Consensus Statement

Criteria for Choosing Clinically Effective Glaucoma Treatment: A Discussion Panel Consensus

John Thygesen, MD[1]; Reinhard Burk, MD[2]; Roberto Carassa, MD[3]; Andrew Crichton, MD[4]; Francisco Javier Goñi, MD[5]; Mitch Menage, MD[6]; Stefano Miglior, MD[7]; Donald Montgomery, MD[8]; John-Philippe Nordmann, MD[9]; Tim Roberts, MD[10]; and Kuldev Singh, MD[11]

[1]Department of Ophthalmology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [2]Department of Ophthalmology, Academic Hospital Bielefeld, Bielefeld, Germany; [3]Department of Ophthalmology and Visual Sciences, San Raffaele Hospital, Milan, Italy; [4]Department of Surgery, University of Calgary, Calgary, Alberta, Canada; [5]Institut de Microcirurgia Ocular (IMO), Universidad Autonoma de Barcelona, Barcelona, Spain; [6]Leeds General Infirmary, Leeds, United Kingdom; [7]University of Milan Bicocca, Milan, Italy; [8]Eye Department, Glasgow Royal Infirmary, Glasgow, United Kingdom; [9]Centre Hospitalier des Quinze-Vingts, Paris, France; [10]Department of Ophthalmology, Royal North Shore Hospital, University of Sydney, Sydney, Australia; and [11]Department of Ophthalmology, Stanford University Medical Center, Stanford, California

ABSTRACT

Background: In the clinical management of patients at risk for or diagnosed with primary open-angle glaucoma (POAG), the aim of medical treatment is to reduce intraocular pressure (IOP) and then maintain it over time at a level that preserves both the structure and function of the optic nerve.

Objective: The objective of this report was to establish a consensus on the criteria that should be used to determine the characteristics of IOP-lowering medication.

Methods: Discussion was held among a panel of 12 physicians considered to be experts in glaucoma to develop a consensus on the criteria used by them to determine the characteristics of the IOP-lowering medication chosen for initial monotherapy and adjunctive treatment of ocular hypertension (OHT) or POAG. Consensus development combined available evidence and the impressions of these physicians regarding the clinical effectiveness of IOP-lowering medication for OHT and POAG. Once the panel identified the criteria, the order of priority and the relative importance of these criteria were then established

Accepted for publication April 26, 2007.
doi:10.1016/j.curtheres.2007.06.002
0011-393X/$32.00

in the setting of 3 risk categories (low, medium, and high) for a patient to experience significant visual disability from glaucoma over their expected life span.

Results: The panel identified 5 criteria to determine the characteristics of IOP-lowering medication for OHT and POAG: IOP-lowering effect, systemic adverse events (AEs), ocular tolerability, compliance/administration, and cost of treatment. IOP-lowering effect was consistently ranked as the highest priority and cost as the lowest. The priority of compliance/administration did not vary by clinical situation. Systemic AEs and ocular tolerability were ranked as higher priorities in initial monotherapy than in adjunctive treatment and ranked lower as the risk for visual disability increased. The priority given to the criteria used to determine clinical effectiveness varied both with the risk for functional vision loss from glaucoma and whether initial monotherapy or adjunctive treatment was being considered.

Conclusion: Glaucoma treatment should be assessed with regard to the need not only to lower IOP but also to minimize systemic and ocular AEs, promote patient compliance, and minimize cost. The order of priority and relative importance given to these treatment criteria will vary as part of individualizing patient care. (*Curr Ther Res Clin Exp*. 2007;68:127–136)

Key words: consensus, criteria, intraocular pressure, glaucoma.

INTRODUCTION

In the clinical management of patients at risk for or diagnosed with primary open-angle glaucoma (POAG), the aim of medical treatment is to reduce intraocular pressure (IOP) and then maintain it over time at a level that preserves both the structure and function of the optic nerve. In recent years, the indirect evidence that had long provided the rationale for IOP lowering as the therapeutic goal of glaucoma management[1–4] has been bolstered by direct evidence that reducing IOP prevents or delays the onset of POAG[5] and the progression of the disease.[6–9]

The IOP-lowering effect of an ocular hypotensive medication might be assumed to be synonymous with its effectiveness in managing patients with ocular hypertension (OHT) or POAG. However, one distinction between efficacy and effectiveness is that the former refers to the outcome as it pertains to a particularly important variable, such as IOP in glaucoma patients, while the latter relates to the overall outcome of an intervention, taking all important variables into consideration.[10] Several factors besides IOP-lowering effect contribute to the effectiveness of medical treatment for OHT and POAG. Systemic adverse events (AEs), ocular tolerability, frequency of administration (which might impact compliance), and the cost of treatment are some of the important variables that ophthalmologists have to consider when selecting treatment.

Another critical aspect of clinical decision making in managing glaucoma is to ensure that any intervention reflects an appropriate balance between the

patient's risk for adverse outcomes due to disease progression and the potential benefit and risk for harm from treatment.

Glaucomatous optic nerve damage can be considered a disease continuum,[11] beginning with the earliest undetectable changes associated with apoptosis, progressing through stages of damage to the optic nerve, and ultimately leading in some cases to blindness.[12] Patients are first seen by an ophthalmologist at different stages of the continuum and their conditions progress at varying rates. The likelihood of ultimate functional vision loss from glaucoma in a given patient is determined by the disease stage at the time of diagnosis, the rate of progression, and the patient's life span.[13] All of these variables make it difficult to judge whether a patient is likely to experience glaucomatous vision loss, as well as how this likelihood should be reflected in any intervention. When considering medical IOP-lowering treatment, part of individualizing the clinical management of each patient perceived to be at risk for vision loss might require changing the relative priority given to the factors that contribute to clinical effectiveness, depending on the magnitude of that risk.

New therapeutic agents for glaucoma have become available during the previous decade. For most of the twentieth century, medical management of glaucoma relied on cholinergic agents, such as pilocarpine and carbachol. In the late 1970s there was a shift to β-adrenergic blockers. In the late 1990s several new classes of topical medications to treat glaucoma—prostaglandin analogues (latanoprost, travoprost, bimatoprost), selective α-adrenergic agonists (apraclonidine, brimonidine, clonidine), and carbonic anhydrase inhibitors (brinzolamide, dorzolamide)—were introduced. Each of these medications has a unique profile in terms of the criteria for clinical effectiveness,[13] presenting the ophthalmologist with greater opportunities, but also with greater challenges, with respect to appropriately individualizing treatment.

To assist the general ophthalmologist in clinical decision-making, professional groups around the world have published guidelines on the diagnosis and treatment of glaucoma.[13–15] These standards continue to evolve, as exemplified by the change in the European Glaucoma Society guidelines between the first edition in 1998, in which a specific recommendation was made regarding initial monotherapy, and the second edition in 2003, which leaves the choice of initial monotherapy to the judgment of the individual physician.

Early intervention to prevent or delay the onset and progression of glaucoma[5,6] and advances in diagnostic technology, such as quantitative imaging and selective functional tests that offer the prospect of detecting glaucoma earlier than ever before, are important reasons to treat glaucoma as soon as possible and in the most effective manner. When glaucoma is diagnosed at a late stage, the emphasis is generally on maximal lowering of IOP.[13] In our opinion, the importance of other variables that determine clinical effectiveness at various stages of the disease have not been well studied and there is a lack of objective evidence on which to base recommendations about medication-selection criteria and individualizing treatment according to risk for glaucomatous vision loss.

Within the framework of evidence-based medicine, however, using a panel approach to incorporate expert opinion by those familiar with available scientific evidence and experienced in clinical practice is accepted as a valid way of providing an overview of clinical decision-making in circumstances where the evidence alone is not enough to make such recommendations.

This paper is based on the conclusions of a panel of glaucoma specialists. The objective of the panel was to establish a consensus on the criteria that should be used to determine the characteristics of the IOP-lowering medication chosen for initial monotherapy and adjunctive treatment of OHT or POAG, taking into consideration the level of risk for significant visual disability in untreated patients at different stages of the disease continuum.

PATIENTS AND METHODS

A panel of 12 glaucoma specialists convened at a roundtable discussion in Amsterdam, The Netherlands, for 2 days in September 2004. Panelists were considered experts in glaucoma with clinical experience and ongoing research interests in glaucoma and were selected to provide expert opinion in glaucoma management. Panelists were drawn from a broad cross-section of worldwide practice in the European Union, United States, Canada, and Australia. The panel included representatives from the executive committees of both the American and the European Glaucoma Societies, and between them have published over 300 peer-reviewed articles.

Individual experience and opinions were pooled to identify the criteria the panelists considered to select initial monotherapy or adjunctive treatment to control IOP, once they decided that such treatment was warranted. To be included in the discussion, a criterion had to be considered an integral factor in the clinical effectiveness of medical treatment and had to allow the ophthalmologist to discern meaningful differences between medications when choosing a treatment. Having identified such criteria, the panel then considered the order of priority and the relative importance of the criteria within the context of 6 hypothetical clinical situations. These situations specified levels of risk for significant visual disability over a patient's lifetime as being low, medium, or high, and were further stratified based on whether treatment was initial or adjunctive. The panel considered a number of real-life case histories to reach a common understanding of these risk categories; however, no attempt was made to define the categories.

Data were to be collected for each criterion in turn for each clinical situation. All panelists were required to express their views in every case. Group discussion was to continue until a consensus view was reached for every question. *Consensus* was defined as acceptance by all of the panelists.

A numeric ranking system was used to assign priorities; the same value might be assigned to multiple criteria. Views on relative importance were determined by asking panelists to assign a percentage value to each criterion. The

sum of the percentages applied to all criteria for a given clinical situation had to total 100%.

RESULTS

The panel agreed on 5 criteria to consider when making decisions regarding medical treatment for OHT and POAG. The first 4—IOP-lowering effect, systemic AEs, ocular tolerability, and compliance/administration—were criteria that the panel considered to be prerequisites for effective treatment and to provide a basis for meaningful differentiation between alternative medications. The fifth criterion, the need to minimize cost, was included to acknowledge the central importance of economic considerations in the real world. The panel considered the potential for a positive effect on ocular blood flow as a possible criterion, but rejected it because there is insufficient evidence to determine what constitutes a positive effect. It was agreed that advances in measuring blood flow would be needed before making any determinations about the relative effect of glaucoma medications on blood flow. Similarly, it was agreed that there was insufficient evidence to support any non–IOP-lowering (ie, neuroprotective) benefit of existing treatment.

The results of the ranking exercises are shown in **Figures 1** and **2**. The need to reduce IOP was allocated the highest priority in every clinical situation, and systemic AEs and ocular tolerability were considered as important as reducing IOP in the case of initial monotherapy in patients at low risk for significant visual impairment (**Figure 1**). The need to maximize the likelihood of patient adherence was ranked highly and fairly uniformly across most clinical situations. In each clinical situation, the lowest priority was given to the need to minimize cost.

The importance of IOP-lowering effect was ranked progressively higher as risk increased and higher for adjunctive treatment than initial monotherapy within each risk category (**Figure 2**). The systemic AEs criterion was ranked lower as the level of risk for visual impairment increased, as was ocular tolerability, although the latter criterion was considered more important in initial monotherapy treatment for a patient at medium risk than in adjunctive treatment for a patient at low risk. In a patient at low risk for significant visual impairment, compliance/administration was assigned a lower relative importance in initial monotherapy than adjunctive treatment. The reverse was true in the other 2 risk categories. Cost was assigned a relative importance value only in the low-risk category.

DISCUSSION

The panel formed a consensus view on 2 fundamental issues. First, the potential clinical effectiveness of medical IOP-lowering treatment needs to be considered with reference to a number of criteria. Second, in selecting medical treat-

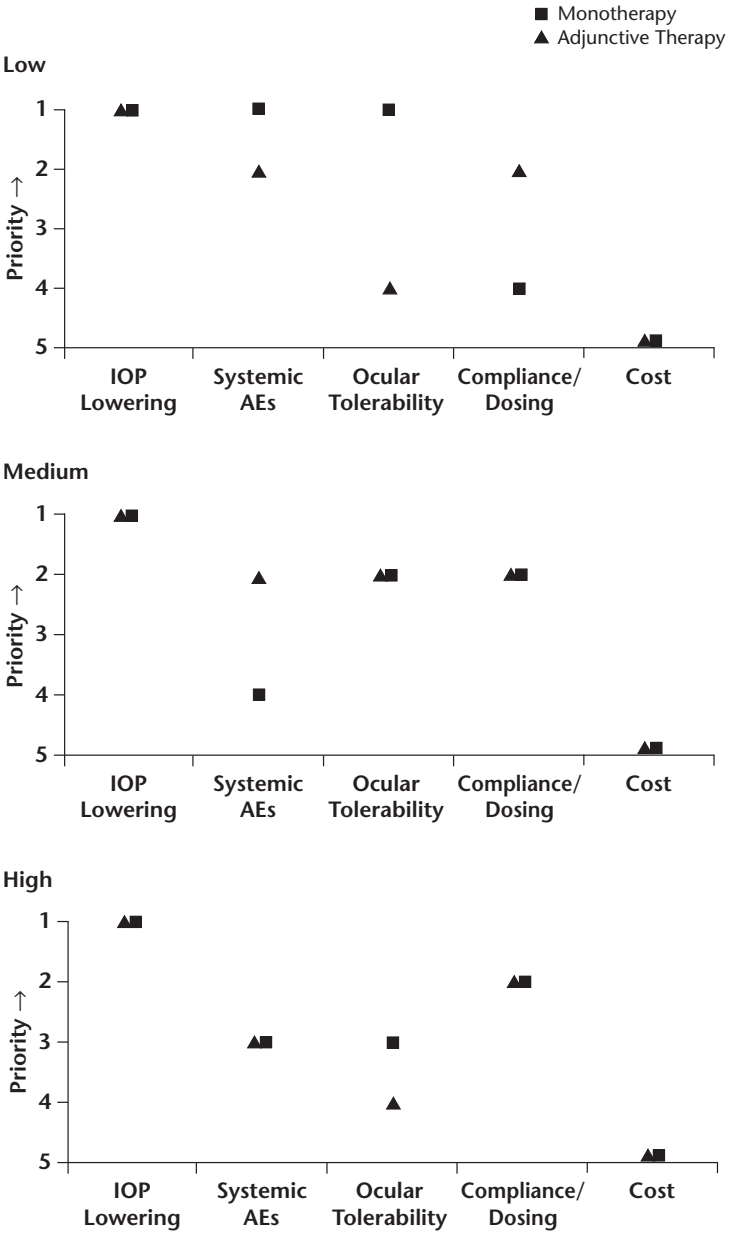

Figure 1. Panelists' priority (1 = high; 5 = low) rating for each of the treatment criteria in initial monotherapy and adjunctive medical treatment of glaucoma by risk for significant visual disability (low, medium, and high). IOP = intraocular pressure; AEs = adverse events.

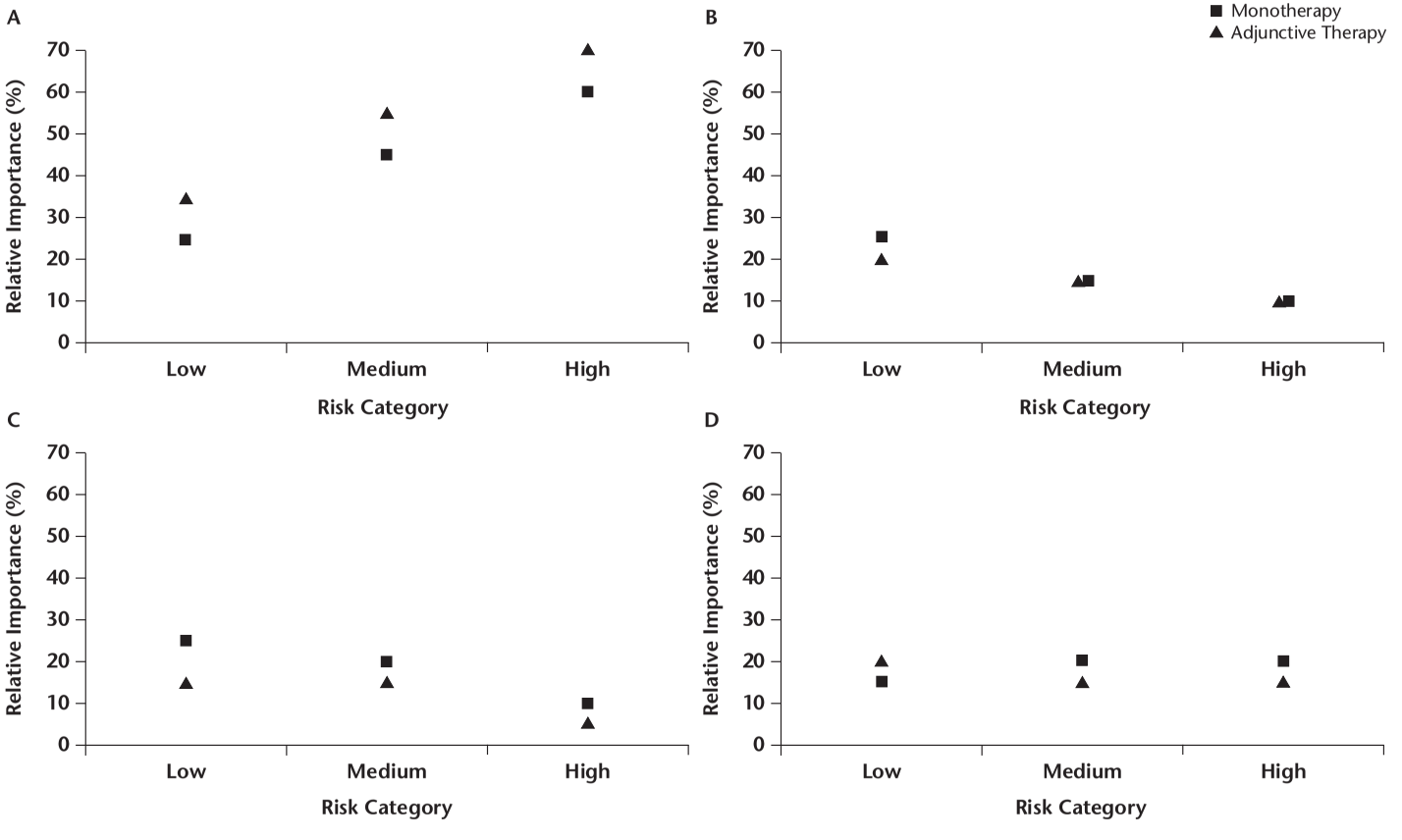

Figure 2. Panelists' reported relative importance of treatment criteria by risk category for initial monotherapy and adjunctive medical treatment in (A) intraocular pressure lowering, (B) systemic adverse events, (C) ocular tolerability, and (D) compliance/administration.

ment, these criteria need to be weighed uniquely for each patient, based on the risk to the patient of significant visual disability from glaucoma over their lifetime.

The panel determined that the choice of clinically effective medical IOP-lowering treatment depends on a composite of needs: to lower IOP; to minimize the risk for systemic AEs; to minimize ocular AEs; to maximize the likelihood of a patient adhering to the regimen; and to minimize cost.

Selecting a treatment that effectively lowers IOP in all clinical scenarios was given primary importance because this is currently the only intervention found to prevent or delay the onset and progression of glaucoma.[2,5–7,9] Only in the case of initial monotherapy for a patient considered at low risk for visual impairment was the need to minimize both the risk for systemic and ocular AEs given the same priority as the need to lower IOP. In a similar patient where adjunctive treatment was indicated, the panel agreed that the degree of IOP lowering superseded the importance of systemic AEs and ocular tolerability. The relative importance assigned to IOP lowering among the treatment goals increased as disease state became progressively more severe.

The need to facilitate patient compliance[16–18] was the other criterion that was ranked consistently across all clinical situations. The panelists' views followed a similar pattern for IOP lowering and compliance/administration. Both of these criteria were considered important, and compared with systemic AEs and ocular tolerability, they became relatively more important as the risk for visual impairment increased, because the threat to the patient's quality of life from the pathology may come to outweigh the threat posed by potential AEs from treatment. Also, the need to lower IOP can be met only if the patient adheres to the medication regimen, thus linking IOP lowering and compliance/administration.

The 2 criteria associated with the greatest variation across clinical situations were systemic AEs and ocular tolerability. This suggests that the panel considered these 2 criteria to be the principal mechanisms for individualizing medical treatment. Considering how to balance the risk for harm from glaucoma with the risk for harm from treatment is the focus of the clinical decision-making process. As far as we are aware, no attempt had previously been made to quantify the relative importance of medication tolerability versus IOP-lowering effect along the continuum of risk for glaucomatous vision loss.

Limitations

One potential limitation of this consensus was the panel's approach to the need to minimize cost. Pharmacoeconomic considerations are often more complex than—and cannot be studied as easily as—some of the other criteria. Cost considerations vary widely from country to country and across different healthcare systems. The panel decided to include the need to minimize cost as a criterion and consistently assigned cost the lowest priority. These findings indicate that perhaps this criterion needs to be addressed separately.

A second limitation concerns the categorization of risk for significant visual disability. What constitutes significant visual disability can vary greatly. Because

the panel did not develop an objective definition, the risk categories (low, medium, and high) were also left undefined. However, given the currently limited ability of ophthalmologists to directly monitor and assess glaucomatous change, to precisely calculate rate of progression, or to determine how these will influence whether a patient is likely to experience visual impairment due to glaucoma in their lifetime, it seems reasonable to regard the question of risk for significant visual disability as a matter for the subjective judgment of the individual physician.

CONCLUSION

Glaucoma treatment should be assessed with regard to the need not only to lower IOP but also to minimize systemic and ocular AEs, promote patient compliance, and minimize cost. The order of priority and relative importance given to these treatment criteria will vary as part of individualizing patient care.

ACKNOWLEDGMENT

The meeting was supported through an unrestricted educational grant provided by Pfizer Ophthalmics, New York, New York. The panel members included cochairs Dr. Kuldev Singh and Dr. Richard Wormald, Moorfields Eye Hospital, London, United Kingdom. Other panelists included Drs. Thygesen, Burk, Carassa, Crichton, Goñi, Menage, Miglior, Montgomery, Nordmann, and Roberts.

REFERENCES

1. Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. *Arch Ophthalmol*. 1991;109:77–83.
2. Leske MC, Heijl A, Hussein M, et al, for the Early Manifest Glaucoma Trial Group. Factors for glaucoma progression and the effect of treatment: The early manifest glaucoma trial. *Arch Ophthalmol*. 2003;121:48–56.
3. Leske MC, Connell AM, Wu SY, et al, for the Barbados Eye Studies Group. Incidence of open-angle glaucoma: The Barbados Eye Studies. *Arch Ophthalmol*. 2001;119:89–95.
4. Leske MC, Connell AM, Wu SY, et al. Risk factors for open-angle glaucoma. The Barbados Eye Study. *Arch Ophthalmol*. 1995;113:918–924.
5. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: A randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701–713, discussion 829–830.
6. Heijl A, Leske MC, Bengtsson B, et al, 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.
7. 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.

8. Lichter PR, Musch DC, Gillespie BW, et al, for the CIGTS Study Group. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology*. 2001;108:1943–1953.
9. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol*. 1998;126:498–505.
10. Heithoff KA, Lohr KN. Promise and limitations of effectiveness and outcomes research. Summary statement of the IOM Core Committee. In: *Effectiveness and Outcomes in Health Care: Proceedings of an Invitational Conference by the Institute of Medicine Division of Health Care Services*. Washington, DC: National Academies Press; 1990:8–18.
11. Weinreb RN, Friedman DS, Fechtner RD, et al. Risk assessment in the management of patients with ocular hypertension. *Am J Ophthalmol*. 2004;138:458–467.
12. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet*. 2004;363:1711–1720.
13. European Glaucoma Society. *Terminology and Guidelines for Glaucoma*. 2nd ed. Savona, Italy: DOGMA Srl; 2003.
14. South East Asia Glaucoma Interest Group. *Asia Pacific Glaucoma Guidelines*. Sydney, Australia: SEAGIG; 2004.
15. American Academy of Ophthalmology. *Age-Related Macular Degeneration*. *Preferred Practice Pattern.* San Francisco, Calif: American Academy of Ophthalmology; 2003.
16. Konstas AG, Maskaleris G, Gratsonidis S, Sardelli C. Compliance and viewpoint of glaucoma patients in Greece. *Eye*. 2000;14:752–756.
17. Taylor SA, Galbraith SM, Mills RP. Causes of non-compliance with drug regimens in glaucoma patients: A qualitative study. *J Ocul Pharmacol Ther*. 2002;18:401–409.
18. Nordmann JP, Auzanneau N, Richard S, Berdeaux G. Vision related quality of life and topical glaucoma treatment side effects. *Health Qual Life Outcomes*. 2003;1:75.

Address correspondence to: John Thygesen, MD, Associate Professor, Department of Ophthalmology 2061, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E-mail: john.thygesen@rh.hosp.dk