eyes in each treatment decision.

Model input

Definition of treatment strategy

As mentioned earlier, the treatment strategies that were defined for the model simulation described in this thesis are not necessarily the most realistic strategies for all clinical settings or jurisdictions. For example, the definition of progression as a loss of 2 dB in the Mean Deviation, regardless of the time span during which the loss occurred, has led to rather rigorous treatment decisions regarding the need for surgery in some of the simulated patients. The 'decision' to operate was only taken in the model when both the IOP was above target despite maximally tolerated medication and progression of visual field loss was observed. However, since progression would be observed in the model whenever a patient's measured MD was 2 dB lower than the baseline measurement, many patients eventually met these conditions. In the low-target-pressure strategy this led to trabeculectomy in 46% of the glaucoma patients. In reality, the time span of the progression will be taken into account in the decision to perform surgery (e.g. did the patient lose 2 dB in one year or in ten years?), as well as the life-expectancy of the patient (e.g. with the current rate of dB loss, is the patient likely to develop impairing visual field loss during his/her lifetime?). The flexibility of the glaucoma disease model allows for relatively easy adjustment to investigate the long-term consequences of such tailored (and therefore usually more complex) treatment strategies. Much research is currently devoted to finding the best method to establish progression in POAG patients, in terms of accurate and early detection.⁴⁸⁻⁵¹ The specifics of various detection methods could be built into the model structure to investigate the long-term consequences of these methods to aid in determining their value in clinical practice.

Patient population

A proportion of uncertainty in the model outcomes is caused by variation in the patient population. Even with perfect information on the model structure and its parameters, the fact that the average population outcome indicates that intensive treatment is better still does not certify that intensive treatment is the better option in each individual patient. Whether or not variation between patients is a problem for the interpretation of model outcomes, depends on both the magnitude of the impact and the degree to which the variation can be anticipated in practice. In the analyses presented here, this was investigated in two ways: by performing subgroup analyses, and by calculating the expected value of individualized care (EVIC). A non-zero value for the overall EVIC calls for partial EVIC analyses in order to indicate whether it might be worthwhile to implement stratified treatment (chapter 7). This thesis only describes the partial EVIC calculation of the comparison between a low target pressure strategy and usual care in POAG, but the overall EVIC for the other

POAG treatment comparisons was non-zero too, as was the EVIC of direct OHT treatment initiation versus watchful waiting. The potential value of individualized care with respect to these treatment strategies could therefore be investigated further. The subgroup analyses reported in this thesis indicate that this is not likely to lead to conclusions in favor of individualized care though. The subgroups were defined based on initial IOP and initial visual field damage (POAG) and initial IOP and conversion risk (OHT), which are the most important risk factors that are actually knowable at the treatment decision. No subgroup had effectiveness or cost-effectiveness outcomes that suggested that the conclusions based on the population outcomes were not valid in that subgroup.

One particular type of patient heterogeneity that was not explicitly considered in the model was heterogeneity in patient preferences. Different patients are likely to have different preferences for everything that has to do with treatment and their expected disease progression. For example, one patient may be extremely bothered by side-effects caused by eye-drops and therefore prefer to remain under watchful waiting, while the other is insecure about the prospect of developing glaucoma and medications bring a sense of relief. Pressure lowering medication will have a different impact on the quality of life in these two patients, and might affect the long-term outcomes of the treatment strategies that were compared here. In clinical practice, such patient preferences are likely to be considered to a certain degree, and consenting to a patient's a priori preference may not always render the highest amount of health, as a patient may not have realistic expectations about disease progression and the effect of treatment. Still, a more detailed simulation of preference heterogeneity could be considered in future versions of the model. Literature about this topic to provide input is not abundant. A few recent studies have used discrete choice experiments to measure patients' relative preference for various aspects of glaucoma treatment, but these have reported the average population outcomes and not focused on preference heterogeneity.^{52, 53} Overall it was found that patients state much higher preference for protection against future blindness than avoiding (side-effects from) medication or surgery. Renewed analyses of those studies could render information about heterogeneity in these preferences, which could then be integrated into the model in order to investigate the value of implementing stratified treatment decisions according to patient preferences.

Model parameters

The estimates for the population level input parameters that were used in the current model structure were surrounded with some uncertainty, which for some estimates was larger than for others. For example, some of the estimates for resource costs,

like the average costs for laser trabeculoplasty, and the average costs of home care as a result of low vision, were quite imprecise. The expected value of perfect information analysis pointed out that the value of reducing all uncertainty in the population estimates for the comparison of a low target pressure versus usual care in POAG, and direct treatment initiation versus watchful waiting in OHT patients was nil. This means that the conclusions from the current analyses would not change if all uncertainty was resolved, and it indicates that no resources for research should be directed at getting more precise population estimates.

Model outcomes

The validity of the model outcomes was tested with, among others, a comparison between predicted incidences of blindness and those observed. The predicted incidence of blindness in untreated POAG patients agreed with the (scarce) data of observational studies, but the predicted incidence of blindness in treated POAG patients was much lower than that reported in literature. It is hard to pinpoint the reason for the low estimate in the model, because blindness is the final outcome of the complete network of relationships defined in the model. Several components of this network were separately tested for their validity, like the average IOP during follow-up, the decrease of MD in time and the duration of life, and these accurately reflected observed data. We speculate that the numbers reported in literature are relatively high, while the numbers predicted by the model are relatively low. The incidence of blindness reported in literature may be high because they concern patients in an era where the new generations of pressure-lowering medication were not available and glaucoma could not be treated as effectively as it can be today. Moreover, the studies were conducted retrospectively in selected patient populations based on the availability of visual field measurements, and may be biased towards higher risk patients than the simulated patient population. On the other hand, the low incidences of blindness predicted by the model may be the result of elements within the current model structure, particularly a “safe IOP” threshold below which glaucoma does not further progress, a linear deterioration of the visual field, and a constant relative risk of pressure lowering on progression rate. Even though these elements of the model structure were based on research findings reported in scientific literature, if they are inaccurate, the current model underestimates the incidence of blindness. Indeed, even though the *direction* of the cost-effectiveness outcomes (i.e. costs per QALY) turned out to remain similar to the base case estimates in structural sensitivity analyses, the incidence of blindness in the model simulations of current care increased from 2.9% to 3.6% without the safe IOP threshold, and to 8.5% when a non-linear (i.e. progressively stronger) decrease of MD in time was introduced. Future research on the occurrence of blindness in glaucoma patients treated with the current array of medical and surgical techniques

will in time give more insight in the validity of the model's estimates, while new information on the disease mechanism of glaucoma will enable fine-tuning of the model structure.

Context

The context of the research in this thesis was limited to individual patients and their course of disease. Scarceness in the availability of medical staff to provide the care was not considered, nor was the effect of waiting lists. In many jurisdictions, the demand for ophthalmological care is larger than can be provided. This means that patients that require care cannot always be seen immediately, and as a result may lose health. Consequently, when waiting lists get longer, more health is lost. For decision making at the meso and macro level, this effect should in fact be considered when decisions are made about intensifying treatment. For example, treating all patients with ocular hypertension according to the current visit schedule would pose an additional burden on eye clinics because patients need to be titrated to the optimal medication scheme. Physicians that spend their time on these patients can no longer spend the same time on another patient, who may in fact have benefited more from the physician's care. Alternatively, intensive treatment in glaucoma patients may reduce the need for intensive monitoring and free ophthalmologists' time to see other patients and thus reduce waiting lists and render additional health. Decreasing the frequency of visual field testing in glaucoma patients in the model resulted in a small amount of health loss, which, in the current scope of the analyses, might lead to the conclusion that it is not a preferable option. However, it also resulted in a reduction of resource costs and it would in practice also result in a reduction of the demand for human resources. The projected health loss due to less visual field testing may be a fraction of the health gain that could be realized if the freed up resources were applied to reduce waiting lists. Decisions about a potential shift in the allocation of resources in an ophthalmology clinic or within a shared care environment could be better informed by economic analyses that adopt a wider scope. The discrete event simulation model structure currently employed allows for such an extension of the scope, as it is able to handle multiple entities (patients) as well as various types of entities (patients, ophthalmologists, optometrists etc), and is actually the recommended modeling technique when interaction between entities and competition for available resources are important elements of the research question.^{54, 55} In addition, dynamic population modeling could be introduced to take account of the predicted growth in the patient population in the future. The current model only makes projections for the current population size and composition.

General recommendations

Over the past decade, attention for personalized medicine has been growing, and the importance of addressing patient heterogeneity both in comparative effectiveness

research and in treatment decisions is now well recognized.⁵⁶⁻⁵⁸ Advances in the field of molecular biology has enabled fundamental research into the genetic sources of heterogeneity in disease development and treatment effect, which ultimately aspires to lead to personalized treatment based on a patient's genetic profile. The relatively new concept of value of information analysis with regard to patient heterogeneity (EVIC) could play a role in this development, as it offers the possibility to quantitatively explore whether resources should be allocated to a specific research question or not. It could even be employed in early stages of fundamental research to aid prioritization of research. For example, a situation could occur in which fundamental research in a specific disease area has identified a number of genes or biomarkers with predictive value for the course of the disease, and researchers need to decide which gene(s) or biomarker(s) to develop further into diagnostic tests. In this case, a preliminary economic evaluation including an EVIC analysis could provide information to the decision that goes beyond properties of the final diagnostic test itself, like sensitivity and specificity, and that already includes the potential role the test could play in clinical decision making. Even though the level of uncertainty in such preliminary analyses could be quite substantial, the modeling exercise will force all stakeholders to explicitly consider all the practical issues involved in the future diagnostic test, and it might still indicate zero value in individualized care even when all uncertainty is taken into account. In addition, we found that EVIC analysis was a very useful tool to screen whether health economic outcomes for heterogeneous patient populations should be further analysed on a subgroup level, and to which patient attribute(s) the subgroups should be stratified. In literature there is only one report about the (proposed) application of EVIC analysis.⁵⁹ In order to explore the full applicability of the EVIC analysis, it should be applied to more economic analyses that were based on patient level data or simulations.

Even though the quantitative nature of value of information outcomes is a great asset for decision making, a potential danger is that it emphasizes the locations and levels of uncertainty that are suitable for value of information analysis, like statistical uncertainties stemming from sampling error (population parameter estimates) or heterogeneity.³³ The value of information regarding uncertainties at the level of scenario uncertainty (e.g. simulate two eyes) or recognized ignorance (e.g. disease mechanism) cannot be assessed quantitatively, but may actually be higher than those from statistical uncertainty. Decision makers concerned with the allocation of research funds should therefore first make sure that they have a broad scope of the existing uncertainties surrounding a decision problem, and then use the best methods available to assist allocation decisions, rather than let the existence of positive value of information outcomes be directive in prioritization.

Throughout this project, the members of the multidisciplinary team involved have experienced that the benefits of modeling do not only pay off in the final model and its outcomes, but also to a more personal extend within the development process itself. The model design process requires explicit discussions about current clinical practice, the evidence from current scientific reports and factors that play a role in clinical decisions regarding the treatment of individual patients. For example, the decision rules regarding treatment changes were discussed and formulated in team meetings without iteration or feedback from the model to see what the outcomes of certain choices would be, in order to prevent bias towards desirable outcomes. In the final simulations though, the amount of trabeculectomies predicted by the model both in the usual care strategy and in the intensive treatment strategy, was perceived as high. This indicated that either the team's perception of the actual frequency of trabeculectomy was biased, or that the model's equations directing the surgery decision does not accurately reflect all the relevant factors. Discussions about the topic revealed the knowledge and beliefs of each of the team members, triggered focused searches in scientific literature and databases, and identified areas of uncertainty. Such dynamics should be transposed to a wider scope of international collaboration. Many specialists and researchers in the field of glaucoma are concerned with the same issues, and many of them develop research activities to address them. Ideally, therefore, these parties should join forces and work together in an international and multidisciplinary team with the aim to develop a communal model for glaucoma. The benefits of such cooperation would be that the highest level of evidence aggregation would be ensured, and that communication of model outcomes would be greatly facilitated through utilization of the same model structure and communal input values. From a joint base, each country could then adjust the structure and input to fit the local healthcare and reimbursement system. Currently, the European Glaucoma Society is making a great effort to stimulate international cooperation through its special interest group for health economics (www.eugs.org). The members of this group can play a vital role in improving health technology assessment for glaucoma management and in enhancing its utilization in all levels of decision making.

Conclusion

The aim of the research presented in this thesis was to investigate whether intensive treatment would be better for the management of ocular hypertension and primary open-angle glaucoma than the current approach in clinical practice. The research has resulted in a simulation model for disease progression and treatment choices in individual patients that lead to projections of intermediate clinical outcomes that

compared well with those of observational studies. Overall, the long-term effectiveness and cost-effectiveness of intensive treatment was more favorable than that of moderate treatment, both in ocular hypertension and in primary open-angle glaucoma, and both in high-risk and in low-risk patients. The simulation model has proven to be a flexible instrument to adjust to new information and new research questions, and will hopefully be able to prove its worth again in future research questions in glaucoma management.

References

- Weinreb RN, Friedman DS, Fechtner RD, Cioffi GA, Coleman AL, Girkin CA, Liebmann JM, Singh K, Wilson MR, Wilson R, Kannel WB. Risk assessment in the management of patients with ocular hypertension. *Am J Ophthalmol* 2004; 138:458-467.
- van Velden M, Severens J, Novak A. Economic evaluations of healthcare programmes and decision making: The influence of economic evaluations on different healthcare decision-making levels. *Pharmacoeconomics* 2005; 23:1075-1082.
- Jansson S, Anell A. The impact of decentralised drug-budgets in Sweden - a survey of physicians' attitudes towards costs and cost-effectiveness. *Health Policy* 2006; 76:299-311.
- Lessard C, Contandriopoulos AP, Beaulieu MD. The role (or not) of economic evaluation at the micro level: can Bourdieu's theory provide a way forward for clinical decision-making? *Soc Sci Med* 2010; 70:1948-1956.
- O'Donnell JC, Pham SV, Pashos CL, Miller DW, Smith MD. Health technology assessment: lessons learned from around the world--an overview. *Value Health* 2009; 12 Suppl 2:S1-5.
- Erntoft S. Pharmaceutical priority setting and the use of health economic evaluations: a systematic literature review. *Value Health* 2011; 14:587-599.
- Erntoft S. The use of health economic evaluations in pharmaceutical priority setting; The case of Sweden. *Lund Institute of Economic Research*. Lund, Sweden: Lund University; 2010.
- Baltussen R, Niessen L. Priority setting of health interventions: the need for multi-criteria decision analysis. *Cost Eff Resour Alloc* 2006; 4:14.
- Gordon MO, Torri V, Miglior S, Beiser JA, Floriani I, Miller JP, Gao F, Adamsons I, Poli D, D'Agostino RB, Kass MA. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. *Ophthalmology* 2007; 114:10-19.
- Dutch Glaucoma Group (Nederlandse Glaucoom Groep). Addendum EGS guidelines 2009. Available at: <http://www.oogheelkunde.org/uploads/9r/qz/9rqzc2g7pragHfQCMraSFg/addendum-EGSguidelines-2009.pdf>. Accessed: August 2011
- European Glaucoma Society. Terminology and guidelines for glaucoma (third edition). Dogma: Savona, Italy; 2008.
- American Academy of Ophthalmology Glaucoma Panel. Primary open-angle glaucoma. Preferred practice pattern. San Francisco: American Academy of Ophthalmology, 2005.
- Oogziekenhuis Maastricht UMC (university Eye Clinic). Available at: www.oogziekenhuismaastricht-tumc.nl. Accessed: October 2011
- Oogziekenhuis Rotterdam (the Rotterdam Eye Hospital). Available at: www.oogziekenhuis.nl. Accessed: October 2011
- Catharina ziekenhuis Eindhoven. Available at: www.cze.nl. Accessed: October 2011
- University Medical Center Groningen (UMCG). Available at: www.umcg.nl. Accessed: October 2011
- Morley AM, Murdoch I. The future of glaucoma clinics. *Br J Ophthalmol* 2006; 90:640-645.
- Quigley H, Broman A. The number of people with glaucoma worldwide in 2010 and 2020. *BMJ* 2006; 90:262-267.
- Tuulonen A, Salminen H, Linna M, Perkola M. The need and total cost of Finnish eyecare services: a simulation model for 2005-2040. *Acta Ophthalmol* 2009; 87:820-829.
- Holtzer Goor KM, Klazinga NS, Koopmanschap M, Lemij HG, Plochg T, Van Sprundel E. Monitoring of stable glaucoma patients; Evaluation of the effectiveness and efficiency of a glaucoma follow-up unit, staffed by nonphysician health care professionals, as an intermediate step towards glaucoma monitoring in primary care. Rotterdam: Erasmus University Rotterdam, Institute of Health Policy & Management, 2010.
- Rathod D, Win T, Pickering S, Austin M. Incorporation of a virtual assessment into a care pathway for initial glaucoma management: feasibility study. *Clin Experiment Ophthalmol* 2008; 36:543-546.
- Gray SF, Spry PG, Brookes ST, Peters TJ, Spencer IC, Baker IA, Sparrow JM, Easty DL. The Bristol shared care glaucoma study: outcome at follow up at 2 years. *Br J Ophthalmol* 2000; 84:456-463.

23. National Collaborating Centre for Acute Care. Glaucoma: diagnosis and management of chronic open-angle glaucoma and ocular hypertension. London: National Collaborating Centre for Acute Care, 2009.
24. Holtzer Goor KM, van Sprundel E, Lemij HG, Plochg T, Klazinga NS, Koopmanschap MA. Cost-effectiveness of monitoring glaucoma patients in shared care: an economic evaluation alongside a randomized controlled trial. *BMC Health Serv Res* 2010; 10:312.
25. Singh K, Shrivastava A. Medical management of glaucoma: Principles and practice. *Indian J Ophthalmol* 2011; 59:S88-92.
26. Singh K, Shrivastava A. Early aggressive intraocular pressure lowering, target intraocular pressure, and a novel concept for glaucoma care. *Surv Ophthalmol* 2008; 53 Suppl1:S33-38.
27. Ziekenfondsraad. Protocol for the use of glaucoma medication (Protocol gebruik glaucoommiddelen). Amstelveen: Health Care Insurance Board (College voor Zorgverzekeringen), 1999.
28. European Glaucoma Society. Terminology and guidelines for glaucoma (second edition). Dogma: Savona, Italy; 2003.
29. Health Care Insurance Board (CVZ). Pharmacotherapeutic compass (Farmacotherapeutisch kompas). Available at: www.fk.cvz.nl. Accessed: August 2011
30. Lee AJ, Goldberg I. Emerging drugs for ocular hypertension. *Expert Opin Emerg Drugs* 2011; 16:137-161.
31. Fogagnolo P, Rossetti L. Medical treatment of glaucoma: present and future. *Expert Opin Investig Drugs* 2011; 20:947-959.
32. Adang E, Voordijk L, Jan van der Wilt G, Ament A. Cost-effectiveness analysis in relation to budgetary constraints and reallocate restrictions. *Health Policy* 2005; 74:146-156.
33. Walker W, Harremoës P, Rotmans J, Van der Sluijs J, Van Asselt M, Janssen P, Krayen von Krauss M. Defining uncertainty; A conceptual basis for uncertainty management in model-based decision support. *Integrated Assessment* 2003; 4:5-17.
34. Caro JJ, Moller J, Getsios D. Discrete event simulation: the preferred technique for health economic evaluations? *Value Health* 2010; 13:1056-1060.
35. Schwartz GF, Quigley HA. Adherence and persistence with glaucoma therapy. *Surv Ophthalmol* 2008; 53 Suppl1:S57-68.
36. Schwartz GF. Compliance and persistency in glaucoma follow-up treatment. *Curr Opin Ophthalmol* 2005; 16:114-121.
37. Olthoff CM, Schouten JS, van de Borne BW, Webers CA. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension an evidence-based review. *Ophthalmology* 2005; 112:953-961.
38. Olthoff CM, Hoevenaars JG, van den Borne BW, Webers CA, Schouten JS. Prevalence and determinants of non-adherence to topical hypotensive treatment in Dutch glaucoma patients. *Graefes Arch Clin Exp Ophthalmol* 2009; 247:235-243.
39. Hoevenaars JG, Schouten JS, van den Borne B, Beckers HJ, Webers CA. Will improvement of knowledge lead to improvement of compliance with glaucoma medication? *Acta Ophthalmol* 2008; 86:849-855.
40. Cate H, Broadway DC. Association between intraocular pressure and adherence: is there one? *Eye (Lond)* 2011; 25:1238.
41. Kobelt G, Jönsson L. Modeling cost of treatment with new topical treatments for glaucoma. *Int J Technol Assess Health Care* 1999; 15:207-219.
42. Nordmann JP, Lafuma A, Deschaseaux C, Berdeaux G. Clinical outcomes of glaucoma treatments over a patient lifetime: a Markov model. *J Glaucoma* 2005; 14:463-469.
43. Althin R, Grima DT, Dhawan R, Bernard LM. Considerations in developing model-based economic evaluations of glaucoma treatment. *J Glaucoma* 2006; 15:541-547.
44. Kymes SM, Kass MA, Anderson DR, Miller JP, Gordon MO. Management of ocular hypertension: a cost-effectiveness approach from the Ocular Hypertension Treatment Study. *Am J Ophthalmol* 2006; 141:997-1008.
45. Peeters A, Schouten JS, Webers CA, Prins MH, Hendrikse F, Severens JL. Cost-effectiveness of early detection and treatment of ocular hypertension and primary open-angle glaucoma by the ophthalmologist. *Eye* 2008; 22:354-362.
46. Rein D, Wittenborn J, Lee P, Wirth K, Sorensen S, Hoerger T, Saaddine J. The cost-effectiveness of routine office-based identification and subsequent medical treatment of primary open-angle glaucoma in the United States. *Ophthalmology* 2009; 116:823-832.
47. Stewart WC, Stewart JA, Nassar QJ, Mychaskiw MA. Cost-effectiveness of treating ocular hypertension. *Ophthalmology* 2008; 115:94-98.
48. Chauhan BC, Garway Heath DF, Goni FJ, Rossetti L, Bengtsson B, Viswanathan AC, Heijl A. Practical recommendations for measuring rates of visual field change in glaucoma. *Br J Ophthalmol* 2008; 92:569-573.
49. Wesselink C, Heeg G, Jansonius N. Glaucoma monitoring in a clinical setting: Glaucoma Progression Analysis versus Nonparametric Progression Analysis. *Arch Ophthalmol* 2009; 127:270-274.
50. Jansonius NM. On the accuracy of measuring rates of visual field change in glaucoma. *Br J Ophthalmol* 2010; 94:1404-1405.
51. Ernest PJ, Schouten JS, Beckers HJ, Hendrikse F, Prins MH, Webers CA. The evidence base to select a method for assessing glaucomatous visual field progression. *Acta Ophthalmol* 2012; 90:101-108.
52. Bhargava JS, Patel B, Foss AJ, Avery AJ, King AJ. Views of glaucoma patients on aspects of their treatment: an assessment of patient preference by conjoint analysis. *Invest Ophthalmol Vis Sci* 2006; 47:2885-2888.
53. Burr J, Kilonzo M, Vale L, Ryan M. Developing a preference-based glaucoma utility index using a discrete choice experiment. *Optom Vis Sci* 2007; 84:797-808.
54. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. *J Health Serv Res Policy* 2004; 9:110-118.
55. Stahl JE. Modelling methods for pharmacoeconomics and health technology assessment: an overview and guide. *Pharmacoeconomics* 2008; 26:131-148.
56. Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered health care. *J Health Econ* 2011; 30:549-559.
57. Basu A. Individualization at the heart of comparative effectiveness research: the time for i-CER has come. *Med Decis Making* 2009; Nov-Dec:N9-N11.
58. Lesko LJ. Personalized medicine: elusive dream or imminent reality? *Clin Pharmacol Ther* 2007; 81:807-816.
59. Sanelli PC, Gold RL, Greenberg ED, Reichman MB, Ugorec I, Segal AZ, Fink M. Work-in-progress toward incorporating patients' preferences in practice guidelines for imaging aneurysmal subarachnoid hemorrhage. *Acad Radiol* 2009; 16:535-540.

Samenvatting

Nawoord

Curriculum Vitae

List of publications

Samenvatting

Dit proefschrift gaat over de behandeling van primair open-kamerhoek glaucoom en oculaire hypertensie. Glaucoom is een verzamelnaam voor een groep oogandoeningen die gekenmerkt worden door schade aan de oogzenuw en daarmee samenhangende uitval in het gezichtsveld. De meest voorkomende vorm in Nederland is primair open-kamerhoek glaucoom. Deze vorm van glaucoom ontwikkelt zich met name op latere leeftijd, en komt voor bij ongeveer 3% van de mensen ouder dan 65 jaar. Een verhoogde oogdruk is een belangrijke risicofactor voor het ontstaan van primair open-kamerhoek glaucoom. Wanneer er verhoogde oogdruk is, maar een patiënt geen tekenen van glaucoom vertoont, wordt gesproken van oculaire hypertensie. De behandeling van zowel oculaire hypertensie als primair open-kamerhoek glaucoom is gericht op het verlagen van de oogdruk. Dat kan met medicatie, met laserbehandeling of met chirurgische ingrepen. Omdat het ziekteproces vaak langzaam verloopt en patiënten de behandeling als belastend kunnen ervaren, is het ook een optie om geen (of milde) oogdrukverlagende therapie te gebruiken en de patiënt regelmatig te controleren.

Het doel van het onderzoek beschreven in dit proefschrift was om na te gaan of het op de lange termijn gunstig is om oculaire hypertensie en primair open-kamerhoek glaucoom intensiever te behandelen dan in de klinische praktijk op dit moment gebruikelijk is. Die vraag hebben we geprobeerd te beantwoorden met kosten-effectiviteitsstudies. De primaire uitkomstmaat van die studies was de verhouding tussen de extra gezondheidswinst van een strategie enerzijds en de extra kosten van die strategie anderzijds, en we gebruikten daarbij een maatschappelijk perspectief. De gezondheidswinst werd uitgedrukt in voor-kwaliteit-van-leven-gecorrigeerde levensjaren (QALY's), en de kosten bestonden uit direct medische kosten (zoals medicijnen), directe niet-medische kosten (zoals vervoer) en indirecte niet-medische kosten (zoals productiviteitsverlies). De gegevens voor de analyses kwamen uit een computersimulatiemodel dat we specifiek voor dit doel hebben ontworpen. Het gebruik van een model stelde ons in staat om analyses te doen die met klinisch onderzoek onmogelijk zouden zijn, terwijl de uitkomsten van het model vanwege de data uit klinische en observationele studies waarop het model gebaseerd was representatief zijn voor waargenomen resultaten bij echte patiënten. Het simulatiemodel bootste het ziekteverloop van een groot aantal patiënten na, waarbij het rekening hield met de eigenschappen van elke individuele patiënt en de kenmerken van de behandelstrategie. De behandelstrategieën die op deze manier werden onderzocht, verschilden van het huidige beleid in de streefdruk, eerste-keus geneesmiddel en de regelmaat waarmee het gezichtsveld werd nagemeten.

We hebben het computersimulatiemodel gebouwd op basis van gegevens over het ziektemechanisme en behandel-effecten zoals beschreven in de wetenschappelijke literatuur. Goede kwantitatieve informatie over de invloed van verslechtering van de ziekte op de kwaliteit van leven ontbrak echter in de literatuur, net zoals kwantitatieve informatie over zorgverbruik bij patiënten die als gevolg van glaucoom slechtziend of blind zijn geworden. Om die reden hebben we zelf een studie gedaan bij 531 Nederlandse patiënten met oculaire hypertensie of primair open-kamerhoek glaucoom, met als doel de ontbrekende data te verzamelen. De uitkomsten van dat onderzoek zijn beschreven in **hoofdstuk twee** van dit proefschrift. De patiënten werden gevraagd een schriftelijke vragenlijst in te vullen. Daarmee werd informatie verzameld over de algemene gezondheid, de huidige behandeling, de behandelgeschiedenis, bijwerkingen van medicatie, en het zorgverbruik gedurende de laatste drie maanden. Bovendien bevatte de vragenlijst vier instrumenten om de gezondheidsgelateerde kwaliteit-van-leven van de patiënt te meten: de glaucoom-specifieke “Glaucoma Quality-of-Life questionnaire” (GQL), de zichts-specifieke “Visual Functioning Questionnaire” (VFQ-25), de generieke “EuroQol-5D” (EQ-5D) en de generieke “Health Utilities Index” (HUI-3). We hebben de gegevens geanalyseerd met meervoudige lineaire regressie, en vonden een onafhankelijke negatieve relatie tussen schade aan het gezichtsveld en kwaliteit-van-leven. De uitkomsten van de analyses werden geïntegreerd in het model via een formule voor de kwaliteit-van-leven van de patiënt op basis van de hoeveelheid gezichtsveldschade, de aanwezigheid van staar, en de bijwerkingen van glaucoommedicatie. Daarnaast hebben we het zorgverbruik dat toe te schrijven was aan slechtziendheid of blindheid bij de ondervraagde patiënten gestratificeerd naar de mate van gezichtsveldverlies, en hebben we de resulterende getallen in het model gebruikt als schatting voor de zorgkosten van slechtziende en blinde patiënten in het model.

In een eenvoudig Markov model, dat is beschreven in **hoofdstuk drie**, hebben we data over het risico op primair open-kamerhoek glaucoom bij oculaire hypertensie en het risico op blindheid bij primair open-kamerhoek glaucoom gebundeld, om daarmee de lange-termijn kans op blindheid bij patiënten met oculaire hypertensie te voorspellen. Dat leverde meer valide schattingen op dan eerder in een soortgelijk onderzoek waren gevonden, maar de Markov modelstructuur leende zich niet voor een goede synthese en extrapolatie van alle data, en leidde tot uitkomsten met grote onzekerheidsintervallen. Om de onderzoeksvragen die in dit proefschrift aan de orde waren te beantwoorden, hebben we daarom verder gebruik gemaakt van een modelstructuur op basis van patiëntensimulatie in een *discrete event simulation* model. Deze modelstructuur had nog andere voordelen, zoals de mogelijkheid om een behandelstrategie tot in detail te definiëren en variëren, en de mogelijkheid om een groot aantal relevante patiëntkenmerken expliciet mee te nemen in de simulatie.

In **hoofdstuk vier** is beschreven hoe we het uiteindelijke model hebben ontwikkeld en gevalideerd. In het kort: het model simuleerde het ziekteverloop van een individuele patiënt door de waarde van relevante patiëntkenmerken op specifieke momenten in de tijd te berekenen. Deze momenten waren representatief voor het optreden van een bepaalde ‘gebeurtenis’, zoals een bezoek aan de oogarts of het overlijden van de patiënt. Enkele voorbeelden van de vele patiëntkenmerken die gesimuleerd werden zijn leeftijd, oogdruk, huidige medicatie en gezichtsveldverlies. Het tijdinterval tot elke volgende gebeurtenis in het model was variabel, en hing grotendeels af van de patiënteigenschappen tijdens de laatst gesimuleerde gebeurtenis. In sommige gevallen werd daarbij ook gebruik gemaakt van toevalsgetallen, om het optreden van een kansproces na te bootsen. Een voorbeeld daarvan is het ontstaan van primair open-kamerhoek glaucoom. Elke gesimuleerde patiënt met oculaire hypertensie liep de kans om glaucoom te ontwikkelen, en die kans was hoger naarmate de oogdruk hoger was. Het toeval bepaalde echter of een conversie ook daadwerkelijk optrad. Nadat de gesimuleerde patiënt primair open-kamerhoek glaucoom had ontwikkeld, werd de ernst van het glaucoom gesimuleerd door middel van een patiëntkenmerk dat representatief was voor de kwaliteit van het gezichtsveld (Mean Deviation, MD). Tijdens een gesimuleerd bezoek aan de oogarts werd de toestand van de patiënt, gerepresenteerd door de waarde van alle patiëntkenmerken op dat moment, geëvalueerd, en werden behandelbeslissingen genomen volgens de regels die voorafgaand aan de simulatie waren ingesteld. Deze regels vormden samen de behandelstrategie. Alle gebruikelijke vormen van oogdrukverlagende interventies waren in het model vertegenwoordigd, en konden achter elkaar of gelijktijdig worden toegepast. De simulatie besloeg de periode van het eerste contact met een oogarts tot het overlijden van de patiënt. We hebben het uiteindelijke model uitgebreid getest op interne en externe consistentie, door populaties en behandelstrategieën uit klinische en observationele studies na te bootsen met het model, en na te gaan of de uitkomsten van het model overeenkwamen met die uit de praktijk. Pas daarna hebben we het model toegepast om de consequenties van nieuwe behandelstrategieën voor oculaire hypertensie en primair open-kamerhoek glaucoom te voorspellen.

Om behandelstrategieën met elkaar te vergelijken, hebben we steeds een cohort van drieduizend virtuele patiënten gesimuleerd onder twee verschillende strategieën. De eigenschappen van de gesimuleerde patiënten binnen een cohort verschilden van patiënt tot patiënt. Op die manier hebben we gepoogd een heterogene populatie patiënten na te bootsen die representatief was voor de patiëntenpopulatie in de meeste klinische praktijken in Nederland. Om te beginnen hebben we in een heterogene populatie van patiënten met primair open-kamerhoek glaucoom berekend hoe een behandelstrategie zoals die op dit moment over het algemeen wordt

toegepast (huidige zorg) zich verhoudt tot het onbehandeld laten van de aandoening. Dit is beschreven in **hoofdstuk vijf**. Daaruit bleek dat de huidige zorg tot grote gezondheidswinsten én kostenbesparingen leidt. Op basis van de modeluitkomsten konden we inschatten dat de huidige zorg per glaucoompatiënt gemiddeld 7,0 extra jaren zonder slechtziendheid en 5,1 extra jaren zonder blindheid oplevert, gedurende een tijdhorizon van ruim 15 jaar. Vertaald naar kwaliteit van leven zou de huidige zorg 1,4 QALY's per patiënt opleveren. De korte-termijn kosten van de huidige zorg waren per patiënt weliswaar ruim € 10.000 hoger vanwege oogartsbezoek, medicijnen en operaties, maar de lange-termijn kosten waren ruim € 40.000 lager door lager verbruik van zorg als gevolg van blindheid. Ook wanneer de resultaten werden verdisconteerd voor het feit dat een deel van het zorgverbruik en gezondheidswinst in de toekomst zullen optreden, bleef de huidige zorg dominant.

In hoofdstuk vijf staat verder beschreven hoe we hebben onderzocht of intensievere variaties op de huidige behandelstrategie mogelijk tot nog efficiëntere zorg zouden kunnen leiden. Met het model evalueerden we een strategie met latanoprost als eerstekeuzemiddel in plaats van timolol (huidige zorg), wat resulteerde in licht verhoogde kosten (€ 90, verdisconteerd) en een kleine gezondheidswinst (0,007 QALY's, verdisconteerd) per patiënt. De verschillen in uitkomsten tussen beide strategieën waren dus klein, maar de kosten-utiliteitsratio van € 12.931/QALY was gunstig in vergelijking met de drempelwaarden van € 30.000/QALY tot € 80.000/QALY die in de context van de accepteerbaarheid van incrementele kosten-utiliteit vaak worden aangehaald. Vervolgens evalueerden we een strategie waarbij direct bij aanvang van de behandeling een lage streefdruk (15 mmHg) gehanteerd werd, in tegenstelling tot de huidige zorg strategie waarbij de streefdruk gedurende de behandeling bijgesteld werd van 21 mmHg naar 18 mmHg en vervolgens naar 15 mmHg als het gezichtsveld verslechterde. Op de lange termijn leidde de lage streefdruk tot een gezondheidswinst van 0,115 QALY's per patiënt (verdisconteerd), terwijl de totale kosten gemiddeld € 1.550 per patiënt lager waren (verdisconteerd). De strategie met de lage streefdruk was daarom vanuit doelmatigheidsoogpunt dominant. Tenslotte simuleerden we twee behandelstrategieën waarbij de regelmaat waarmee een gezichtsveldmeting werd verricht om glaucoomprogressie vast te stellen afweek van die in de huidige zorg. Bij een hogere regelmaat van gezichtsveldmetingen, twee maal per jaar in plaats van eenmaal per jaar, duiden de modeluitkomsten op een kleine gezondheidswinst (0,006 QALY's, verdisconteerd) en hogere kosten (€ 1.063, verdisconteerd) per patiënt. De incrementele verdisconteerde kosten-utiliteitsratio van twee gezichtsveldmetingen per jaar was daarmee € 173.486/QALY en dus erg ongunstig ten opzichte van gangbare drempelwaarden. Bij een lagere regelmaat van gezichtsveldmetingen, eens per twee jaar, duiden de modeluitkomsten op een klein verlies van gezondheid (– 0,015 QALY's, ver-

disconteerd) en lagere kosten (– €319, verdisconteerd). De kosten-utiliteitsratio van een gezichtsveldmeting per twee jaar was daarmee € 21.516/QALY. Deze ratio ligt in lijn met de gangbare drempelwaarden voor accepteerbaarheid, maar zou desondanks onacceptabel kunnen zijn vanwege het verlies aan gezondheid. In aanvullende gevoeligheidsanalyses hebben we de robuustheid van de resultaten getoetst, en hebben we de onzekerheid rondom de uitkomsten in kaart gebracht. Daaruit bleek dat, ook met inachtneming van bestaande onzekerheid, we kunnen concluderen dat intensivering van glaucoombehandeling in de zin van eerstekeuzemiddel en streefdruk vanuit het oogpunt van doelmatigheid aan te bevelen zou zijn, maar dat intensivering van de monitoring middels frequentere gezichtsveldmetingen een ondoelmatige investering zou zijn.

Met betrekking tot de behandeling van oculaire hypertensie (**hoofdstuk zes**) hebben we met het model steeds twee strategieën nagebootst. De referentiebehandeling bestond uit een gecontroleerd afwachtend beleid, waarbij een patiënt geen oogdrukverlagende therapie ontving, maar wel jaarlijks bij de oogarts terugkwam voor controle. Zodra daarbij werd gezien dat er glaucoom was ontstaan, werd behandeling volgens gebruikelijke zorg voor glaucoom gestart. De alternatieve behandeling bestond er uit dat een patiënt direct met oogdrukverlagende medicijnen begon, zonodig uitgebreid met laserbehandeling. Bij conversie volgde verder behandeling volgens gebruikelijke zorg voor glaucoom. In eerste instantie hebben we één heterogene patiëntenpopulatie met een representatieve spreiding van het risico op glaucoom nagebootst. Omdat het echter aannemelijk is dat de gevolgen van direct behandelen gunstiger zijn naarmate de patiënt een groter risico op het ontwikkelen van glaucoom heeft, hebben we de twee strategieën ook gesimuleerd in specifieke patiëntensubgroepen die van elkaar verschilden in het totale risico op glaucoom.

In de heterogene populatie ontwikkelde 15% van de patiënten met een afwachtend beleid binnen vijf jaar glaucoom. Over de levenslange tijdshorizon van gemiddeld 26 jaar was dat 57%. Met directe oogdrukverlagende therapie waren deze percentages lager, respectievelijk 8% en 37%. Ook de levenslange incidentie van blindheid was lager bij directe behandeling: 0.4% in plaats van 1.5%. Deze resultaten vertaalden zich in een gemiddelde gezondheidswinst van 0,27 QALY's en een kostenbesparing van € 649 per patiënt (beiden verdisconteerd) voor directe aanvang van medicamenteuze behandeling in vergelijking met een gecontroleerd afwachtend beleid.

In de subgroepanalyses hebben we de twee behandelstrategieën nagebootst in patiëntenpopulaties waarin het totale risico op het ontwikkelen van glaucoom varieerde van 4% tot 33% uitgedrukt als cumulatieve incidentie in vijf jaar. De strategie met

directe medicamenteuze behandeling bleek ook in alle subgroepen gezondheids-winst op te leveren, variërend van 0,08 tot 0,73 (verdisconteerde) QALY's per patiënt. In de subgroepen van patiënten met een risico hoger dan 8% tot 10% ging directe behandeling bovendien gepaard met kostenbesparingen tot ruim € 6.000 per patiënt (verdisconteerd). In de lagere risicogroepen leidde directe behandeling tot additionele kosten, die samen met de gezondheidsuitkomsten resulteerden in incrementele kosten-uiteitsratio's tot maximaal € 15.000/QALY. Ook in deze analyses hebben we aandacht besteed aan de onzekerheid rondom de uitkomsten. We concludeerden op basis van de studieresultaten dat het vanuit het oogpunt van doelmatigheid beter zou zijn alle patiënten met oculaire hypertensie direct oog-drukverlagende medicatie voor te schrijven, tenzij daar vanuit de patiënt bezwaren tegen zouden zijn.

De meeste conclusies over de doelmatigheid van een bepaalde behandelstrategie waren gebaseerd op de *gemiddelde* uitkomsten van elk van de strategieën in de hele patiëntenpopulatie. Die informatie is van belang bij besluitvorming op populatie niveau, zoals voor behandelrichtlijnen of vergoedingen. Het lag vervolgens voor de hand ons af te vragen of de behandeling die op populatieniveau het beste is, ook voor alle individuele patiënten het beste is. Dat laatste is vooral van belang voor de besluitvorming op persoonlijk (micro) niveau, in de spreekkamer van de oogarts. De subgroepanalyses in hoofdstuk 6 tonen een voorbeeld van hoe een dergelijke vraag kan worden onderzocht, maar in die methode was de indeling in subgroepen enigszins ad hoc. De verkenning van het 'Expected value of individualized care framework' (EVIC) in **hoofdstuk zeven** liet zien dat er een efficiëntere manier is om de potentiële waarde van subgroepenanalyses en subgroepenbeleid in kaart te brengen. In dat hoofdstuk hebben we onderzocht welke waarde een EVIC analyse kan hebben in gezondheidseconomische analyses en bij medische besluitvorming. De EVIC analyse is gebaseerd op het feit dat het relatieve voordeel van de ene behandeling ten opzichte van de andere van patiënt tot patiënt kan verschillen, mede als gevolg van de unieke eigenschappen van elke patiënt (heterogeniteit). In een EVIC analyse worden de incrementele effecten en kosten van een interventie ten opzichte van een referentiebehandeling op het niveau van een individuele patiënt gewaardeerd met de *net benefit* methode, waarbij de consequenties op het vlak van gezondheid en zorgverbruik in dezelfde eenheid worden uitgedrukt, en vergeleken met een drempelwaarde om te bepalen of de consequenties acceptabel zijn of niet. Op die manier drukt de hoogte van de EVIC uit hoeveel potentiële waarde er verloren gaat als alle patiënten op dezelfde manier behandeld zouden worden, en dus hoeveel potentiële (gezondheids)winst er te behalen valt met een meer individuele benadering. We hebben in kaart gebracht op welke punten een EVIC analyse verschilt van een 'Expected value of perfect information' (EVPI) analyse,

en hebben vastgesteld dat de interpretatie van de uitkomst van een EVIC analyse afhangt van de bron van de variabiliteit. Met een parameter-specifieke EVIC analyse kunnen de mogelijkheden voor efficiëntere zorg verder geconcretiseerd worden. In hoofdstuk zeven hebben we de data die we uit het model hadden verkregen in het onderzoek naar de kosten-effectiviteit van een lage streefdruk bij patiënten met primair open-kamerhoek glaucoom gebruikt als case study, en hebben we de totale EVIC en parameterspecifieke EVIC berekend. Uit deze analyse bleek dat er over het geheel genomen weliswaar waarde leek te zijn in een individuele besluit-vorming over de streefdruk bij glaucoompatiënten, maar dat deze in de praktijk niet geëffectueerd kan worden met patiëntkenmerken die bekend zijn (of kunnen zijn) op het moment waarop het besluit over de behandelstrategie genomen moet worden.

De implicaties van het onderzoek voor medische besluitvorming op zowel micro, meso als macro niveau worden in de algemene discussie in **hoofdstuk acht** besproken. Daarnaast wordt in de algemene discussie aandacht besteed aan de belangrijkste bronnen van onzekerheid in de huidige resultaten, en aan mogelijke manieren en om die onzekerheid met aanvullend onderzoek te reduceren. Tenslotte wordt besproken welke andere inzichten het onderzoek heeft opgeleverd met betrekking tot economische evaluaties in het algemeen, en de economische evaluatie van behandelstrategieën voor glaucoom in het bijzonder. Op basis daarvan worden enkele algemene aanbevelingen gedaan over het uitwerken van het EVIC instrument, het prioriteren van toekomstig onderzoek en het stimuleren van multidisciplinaire internationale samenwerking.

Het onderzoek beschreven in dit proefschrift heeft geleid tot een concreet inzicht in de consequenties van verschillende behandelstrategieën voor oculaire hypertensie en primair open-kamerhoek glaucoom op de lange termijn, en heeft expliciet gemaakt op welk vlak nog onzekerheden bestaan in het wetenschappelijk bewijs. Over het algemeen bleek uit de berekeningen dat een intensivering van de behandeling van oculaire hypertensie en primair open-kamerhoek glaucoom leidt tot meer gezondheid en tot netto besparingen in maatschappelijke uitgaven. Vanuit het oogpunt van doelmatigheid zou het daarom voor de huidige klinische praktijk aan te bevelen zijn om bij de afweging tussen intensief monitoren of intensief behandelen te kiezen voor het laatste.

Nawoord

Nu het hele boekje dan eindelijk, per hoofdstuk uitgeprint en bij elkaar geniet, tastbaar voor me op tafel ligt, vallen me twee dingen op. Ten eerste dat ik 'bondigheid' beter niet tot een van mijn kernkwaliteiten kan rekenen. Elk artikel dat ik schreef bevatte het maximale aantal woorden dat een tijdschrift me verleende, en wat me verder nog op het hart lag heb ik gevoeglijk in een appendix ondergebracht. Ik hou blijkbaar van appendices. Ik beschouw dit nawoord nu ook als zodanig. Als een overkoepelende appendix van het geheel; om te verwoorden wat ik niet kwijt kon in de hoofdstukken, en om recht te doen aan alle inzet die er achter de artikelen schuil is gegaan. Want dat is het tweede dat me nu opvalt: hoe bedrieglijk vanzelfsprekend een wetenschappelijk artikel is wanneer het eenmaal in druk verschenen is. Maar wij weten wel beter, u en ik: vanzelfsprekend is het allerm minst. Ik ben dan ook intens dankbaar voor alle hulp die ik kreeg.

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Curriculum Vitae

Aukje van Gestel was born on the 29th of May 1976 in Helmond, the Netherlands. She went to primary school 't Hout in Helmond from 1980 until 1988, and received her pre-university education at the Jan van Brabant School in Helmond from 1988 until 1994. She enrolled at Leiden University to study bio-pharmaceutical sciences in 1994, and graduated cum laude in 1999 with a specialization in pharmacology. Aukje was awarded the KNMP student award in 1998.

After a short period as a PhD student at the department of biological psychiatry at the University Medical Center in Utrecht, Aukje was recruited to join Pharmerit BV in 2001. In her role as research associate and consultant, she was introduced and educated into the field of health technology assessment. In 2005 Aukje started her research on the cost-effectiveness of different strategies for the treatment and monitoring of ocular hypertension and glaucoma at the department of ophthalmology at the University Hospital Maastricht. The research project was directed by Dr. Jan Schouten with a grant from the Netherlands Organization for Health Research and Development (ZonMW). At the same time, Aukje enrolled at Maastricht University to study public health, and graduated cum laude for the master in epidemiology in 2008. The final report documenting the results of the research project on ocular hypertension and glaucoma was delivered to ZonMW in May 2008, after which Aukje continued to work at the University Eye Clinic in the Maastricht University Medical Center to extend the research and document the results in scientific papers. In January 2011 Aukje joined an operational management team at the Fontys University of Applied Sciences in Eindhoven, and she has been working as a freelance research consultant since January 2012.

Papers

Van Gestel A, Webers CAB, Severens JL, Beckers HJM, Jansonius NM, Hendrikse F, Schouten JSAG. The long term outcomes of four alternative treatment strategies for primary open-angle glaucoma. *Acta Ophthalmologica Scandinavica*, 2012; 90(1): 20-31.

Van Gestel A, Grutters JP, Schouten JAG, Webers CAB, Beckers HJM, Joore MA, Severens JL. The role of the expected value of individualized care in cost-effectiveness analysis and decision making. *Value in Health*, 2012; 15(1): 13-21.

Van Gestel A, Webers CAB, Beckers HJM, Van Dongen MCJM, Severens JL, Hendrikse F, Schouten JSAG. The relationship between visual field loss in glaucoma and health-related quality-of-life. *Eye*, 2010, 24(12): 1759-1769.

Van Gestel A, Severens J, Webers C, Beckers H, Jansonius N, Schouten J. Modeling complex treatment strategies: construction and validation of a discrete event simulation model for glaucoma. *Value Health* 2010;13(4):358-67.

Heeg B, **Van Gestel A**, Van Hout B, Olsen J, Haghfelt TH. Cost-effectiveness of clopidogrel vs. aspirin treatment in high-risk acute coronary syndrome patients in Denmark. *Ugeskrift for Laeger* 2006;168(35):2911-5.

Moller HJ, Laux G, Naber D, Gastpar MT, Klosterkotter J, Schmauss M, Heeg B, **Van Gestel A**, Van Hout B, Mehnert A. Costs and effects of long-acting risperidone in comparison to oral atypical and conventional depot formulations for the treatment of patients with schizophrenia in Germany. *Psychopharmakotherapie* 2005;12(5): 183-92.

Bakker J, Levi M, Van Hout BA, **Van Gestel A**. Sepsis, a complicated syndrome with major medical and social consequences. *Ned Tijdschr Geneesk* 2004; 148(20): 975-978

Van Gestel A, Bakker J, Veraart C, Van Hout BA. Prevalence and incidence of severe sepsis in Dutch intensive care units. *Critical Care* 2004; 8(4): R153-R162

Zuideveld KP, **Van Gestel A**, Peletier LA, Van der Graaf PH, Danhof M. Pharmacokinetic-pharmacodynamic modelling of the hypothermic and corticosterone effects of the 5-HT_{1A} receptor agonist flesinoxan. *Eur J Pharmacol*, 2002; 455: 53-54.

Reports

Van Gestel A, Schouten J, Webers C, Beckers H, Severens J. Kosten-effectiviteit van de behandeling en monitoring van oculaire hypertensie en glaucoom. Eindverslag ZonMW, Dossiernummer 94504451, mei 2008.

Van Oostenbruggen MF, Tergau AC, **Van Gestel A**, Van Hout BA, Rutten FFH. Kies Keurig; Een verkennend onderzoek naar de optimalisatie van het besluitvormingsproces over de vergoeding van extramurale geneesmiddelen. PharMerit, Capelle Aan Den IJssel 2002.

Presentations

Van Gestel A, Grutters J, Joore M, Severens J, Schouten J, Webers C, Beckers H. The role of the expected value of individualized care in cost-effectiveness analyses and decision making. International Health Economics Associations (iHEA) conference, July 2011, Toronto, Canada. Oral presentation in the organized session "Every person is unique; heterogeneity in economic evaluation and decision-making".

Van Gestel A, Grutters J, Joore M, Severens J, Schouten J, Webers C, Beckers H. Exploring the role of the expected value of individualized care in cost-effectiveness analyses and decision making. Lowlands Health Economists Study Group conference. May 27-28 2010, Egmond aan Zee, the Netherlands.

Van Gestel A, Schouten J, Webers C, Beckers H, Jansonius N, Severens J. Construction and validation of a decision analytic model for ocular hypertension and glaucoma. European Glaucoma Society conference, Health Economics Special interest group session. 17 September 2010, Madrid, Spain. Oral presentation and discussion.

Van Gestel A, Schouten J, Webers C, Beckers H, Jansonius N, Severens J. Validatie van een OHT-POAG ziekteprogressie model. Nederlands Oogheelkundig Gezelschap, 26 March 2009, Groningen, the Netherlands. Oral presentation.

Van Gestel A, Schouten J, Webers C, Beckers H, Severens J. A novel approach to establish at which IOP to start treatment for ocular hypertension. World Glaucoma Congress, 8-11 July 2009, Boston, USA. Poster presentation.

Van Gestel A, Schouten J, Webers C, Beckers H, Severens J. Does every bit of visual field loss count? World Glaucoma Congress, 8-11 July 2009, Boston, USA. Poster presentation.

Van Gestel A, Schouten J, Webers C, Beckers H, Severens J. Kwaliteit van leven bij oculaire hypertensie en glaucoom. Nederlands Oogheelkundig Gezelschap, 3 April 2008, Maastricht, the Netherlands. Oral presentation.

Van Gestel A, Schouten J, Webers C, Beckers H, Severens J. Risk of blindness in patients with ocular hypertension. Joint Congress of SOE/AAO, 9-12 June 2007, Vienna, Austria. Rapid Fire Presentation

Van Gestel A, Schouten J, Webers C, Beckers H, Severens J. Primary open-angle glaucoma: the impact on quality-of-life and utility. Joint Congress of SOE/AAO, 9-12 June 2007, Vienna, Austria. Poster presentation and oral presentation at Best Poster Session.

Van Gestel A, Schouten J, Webers C, Beckers H, Severens J. Een discrete event model voor oculaire hypertensie en glaucoom: concept, opbouw en eerste resultaten. Nederlandse Glaucoom Groep, 11 November 2007, Utrecht, the Netherlands.

Van Gestel A, Schouten J, Webers C, Beckers H, Severens J. Health related quality of life and utility in Dutch glaucoma patients. European Conference of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 29-31 October 2006, Copenhagen, Denmark. Poster presentation.

"Stretch"

Baz Luhrmann, Everybody's free (to wear sunscreen)