Management of Ocular Hypertension: A Cost-effectiveness Approach From the Ocular Hypertension Treatment Study

STEVEN M. KYMES, PHD, MICHAEL A. KASS, MD, DOUGLAS R. ANDERSON, MD, J. PHILIP MILLER, AB, MAE O. GORDON, PHD, AND THE OCULAR HYPERTENSION TREATMENT STUDY GROUP (OHTS)

• PURPOSE: The Ocular Hypertension Treatment Study (OHTS) demonstrated that medical treatment of people with intraocular pressure (IOP) of ≥24 mm Hg reduces the risk of the development of primary open-angle glaucoma (POAG) by 60%. There is no consensus on which people with ocular hypertension would benefit from treatment.

• DESIGN: Cost-utility analysis with the use of a Markov model.

• METHODS: We modeled a hypothetic cohort of people with IOP of ≥24 mm Hg. Four treatment thresholds were considered: (1) Treat no one; (2) treat people with a ≥5% annual risk of the development of POAG; (3) treat people with a ≥2% annual risk of the development of POAG, and (4) treat everyone. The incremental cost-effectiveness ratio was evaluated.

• RESULTS: The incremental cost-effectiveness ratios for treatment of people with ocular hypertension were $3670 per quality adjusted life-year (QALY) for the Treat ≥5% threshold and $42,430/QALY for the Treat ≥2% threshold. "Treat everyone" cost more and was less effective than other options. Assuming a cost-effectiveness threshold of $50,000 to 100,000/QALY, the Treat ≥2% threshold would result in the most net health benefit. The decision was sensitive to the incidence of POAG without treatment, treatment effectiveness, and the utility loss because of POAG.

• CONCLUSION: Although the treatment of individual patients is largely dependent on their attitude toward the risk of disease progression and blindness, the treatment of those patients with IOP of ≥24 mm Hg and a ≥2% annual risk of the development of glaucoma is likely to be cost-effective. Delay of treatment for all people with ocular hypertension until glaucoma-related symptoms are present appears to be unnecessarily conservative. (Am J Ophthalmol 2006;141:997–1008. © 2006 by Elsevier Inc. All rights reserved.)

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From the Department of Ophthalmology and Visual Sciences (S.M.K, M.M.K., M.O.G.) and Division of Biostatistics (S.M.K., J.P.M., M.O.G.), Washington University School of Medicine, St Louis, Missouri; Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida (D.R.A.).

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For a complete list of OHTS investigators, please see the OHTS website at https://vrcc.wustl.edu

Inquiries to Steven M. Kymes, PHD, Washington University School of Medicine, Department of Ophthalmology and Visual Sciences, 660 South Euclid, Campus Box 8096, St Louis, MO 63110-1093; e-mail: kymes@vrcc.wustl.edu

GLAUCOMA IS THE SECOND MOST COMMON CAUSE of blindness in the United States, accounting for >11% of all cases of blindness in this country.[1] The various glaucomas are estimated to affect >2.2 million individuals in the United States who are >40 years old with primary open-angle glaucoma (POAG) the most common form.[2] Glaucoma is the leading cause of blindness among African-Americans,[3] and African-Americans are three to five times more likely to have the disease than Caucasians.

Ocular hypertension, which generally is defined as intraocular pressure (IOP) of >21 mm Hg,[4] is an important risk factor for glaucoma, and the risk of POAG has been shown to increase with higher IOP.[5] Estimates of the prevalence of ocular hypertension range from 4.5% to 9.4% for individuals who are >40 years old,[4] and the prevalence increases with age.[4,6] For many years, ophthalmologists have used ocular hypotensive medications to treat ocular hypertension without a fully validated rationale for the approach.[7] In 2002, the Ocular Hypertension Treatment Study (OHTS) demonstrated that medical treatment to lower IOP reduced the incidence of POAG in people with ocular hypertension (defined in OHTS as IOP

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of ≥24 mm Hg).[8] However, there is no consensus concerning preventive treatment before the loss of visual field or the onset of optic disk deterioration.[9] Critics of early treatment cite the low incidence of POAG among people with ocular hypertension, the typically slow progression of POAG, and the apparently modest impact of POAG on a patient's quality of life during the early stages of the disease.[10,11]

We examined the conditions at which the treatment to lower IOP before glaucoma-related damage is cost-effective. In this, we used cost-utility analysis, a cost-effectiveness method in which effectiveness is defined as the patient's perception of quality of life.[12]

METHODS

WE CONSTRUCTED A MARKOV DECISION MODEL TO COMpare the cost and effectiveness of treating ocular hypertension over a lifetime. Parameters in the model included estimates of the risk of POAG among those patients for whom pressure lowering medication were prescribed and those patients for whom they were not, the probability of progression of POAG to unilateral blindness, the probability of bilateral blindness among patients with unilateral blindness, and estimates of the impact of POAG and blindness on quality of life. We considered cost of medical treatment of ocular hypertension and POAG by stage of disease and the cost of blindness. Variability in the result was evaluated with sensitivity analysis and Monte Carlo simulation.

• **MODELING THE COSTS AND EFFECTIVENESS OF TREATMENT OF OCULAR HYPERTENSION:** *Ocular hypertension* was defined according to the OHTS: IOP ≥24 mm Hg and ≤32 mm Hg in at least one eye, IOP ≥21 mm Hg and ≤32 mm Hg in the fellow eye, and normal visual fields and optic disks in both eyes at the time of diagnosis. The *development of POAG* was defined as the development of a reproducible visual field abnormality, optic disk deterioration attributed to POAG, or both.[13] The *progression of POAG* was defined by a recently reported adaptation[14] of the Hodapp-Anderson-Parrish (HAP) model[15] that described five stages of POAG, with the fifth stage being significant visual impairment in the worst eye that required visual rehabilitation (Table 1). *Bilateral blindness* was defined as visual acuity of 20/200 or worse in the better seeing eye.

The Markov model is an analytic tool that allows an investigator to estimate the costs and consequences of a disease process.[16] The disease progression in a cohort of people with a particular condition is modeled from the time of diagnosis. During a Markov cycle (for example, 1 year) each living cohort member is exposed to the risks, benefits, and costs that are associated with the progression and treatment of a disease as they progress through associated health states. During each cycle, a proportion of people die, as estimated from actuarial sources. Our Markov model is illustrated in Figure 1.

Using the Markov model, we evaluated four treatment thresholds: (1) treat no one with IOP ≥24 mm Hg until they developed POAG ("Treat no one"); (2) treat only persons with IOP of ≥24 mm Hg and an annual risk of the development of POAG of ≥5% ("Treat ≥5%"), which is approximately 10% of people in the OHTS; (3) treat only persons with IOP of ≥24 mm Hg and an annual risk of the development of POAG of ≥2% ("Treat ≥2%"), or approximately 30% of people in OHTS; and (4) treat everyone with IOP of ≥24 mm Hg ("Treat everyone"). We assumed that anyone who was not receiving treatment before conversion to POAG began treatment at conversion.

• **DATA AND ASSUMPTIONS:** Table 2 details the parameters used in the Markov model, with the ranges that were used in sensitivity analyses. Among the parameters that were estimated from the OHTS sample were the reduction in risk of the development of POAG because of treatment, the cost of topical medical treatment, and the risk of cataract surgery that is associated with treatment.[5,8,13] The incidence of POAG in those who were treated and those who were not treated and the proportion of persons with ocular hypertension who met the treatment threshold of "Treat ≥5%" and "Treat ≥2%" were also estimated from OHTS. We constructed a logistic regression model that incorporated parameters that were reported previously by OHTS investigators as predictive of POAG: age, central corneal thickness, baseline IOP, and baseline vertical cup/disk ratio.[5] Risk among participants was found to approximate a log-normal distribution. The cumulative distribution function was used to estimate the proportion of people with ocular hypertension that was treated at each treatment threshold. The incidence of POAG among those treated and untreated patients was estimated by a distribution free method (see *AJO.com* for further details).

The prevalence of ocular hypertension increases with age.[4,17] Therefore, we stratified the Markov model by age decade (that is, 40 to 49, 50 to 59, 60 to 69, 70+ years) using the prevalence of ocular hypertension by age that was found in The Baltimore Eye Study (Katz J, written communication, September 16, 2003), which sampled equally Caucasian and African-American patients (see *AJO.com* for supplemental information on the derivation of these estimates).

During OHTS, we tracked the medication that was given to participants who were randomly assigned to treatment. OHTS investigators were free to choose any commercially available medication that was approved by the US Food and Drug Administration for the lowering of IOP (or combination thereof) that resulted in the participant meeting the OHTS treatment goal (that is, a 20% reduction from baseline IOP, with a resultant IOP of

TABLE 1. Staging Model for Primary Open-angle Glaucoma

Variable	MD Score		Probability Plot (Pattern Deviation)		Decibel Plot (Stages 2–4) or CPSD/PSD (Stage 1)		Decibel Plot (Stage 2–4) or Hemifield Test (Stage 1)
Stage 1-Early glaucoma	–0.01 to –6.00 ($P < .05$)	and	Points below 5%, >3 contiguous, and >1 of the points below 1%	or	CPSD/PSD significant at $P < .05$	or	Glaucoma hemifield test "outside normal limits"
Stage 2-Moderate glaucoma	–6.01 to –12.00		Points below 5%: 19–36; points below 1%: 12–18		Point(s) within central 5° with sensitivity of <15 dB: >1, and point(s) within central 5° with sensitivity <0 dB: none (0)		Points with sensitivity <15 dB within 5° of fixation: only 1 in hemifield (1 or 2)
Stage 3-Advanced glaucoma	–12.01 to –20.00		Points below 5%: 37–55, and points below 1%: 19–36		Point(s) within central 5° with sensitivity of <0 dB: 1 only		Points with sensitivity <15 dB within 5° of fixation: both hemifields at least 1 in each
Stage 4-Severe glaucoma	–20.01 or worse		Points below 5%: 56–74, and points below 1%: 37–74		Point(s) within central 5° with sensitivity of <0 dB: 2–4		Points with sensitivity <15 dB within 5° of fixation: both hemifields 2 in each (all)
Stage 5-End-Stage glaucoma/blind	No static threshold for perimetry in "worst eye"	Static threshold perimetry not possible because of central scotoma in "worst eye" or "worst eye" acuity of 20/200 or worse due to glaucoma; "best eye" may fall into any of above stages					

CPSD = corrected pattern standard deviation; PSD = pattern standard deviation.

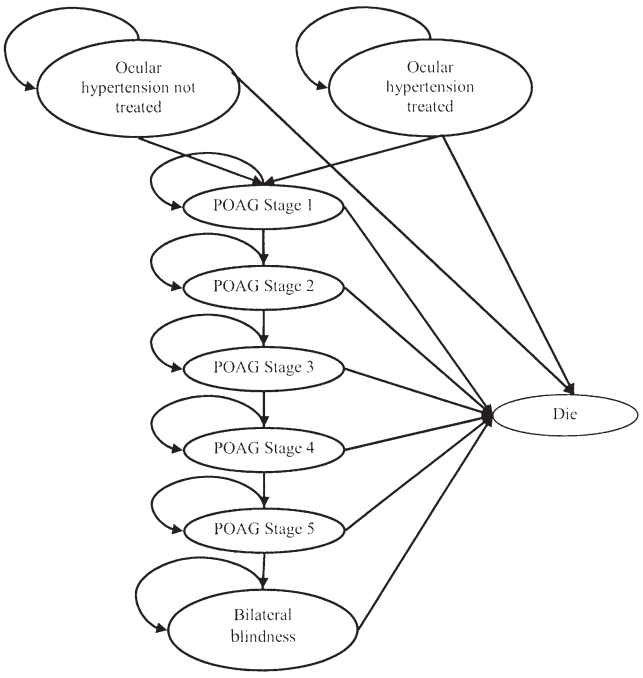

FIGURE 1. Markov decision model for treatment of ocular hypertension to prevent primary open angle glaucoma. This describes the potential progression of disease for a patient with ocular hypertension in the model. All members of the hypothetic cohort begin with ocular hypertension (Top). During a year (Markov cycle), a cohort member can remain in the health state in which they begin, die, or progress to the next health state. No cohort member can regress (move backwards) on the clinical pathway.

≤24 mm Hg). We created a weighted average of the cost of medication (at 2005 average wholesale price)[18] during the first eight years of the study by those originally randomly assigned to the treatment arm of the study. We made the assumption that all patients were treated initially with one medication. In each subsequent year, a proportion of cohort members added a second medication. The probability of this addition to the treatment regimen was estimated from OHTS data.

The cost that was associated with treatment of glaucoma among people who progressed from ocular hypertension and the probability of progression across the five stages of POAG was taken from estimates that were developed by Lee and associates.[14] There are no published estimates for the cost of glaucoma-related blindness, and estimates of cost for other conditions vary widely. A recent review found that personal and governmental costs ranged from $3084 to $11,067 per year for diabetic retinopathy and macular degeneration (converted from British pounds to US dollars at a rate of $1.8681 = 1.00 pound sterling).[19] Lacking a precise estimate for the cost of glaucoma-related blindness, we estimated the annual cost of bilateral blindness by taking the mean of the reports in the Meads and Hyde review.[19]

• **ESTIMATING THE VALUE OF THE OUTCOMES OF TREATMENT:** In valuing the outcomes of a medical intervention among people with chronic disease, the investigator should consider the impact of the intervention on the quality of life of the patient who is being treated.[20] In our investigation, we measured quality of life using "utility." In contrast to functionally based quality of life measures, such as the NEI-VFQ, the utility is a preference-based measure that quantifies the person's perception of the importance of functional limitation.[21] The utility is measured on a scale from 0.0 to 1.0, with zero indicating the value of a state of health comparable to death and 1.0 the value for perfect health. These methods have been discussed fully elsewhere.[22,23]

The utility is used to calculate a quality adjusted life-year (QALY). The QALY is a measure of a person's expected life span that is weighted by the quality of life. The utility loss because of POAG has not been investigated widely. Jampel and associates[23] found a utility loss among those with glaucoma of 0.07; in another study, glaucoma suspects had a utility loss of 0.026. Alm and associates (Alm A. ARVO 2005, Poster Presentation), who used the EQ-5 diopters,[24] reported a utility loss of 0.16 for people with HAP stage 1, 0.20 for people with HAP stages 2 to 4, and 0.28 for HAP stage 5. For the Markov model, we used Jampel's estimate from "glaucoma suspects" for stage 1, and we used unpublished data that were collected by Washington University investigators from 99 people with glaucoma at urban and suburban clinical settings in the St Louis area for stages 2 to 5 (Sumner W, written communication, April 2005; see *AJO.com* for further detail). We used the unpublished data for more severe disease because these were collected by the standard gamble method, a preferred method of utility estimate,[25] and represented a conservative estimate compared with the other reports. We defined bilateral blindness as visual acuity of 20/200 or worse in the better seeing eye and used the estimate of utility loss of 0.35 by Brown and associates.[26] Although Brown and associates also reported much higher estimates of utility loss for patients with "count fingers" or "no light perception" in their better seeing eye, the legal blindness estimate provides a conservative estimate in our model.

• **ESTIMATING THE INCREMENTAL COST-EFFECTIVENESS (UTILITY) OF TREATMENT:** The cost-utility of an intervention is estimated by dividing the incremental cost (in monetary units) of an intervention by its incremental effectiveness, measured by QALYs. This ratio is referred to as the incremental cost-effectiveness ratio (ICER).[12]

An intervention is considered "cost-effective" if the value society places on a QALY is greater than the resources required to "purchase" the QALY. This is based on the "willingness to pay" (WTP), or the social value of the QALY. However, there is no generally accepted WTP threshold.[27] Most health economists have recognized $100,000/QALY as the upper limit,[28] and some economists

TABLE 2. Parameters Used in Economic Evaluation of Treatment of Ocular Hypertension to Prevent Primary Open-angle Glaucoma (POAG)

Variable	Value	Source	Range for Sensitivity Analyses
Age distribution of ocular hypertension* (%)			
Age 40–49 y	13.4	Baltimore Eye Study (personal communication, see text)	See text
50–59 y	23.3		
60–69 y	31.8		
70+ y	31.5		
Annual risk of the development of POAG without treatment (%)			
Age 40–49 y	1.50	OHTS (unpublished)	±80
50–59 y	1.90		
60–69 y	2.27		
70+ y	2.69		
Proportion of people with intraocular pressure ≥24 mm Hg who met treatment threshold (%)			
Treat no one	0		N/A
Treat ≥5% annual risk			
Age 40–49 y	5	OHTS (unpublished)	5–10
50–59 y	8		8–16
60–69 y	11		11–22
70+ y	15		15–30
Treat ≥2% annual risk			
Age 40–49 y	22	OHTS (unpublished)	22–44
50–59 y	31		31–62
60–69 y	37		37–74
70+ y	46		46–92
Treat everyone	100		N/A
Reduction in risk of POAG caused by treatment (%)	53	Reference 8	25–65
Annual probability of progression of one HAP POAG stage (%)	5.0	Reference 14	0.005–10
Annual probability of progression to bilateral blindness in persons with unilateral blindness (%)	1.65	Reference 51	0.1–2.9
	Census estimate	Reference 52	N/A
Annual death rate			
Weighted average cost of medication for one year (based on OHTS distribution; 2005 AWP)	$465.31	OHTS (unpublished)	$300–$800
Annual probability of addition of a second medication to treatment regimen:			
(Ocular hypertension only (%))	4.80	OHTS (unpublished)	2.5–7.5
Office visit (CPT 92012)	$63.03	2005 Medicare allowable	$41–$161
Average cost of travel to office visit	$11.12	Reference 53	$1–$38
Patient's time for office visit	$31.64	Reference 43	$10–$100
Cost of POAG			
Stage 1	$1343	Reference 14	$940–$1743
Stage 2	$1520	"	$1060–$1980
Stage 3	$1668	"	$1167–$2168
Stage 4	$2162	"	$1512–$2812
Stage 5 (unilateral blindness)	$2203	"	$1000–$3000
Increased annual risk of cataract surgery due to treatment: Additive (%)	0.33	OHTS (unpublished)	0.0–6.0
Cost of cataract surgery	$2525	Reference 30	$500–$5000

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TABLE 2. (Continued) Parameters Used in Economic Evaluation of Treatment of Ocular Hypertension to Prevent Primary Open-angle Glaucoma (POAG)

Variable	Value	Source	Range for Sensitivity Analyses
Utility loss because of cataract surgery	0.148	Reference 30	0–25
Annual social cost of bilateral blindness	$8130	Reference 19	$2000–$50,000
Utility loss: POAG			
Stage 1	2.6	Reference 23	0–0.10
Stage 2	11.45	Sumner W, written communication, April 2005	0.05–0.25
Stage 3	11.45	"	0.05–0.25
Stage 4	14.80	"	0–0.50
Stage 5 (unilateral blindness)	14.80	"	0–0.50
Bilateral blindness	0.35	Reference 26	0.15–0.50

*Intraocular pressure ≥24 mm Hg in at least one eye. N/A = Not available. HAP = Hodapp-Anderson-Parish; AWP = average wholesale price; CPT = current procedure terminology.

have argued for a threshold in excess of $200,000.[27] In this analysis, we defined cost-effectiveness at a WTP of $100,000/QALY and used the more conservative WTP of $75,000/QALY as a critical value for sensitivity analysis.

We conducted this evaluation according to the guidelines described by the Panel on Cost-Effectiveness in Health and Medicine.[29] We took a societal perspective, which means that all relevant costs and benefits that are associated with the intervention were considered whether they were borne by the person or society. Because the costs and benefits are experienced over the person's lifetime, we discounted future costs and benefits at a 3% rate.[29]

• **THE SIDE-EFFECTS OF MEDICAL TREATMENT:** The OHTS did not find a substantive difference in participant-reported side-effects between the observation and medication groups, other than cosmetic changes that are associated with use of prostaglandin analogues.[8] Therefore, we did not consider transient medication side-effects such as blurred vision, tearing, or stinging in our model. A trend toward increased cataract extraction in the medication group was reported in the OHTS trial, although this increase was not statistically significant.[8] Nonetheless, we included the increased risk of cataract extraction in our model as a risk that is associated with treatment. The cost of cataract surgery and the utility loss that is associated with having a cataract were taken from an economic evaluation of cataract surgery.[30]

• **ADDRESSING UNCERTAINTY IN PARAMETER ESTIMATES:** Estimating cost-effectiveness from an economic model requires that assumptions be made regarding the progression of the disease and the value of parameters. The influence of these assumptions on the ICER must be evaluated in a systematic fashion.[29] We did this using one- and two-way sensitivity analyses. We calibrated the model by conducting a first-order Monte Carlo simulation, resampling the model 10,000 times to estimate the incident cases of POAG and unilateral and bilateral blindness.[31] Second-order Monte Carlo simulation[32] was conducted, resampling the model 50,000 times to assess the variability of the cost-effectiveness decision in the model (see *AJO.com* for further detail concerning this process).

All statistical analyses were performed with SAS software (version 8.0.2; SAS® Institute Inc, Cary, North Carolina, USA). Decision analyses and Monte Carlo simulations were performed with TreeAge Pro 2005 software (Healthcare version release 1.1; TreeAge Software Inc, Williamsport, Massachusetts, USA).

RESULTS

THE COST-EFFECTIVENESS OF TREATMENT OF OCULAR HYpertension at each treatment threshold is shown in Figure 2. Each point represents the combination of expected lifetime cost (on the vertical axis) and QALYs gained (on the horizontal axis) that are associated with each treatment threshold: "Treat no one," "Treat ≥5%," "Treat ≥2%," and "Treat everyone." In Table 3, the thresholds are ranked according to the expected lifetime cost of treatment/person, with "Treat no one" the least expensive and "Treat everyone" the most expensive. The second and third columns present the average total lifetime cost and benefit (QALYs) of treatment/person in the cohort (that is, the average total cost of treatment of ocular hypertension, glaucoma, and blindness for the cohort and the average total QALYs gained for the cohort). The last column presents the incremental cost-effectiveness of each threshold, relative to the preceding one, which indicates

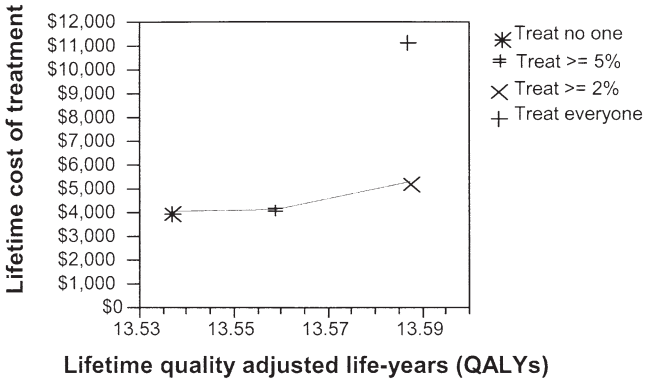

FIGURE 2. Cost-effectiveness of treatment for ocular hypertension. Each point in the graph represents a combination of cost and effectiveness (measured in quality adjusted life-year). The line that connects the points as they run from left to right represents the incremental cost-effectiveness ratio. As the line becomes steeper with relation to the x-axis, the incremental cost-effectiveness ratio becomes larger. The plus sign in the northeast corner represents the "Treat everyone" option. The strategy results in less effectiveness, but costs more than the "Treat ≥2%" option; thus, it is "dominated" and has no line because it has no meaningful associated incremental cost-effectiveness ratio.

the resource use that is required to "purchase" one additional QALY over those generated at the preceding threshold.

Treating people with IOP ≥24 mm Hg and an annual risk of POAG of ≥5% (that is, a five-year risk of >25%) would have an ICER of $3670, although a strategy based on an annual risk of ≥2% (that is, a five-year risk of >10%) would have an ICER of $42,430, compared with the ≥5% threshold. This indicates that treatment of patients with IOP ≥24 mm Hg and an annual risk of POAG of ≥2% would be cost-effective at current cost/QALY thresholds.[28]

Note that treatment of all persons with IOP of ≥24 mm Hg is "dominated" by the "Treat ≥2%" threshold. In the parlance of health economics, this indicates that the "Treat all" threshold costs more per person with IOP of ≥24 mm Hg but is less effective (that is, results in fewer QALYs/person). This is due to the increased risk of cataract surgery because of treatment. There have been recent reports of the development of lens opacities that are associated with the use of ocular hypotensive medication[33,34]; however, the OHTS did not find a statistically significant increase in cataract extraction. If it were found that there is no link between pressure-lowering medication and lens opacification, the "Treat all" threshold would no longer be dominated by the "Treat ≥2%" threshold; however, the resulting ICER would be in excess of $1.7 million.

• **SENSITIVITY ANALYSIS:** Our sensitivity analyses are summarized in Table 4. It is important to note that, in all cases, the change in the cost-effectiveness decision resulted in the selection of "Treat ≥5%" as the most cost-effective treatment threshold. We present only those parameters for which clinically relevant changes in assumptions resulted in a change in the cost-effectiveness decision, with the use of a net health benefits approach and a threshold value of $75,000/QALY.[35] The cost-effectiveness decision in our model was sensitive to the incidence of POAG without treatment, proportion of people treated, reduction of risk because of treatment (that is, size of treatment effect), cost of medication, and utility loss because of POAG. In the latter case, estimates of utility loss at each stage were correlated positively; however, the model was sensitive only to the utility loss in the first stage.

Although we report the results for influence of progression of POAG, increased risk of cataract, and utility loss in stages 2 and 3 of POAG, the critical values that are associated with these parameters are outside the clinically relevant range. We confirmed the results of the one-way analyses in our two-way sensitivity analyses and found no interactions that would affect the cost-effectiveness decision (see *AJO.com* for further information on sensitivity analyses).

• **PROBABILISTIC SENSITIVITY ANALYSES (SECOND-ORDER MONTE CARLO SIMULATION):** The results of the second-order Monte Carlo simulation are illustrated in Figure 3. The net-benefits acceptability curves represented here are analogous to confidence intervals more typically seen in association with statistical estimates, in that they are a graphic representation of the uncertainty that is associated with the estimate of cost-effectiveness.[36]

For each sampling in the Monte Carlo process, net health benefits were calculated for each treatment threshold. Net health benefits represent the QALYs that are generated for the treatment threshold multiplied by the "WTP" less the total cost of the intervention.[35] The treatment threshold that results in the most net health benefits for each sample is identified. This process is repeated for each WTP threshold, and the proportion of samples for which the treatment threshold is the most cost effective is graphed across the range of WTP thresholds.

Figure 3 shows that, as the WTP threshold increases past $43,000, it is more likely that the "Treat ≥2%" threshold is the most cost-effective treatment threshold; although below a WTP of $43,000, the "Treat ≥5%" threshold is more likely to be the most cost-effective. Note particularly that the "Treat no one" threshold is likely to be the most cost-effective option at only the lowest level of WTP, and as one moves to the WTP that is accepted in most industrialized nations, the "Treat no one" option is most cost effective in <20% of samples. (Further discussion of this simulation and the results of the first-order simulation are provided at *AJO.com*.)

TABLE 3. Comparison of the Cost-effectiveness of Strategies for Treatment of Persons With Ocular Hypertension

Strategy	Total Cost ($)	Total Effectiveness (QALYs)*	Incremental Cost ($)	Incremental Effectiveness (QALYs)*	Incremental Cost-effectiveness Ratio (Cost [$]/QALYs)*
Treat no one	4006	13.5370			
Treat ≥5% annual risk of development of primary open-angle glaucoma	4086	13.5588	80	0.0218	3670
Treat ≥2% annual risk of development of primary open-angle glaucoma	5308	13.5876	1222	0.0288	42430
Treat all persons with ocular hypertension	11245	13.5870	5937	–0.0006	Dominated

*QALYs = Quality adjusted life-years.

TABLE 4. Summary of One-way Sensitivity Analysis

Variable	Value in Base Case	Value That Threshold for Treatment Changes From "Treat ≥2%" to "Treat ≥5%"*
Incidence of POAG without treatment: All people with ocular hypertension (%)	2.2	1.496
Proportion of people with ocular hypertension to be treated	See Table 2	30% increase†
Reduction in risk because of medical treatment (%)	53	30
Annual probability of progression of a POAG stage (%)	5.0	0.5
Cost of one medication	$465/y	$718
Increased annual risk of cataract surgery due to treatment: Additive (%)	0.33	2.8
Utility loss because of POAG (all correlated with stage 1)	0.026	0.0132
Utility loss in POAG stages 2 and 3 (no correlation with stage 1)	0.1145	None‡

*Assumes a willingness to pay (WTP) of $75,000.
†An increase of 90% in proportion of people treated results in "Treat no one" being the most cost-effective.
‡At a willingness to pay (WTP) of $50,000 the critical value is 0.089.

DISCUSSION

A CLINICAL MANAGEMENT STRATEGY THAT TARGETS A 20% reduction in IOP in people with ocular hypertension has been shown to delay or prevent the onset of glaucoma.[8] However, many clinicians continue to maintain that treatment of ocular hypertension is not warranted.[9,37] We have shown that the treatment of people with the highest risk (that is, an annual risk of ≥5% or a five-year risk in excess of 25%; at least 10% of people with IOP of ≥24 mm Hg in the OHTS sample) is highly cost-effective at a cost/QALY of $3670. Our analyses also show that the treatment of people with an annual risk of POAG of ≥2% (that is, a five-year risk of ≥10%) meets the standard for cost-effectiveness that is accepted in most developed nations. Based on the OHTS sample, the setting of a treatment threshold at this level would imply that one in three people with IOP of ≥24 mm Hg would benefit from treatment. If the distribution of risk factors in the general population is similar to that found in the OHTS, this would imply that up to 2.5 million people in the United States would benefit from treatment. These findings should give clinicians confidence that they can recommend treatment to those patients with important risk factors who have a preference for avoiding the progression of their disease. Conversely, these findings also lend support to a decision not to treat patients who are at lower risk if the patient and clinician agree that the patient's health status and expected longevity make treatment by "watchful waiting" preferable.

Our choice of treatment thresholds may appear arbitrary. If the treatment of people with a 5% risk is highly cost-effective, why do we not consider 3%? or 1%? A first

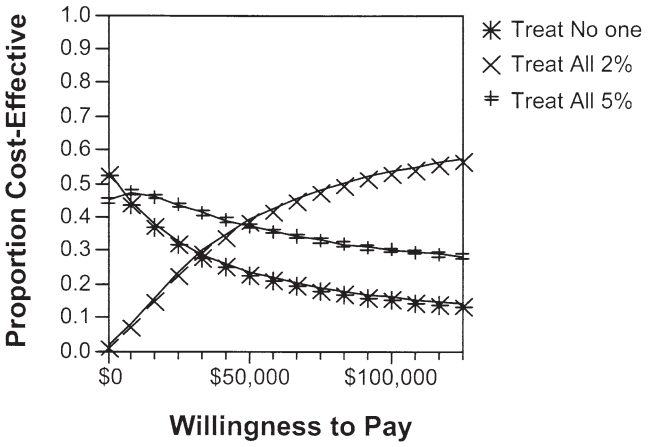

FIGURE 3. Results of Monte Carlo simulation. The three curves describe the proportion of times that the indicated treatment threshold provides the most net benefit (that is, most cost-effective) in the 50,000 Monte Carlo samples. As the "willingness to pay threshold" (that is, the cost/ quality adjusted life-year /quality adjusted life-year that defines cost-effectiveness) increases, the "Treat ≥2%" threshold is more likely to be the most cost-effective threshold, although the "Treat no one" and "Treat ≥5%" thresholds are less likely to be the most cost-effective.

consideration in our analysis was the precision of available estimates of risk. It is not realistic to assume that available risk models have the resolution to distinguish between a 2% and 3% annual risk in an individual patient. We selected thresholds with a reasonable separation, in this case 2% and 5%. We also chose thresholds that were as inclusive as possible to maximize the social benefit that is gained.

• **WHO SHOULD BE TREATED?:** At present, published risk models for the progression to POAG do not describe the precision of the estimate of risk.[38,39] Therefore, the results of such models should be viewed with caution in characterizing risk for an individual patient. This limits the ability of clinicians to implement our recommendations fully. At this time, however, clinicians might gain some direction from current reports of risk that is associated with specific characteristics. A recent review suggested that the strongest predictors of progression to POAG are elevated IOP, larger vertical cup-to-disk ratio, thinner cornea, and older age.[40] In the OHTS, participants with central corneal thickness of <555 μm had an average annual risk of the development of POAG of 3.4%, although people with a vertical cup-to-disk ratio of >0.30 had an annual risk of 2.5%, on average.[5] On average, African-American patients in the OHTS had an average annual risk of progression to POAG in excess of 2%.[41] However, the OHTS model suggests that race is not an independent risk factor after adjustment for corneal thickness and cup-to-disk ratio.[5,40]

• **IMPORTANT FACTORS THAT INFLUENCE THE COST-EFFECTIVENESS DECISION:** Our findings were found to be sensitive to the incidence of POAG in the population at risk and the proportion of people with IOP of ≥24 mm Hg who met the treatment criteria. We found that, if the true annual incidence of POAG among persons with IOP of ≥24 mm Hg is <1.496%, the "Treat ≥2%" treatment threshold would not be cost-effective. Our model assumed (based on the OHTS results) an annual incidence of POAG of 2.2% among people with IOP of ≥24 mm Hg. Earlier studies of the incidence of POAG among people with IOP of ≥21 mm Hg reported incidence well below 2.2%; however, some of these studies relied on relatively insensitive measures of glaucoma-related damage.[4] More recently, The Barbados Eye Study reported an annual incidence of 3.3% in an Afro-Caribbean population with IOP >23 mm Hg,[42] and the Vision Impairment Project reported an annual incidence of 1.3% in a largely Caucasian population with IOP >21 mm Hg.[43] On the basis of these studies, it does not seem likely that the true incidence of POAG among people with IOP of ≥24 mm Hg would be as low as 1.496%.

It has been demonstrated that the treatment effect that is found in randomized clinical trials frequently does not correlate well to that found in clinical practice.[44] Our sensitivity analyses showed that, if our treatment effect were reduced to one-half of that reported in the OHTS (that is, to a 30% reduction in risk of POAG), the "Treat ≥5%," not the "Treat ≥2%," would be the most cost-effective treatment threshold. The primary reason for the reduction in effect size from clinical trials to clinical practice is due to the attempt to apply the effect that is yielded by a rigorous trial protocol to a less structured clinical setting.[45] The OHTS tested the effectiveness of a treatment strategy for people with ocular hypertension (that is, a 20% reduction in IOP), not the effectiveness of medication. In the trial, IOP was measured at semi-annual study visits, and treatment was adjusted accordingly. Patient compliance with treatment between visits was not monitored. Thus, although the generalization of the OHTS treatment strategy to the general population is limited by the extent to which the semi-annual monitoring of IOP may affect patient compliance with treatment, our results are not dependent on consistent patient compliance with medication protocols. A second concern in attempting to generalize results of clinical trials to clinical practice is the extrapolation of results from study participants that is optimized to identify a treatment effect to patients with a marginal risk of disease. The influence of this limitation is reduced because we specifically are recommending treatment only of those patients who are at higher risk of disease (that is, patients with a ≥2% annual risk of POAG), not those patients at the margin.

Utility loss because of POAG was particularly influential in our analyses. Utility loss is a measurement of the impact of POAG on quality of life because of the loss of visual

function and fear of disease progression. Some clinicians have questioned whether a nonfatal disease with modest early impact on functional status should be considered to have a significant impact on quality of life.[9] The model was most sensitive to the utility loss that is experienced in stage 1 of the disease, where we assumed the utility loss was small (that is, 0.026). If the true estimate of utility loss among people with ocular hypertension were 50% lower, then the ≥5% threshold would be the most cost-effective option. On a population basis, it seems unlikely that we would find a mean utility loss well below 2% among people who have a potentially blinding disease. However, it is also likely that there is wide variability among individual patients in their perception of the risk of glaucoma to their quality of life. Clinicians should make certain that their patients have a clear understanding regarding the risk of disease progression and its potential impact on their quality of life in advising them concerning treatment options. Those patients who are more risk averse are more likely to view treatment as beneficial, although those patients with greater tolerance for risk of progression and an aversion to medication may perceive less benefit.

We have characterized the progression of POAG using a taxonomy based on visual field characteristics.[14] Conversely, in the OHTS, almost 60% of the participants who progressed to POAG did so based on optic disk deterioration.[8] If we assume that the loss of function for people who are diagnosed with POAG because of optic disk progression is slower than in those patients who are diagnosed because of visual field loss, this may imply that our estimate of progression may be overestimated. However, note that in Table 4, we have shown that the rate of progression from stage 1 to stage 2 can be as little as 0.5%, and treatment of those with an annual risk of POAG of ≥2% would remain the most cost-effective option.

In sensitivity analyses, we found that the treatment threshold of ≥2% remains cost-effective, if we assume an annual incidence of bilateral blindness of as little as 0.10% (vs 1.65% used in the model) among people with unilateral blindness. Similarly, there was little influence on the treatment decision because of changes in the cost or utility loss that was associated with unilateral or bilateral blindness. Fewer than 1% of people with IOP of ≥24 mm Hg in our model progress to bilateral blindness over their lifetime and <2% progress to unilateral blindness. Thus, changes in the risk, cost, or utility loss that is associated with blindness have modest influence on the treatment threshold.

• **UNCERTAINTY AND THE COST-EFFECTIVENESS DECISION:** Figure 3 details the result of our Monte Carlo simulation. It demonstrates that, in countries or settings in which health care resources are more dear (that is, the "WTP" for a QALY is <$43,000), the "Treat ≥5%" threshold may be preferred. However, most industrialized nations would consider a WTP of $43,000 to be low, and the "Treat ≥2%" threshold would provide the most benefit. The exception to this may be seen in certain government programs where funding restrictions exist. In such settings, the ≥5% threshold may be preferred, but even in such settings, it is not likely that the "Treat no one" threshold would be viewed as the option that provides the most benefit.

Our Monte Carlo simulation also makes clear the significant limits, to our knowledge, of important aspects of the natural history of glaucoma and its impact on quality of life. At even the highest levels of "WTP," the "Treat ≥2%" threshold provides the most benefit in no >60% of samples, and the "Treat no one" threshold still provides the most benefit in 10% of the samples. This is a reflection of the large variation that is associated with important model parameters. Among the most influential parameters in the model are the utility loss that is associated with POAG and our estimate of the progression of POAG. Our results demonstrate that investigation concerning these aspects of the disease would provide important information to support future evaluations of treatment to prevent glaucoma or slow its progression.

• **ADVERSE EFFECTS OF TREATMENT:** Many authors cite side-effects of medical treatment as a reason to delay the initiation of medical management of ocular hypertension.[9,38] The OHTS found little evidence of patient-reported side effects associated with treatment; therefore, we did not consider side-effects other than cataract extraction in our model. Had we chosen to do so, this would have been done by increasing the cost of medical treatment for the medication group to account for the burden created by side-effects. For example, it has been reported that people are willing to pay an additional 40% for eye drops without hypothetical side-effects such as blurred vision or impaired sexual performance.[46] If this is the case, our estimate of the cost of medication in year one (that is, $465) would be understated (that is, the "true" cost of medication in the first year, including side-effects would be $465 × 1.40 = $651). We found that the threshold of "Treat ≥2%" is cost-effective if the cost of medication is <$718 per year. Clinicians have a wide range of options in selecting a medication to minimize patient side-effects. Should side-effects be considered important to an individual patient, it is unlikely that the cost-effectiveness of treatment would be strongly influenced.

Recent reports have suggested that glaucoma and macular degeneration may be associated with an increase in mortality rates.[47,48] Some clinicians have suggested that, in the case of glaucoma, this might be due to topical medication,[49] although this association has not been found to be statistically significant in prospective studies that include the OHTS.[8,34] If such a relationship did exist, the tentative evidence of increased mortality rates that are associated with treatment of visual impairment would need

to be weighed against the benefit of preserving visual function.[50]

• **LIMITATIONS:** The external validity of an economic model is dependent on the degree to which it reflects the natural history of disease and the manner in which care is delivered. The clinical pathway described here has been reviewed by experienced glaucoma specialists to ensure its consistency with current clinical practice and guidelines. We also conducted a validation study that compared the results of our model to epidemiologic reports (see *AJO.com* for these results). This analysis showed that, if there is an error in our model, it is likely that we underestimated the incidence of POAG and blindness in the United States. This being the case, it is likely that the direction of any error in the model would be to underestimate the cost-effectiveness of the "Treat ≥2%" threshold. However, if clinical practice departs widely from these guidelines or new genetic or neurobiologic treatments that stop disease progression become available, our conclusions would need to be re-evaluated.

When clinicians and their patients consider medical treatment of ocular hypertension, they must weigh the costs, risks, and benefits of treatment. The decision to treat must always be individualized based on the patient's clinical factors (including general health and life-expectancy) and fears and expectations regarding disease progression. The results of our model show that, on average, the treatment of people with IOP of ≥24 mm Hg and a ≥2% annual risk of the development of POAG is likely to be cost-effective. This indicates that a substantial proportion of people with ocular hypertension could benefit from treatment. On the basis of the distribution of risk factors in the OHTS, this may be one-third of those individuals with IOP of ≥24 mm Hg. We have also demonstrated that delaying treatment of anyone other than those patients with the lowest risk of progression to POAG is not likely to represent an effective use of society's health resources.

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Biosketch

Steven M. Kymes, PhD, is a Research Assistant Professor in the Department of Ophthalmology and Visual Sciences at Washington University in St Louis, Missouri. Dr Kymes is an Assistant Director of the Vision Research Coordinating Center. Before entering academic life, Dr Kymes held various management and marketing positions with health care and managed care organizations. Dr Kymes' research interests concern cost-effectiveness of medical treatment and testing, assessment of health-related quality of life, and the relationship between insurance plan design and health outcomes.

Biosketch

Mae O. Gordon, PhD, is a Professor in the Department of Ophthalmology and Visual Sciences at Washington University in St Louis, Missouri. Dr Gordon is the Director of the Vision Research Coordinating Center at Washington University and is Co-Chairman of the Ocular Hypertension Treatment Study. Among her areas of research are clinical trial design, assessment of quality of life, and persistency in treatment of glaucoma.