

PROJECTED IMPACT OF TRAVOPROST VERSUS BOTH TIMOLOL AND LATANOPROST ON VISUAL FIELD DEFICIT PROGRESSION AND COSTS AMONG BLACK GLAUCOMA SUBJECTS

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ABSTRACT

Purpose: We compared differences associated with use of travoprost and latanoprost on both progression of perimetric loss over time and associated costs among black patients.

Methods: Patients with primary open-angle glaucoma or ocular hypertension were randomly assigned to one of four arms in a 12-month, double-masked study: travoprost (0.004% or 0.0015%), latanoprost (0.005%), or timolol (0.5%). Forty-nine patients received 0.004% travoprost, 43 received latanoprost, and 40 received timolol. We applied algorithms found in published studies that link intraocular pressure (IOP) control to visual field progression and calculated the likelihood of visual field deterioration based on IOP data. This was used to estimate differences in medical care costs.

Results: The average IOP was lower for patients receiving travoprost than for patients receiving latanoprost or timolol (17.3 versus 18.7 versus 20.5 mm Hg respectively, $P < .05$). Travoprost-treated patients had a smaller predicted change in visual field defect score (VFDS) than latanoprost-treated patients and timolol-treated patients, and significantly fewer were expected to demonstrate visual field progression. Medical care costs would be higher for latanoprost-treated and timolol-treated patients.

Conclusions: Recent studies have provided algorithms linking IOP control to changes in visual fields. We found that treatment with travoprost was associated with less visual field progression and potential cost savings.

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INTRODUCTION

Primary open-angle glaucoma (POAG) can be defined by optic nerve damage leading to progressive visual impairment. Extrapolating from both the Baltimore Eye Study and the Beaver Dam Eye Study, about 2 million to 3 million Americans have POAG, and as many as half of them may be unaware of it.^{1,2} Prevent Blindness America just published its latest version of *Vision Problems in the US* and conservatively estimated that the number of Americans with glaucoma is 2.2 million.³ Worldwide, it was estimated that the prevalence of glaucoma in the year 2000 was almost 67 million individuals.⁴ Approximately 80,000 people in the United States are legally blind on account of glaucoma.⁵ The total direct cost of glaucoma in the United States was estimated to be \$1.6 billion in 1991.⁶

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Over the last decades, we have realized that elevated intraocular pressure (IOP) cannot solely be used to effectively screen for glaucoma, because it is neither sensitive nor specific, but IOP is an important risk factor for glaucoma.⁶⁻⁹ In the treatment of glaucoma, however, IOP lowering has been found to strongly correlate with the preservation of vision. Additionally, the degree of IOP lowering achieved has a relative dose-response relationship to visual preservation.¹⁰⁻¹² Other significant risk factors for glaucoma include older age, race, and a family history of glaucoma.^{6,9,13}

POAG is also more common in the black population. The rate of glaucoma in the United States in 1990 through 1992 was reported to be 9.9 per 1,000 individuals among the white population and 11.0 per 1,000 among the black population.¹⁴ The prevalence of glaucoma in the populations of both Barbados and St Lucia is far greater, at all ages, than in whites in other studies.⁶ Similarly, in Baltimore, Maryland, the prevalence of glaucoma is far greater among blacks than whites. The age-adjusted prevalence of open-angle glaucoma among blacks is 4.3 times that of whites.¹⁵ Some investigators have suggested that open-angle glaucoma is a more severe condition among blacks, in that it appears to begin at an earlier age, resulting in the possibility that it may be more advanced at the time of diagnosis.⁶ Further, black patients may not

respond as well to some therapies as white patients. This potential lack of efficacy may lead to greater rates of visual loss and blindness.^{14,16,17}

Over the past decade, the number of new classes of eye pressure-lowering medications has almost doubled. These newer medications include topical carbonic anhydrase inhibitors (brinzolamide and dorzolamide), alpha agonists (apraclonidine and brimonidine), and prostaglandin analogues (latanoprost, travoprost, isopropyl unoprostone, and bimatoprost). Latanoprost (Xalatan, Pharmacia) was the first prostaglandin approved in the United States for reduction of elevated IOP in subjects with open-angle glaucoma or ocular hypertension. More recently, travoprost (Travatan, Alcon), bimatoprost (Lumigan, Allergan), and isopropyl unoprostone (Rescula, Ciba) have been approved for this indication. Travoprost is the first IOP-lowering medication used in the treatment of glaucoma that has demonstrated a comparable efficacy in white persons, yet a greater effectiveness in the black population.¹⁸ This finding is potentially important, because with better screening instrumentation, more black persons may be found to have glaucoma in the coming years, and the most effective and cost-effective IOP-lowering medications may be very important.

Historically, the treatment of glaucoma has largely focused on reduction of IOP. The relationship between IOP lowering and visual field loss is likely to involve differential threshold values and patterns of IOP elevation over time. The Advanced Glaucoma Intervention Study (AGIS)¹² found that both the degree and the consistency of IOP lowering are directly correlated with the preservation of visual field. Some investigators have found that there is more to glaucoma damage than blindness. That is, with increasing visual field changes, prior to blindness, a subject's quality of life may directly diminish. Factors such as driving ability seem to decrease in a linear fashion with a decreasing AGIS visual field score.¹⁹ We performed the current analysis to compare projections of visual field loss, and the potential financial implications of these differences in visual field loss, when either travoprost, timolol, or latanoprost is used to lower IOP in black subjects. These estimations are based on data from a previously published randomized clinical trial.²⁰

METHODS

Data for this analysis were obtained from a 12-month randomized, double-masked, phase III clinical trial.²⁰ In brief, this article describes subjects with open-angle glaucoma or ocular hypertension (OHT) who were randomly assigned to one of four treatment groups: travoprost 0.004%, travoprost 0.0015% (not currently available commercially), latanoprost (0.005%), or timolol (0.5%). Subjects in the timolol treatment group received one drop of timolol in each eye twice daily, at 8 AM and 8 PM. Subjects receiving

travoprost and latanoprost received one drop of active agent in each eye daily at 8 PM. These subjects also received one drop of placebo (to mask the twice-daily timolol treatment arm) in each eye daily at 8 AM. Data were collected at baseline (week 0) and at visits at weeks 2, 6, 12, 18, 24, 36, and 48. At each study visit, IOP was recorded at 8 AM, 10 AM, and 4 PM.

STUDY POPULATIONS

We enrolled a total of 596 subjects in the travoprost (0.004%), latanoprost, and timolol arms. Of these, 132 (22%) were black. Forty-nine of the 132 were randomly assigned to receive travoprost (0.004%), 43 to receive latanoprost, and 40 to receive timolol. All 132 black subjects were included in the present analysis. Missing data were not interpolated, and IOP values for subjects discontinuing early were not "carried forward." Forty subjects in the travoprost and forty subjects in the the latanoprost groups completed all 48 weeks of the study, while 33 subjects in the timolol group completed all 48 weeks. Among those not completing 48 weeks, four subjects completed 2 study weeks (one travoprost, two latanoprost, one timolol), three subjects completed 6 study weeks, (one travoprost, two timolol), four subjects (all travoprost) completed 12 study weeks, two subjects (one travoprost, one latanoprost) completed 18 study weeks, five subjects (two travoprost, three timolol) completed 24 weeks, and one subject (timolol) completed 36 weeks. Only one subject (in the travoprost arm) discontinued early on account of an ocular adverse event.

RELATIONSHIP OF IOP AND VISUAL FIELD DEFECT SCORES

Multiple recent reports have indicated that the likelihood of progression of visual field deficit among subjects with POAG cannot be predicted on the basis of mean IOP alone. Rather, mean IOP values above a particular threshold, the pattern of IOP over time, and incidence of IOP peaks appear to be more predictive. To evaluate the projected change in visual field over time for subjects in each treatment group, we applied the algorithms developed by the AGIS.¹² Changes in visual field were assessed by using the visual field deficit score (VFDS), ranging from 0 (no defect) to 20 (end-stage).

The AGIS presented two different algorithms that related IOP patterns over the study period to change in VFDS. First, in a predictive analysis, mean IOP was separated into three categories: <14 mm Hg, 14 to 18 mm Hg, and ≥18 mm Hg. (The originally published AGIS¹² reported 17.5 mm Hg, rather than 18 mm Hg, as the threshold compared, but we were notified of a correction by coauthor E.K. Sullivan.) The predictive AGIS analysis found that subjects with a mean IOP of <14 mm Hg during the first 18 months of follow-up, compared with those with an IOP of 14 to 18 mm Hg, had an adjusted increase in the VFDS

of 0.76 AGIS visual field units at 84 months (7 years). Subjects with an initial mean IOP of ≥ 18 mm Hg had an adjusted increase in the VFDS of 1.89 AGIS units over 7 years. For analysis of the travoprost, latanoprost, and timolol clinical trial data, we therefore applied a relative increase in VFDS to each subject on the basis of his or her mean IOP over the study period. For example, a subject with an average IOP of 15 mm Hg would have an adjusted increase in VFDS of 0.76. This value was added to the values for all other subjects in a treatment group and divided by the total number of subjects in a treatment group to find the average. We then determined the overall change in VFDS for each treatment group.

The second associative AGIS analysis was based on the percentage of visits during the entire study period in which a patient's IOP was < 18 mm Hg. Subjects with all visits in which their IOP was < 18 mm Hg served as the reference group. Those whose IOP reading was < 18 mm Hg at 75% to less than 100% of visits had a relative increase in VFDS at 84 months of 1.00. Those whose IOP reading was < 18 mm Hg at 50% to less than 75% of visits or at less than 50% of visits had VFDS increases of 2.05 and 1.93, respectively. We determined the proportion of visits in which subjects had IOP readings < 18 mm Hg, then assigned each subject a change in VFDS value based on this proportion (ie, subjects who had an IOP reading < 18 mm Hg at less than 50% of visits had a VFDS of 1.93, while those with IOP < 18 mm Hg at 75% to less than 100% of visits had a VFDS of 1.0). For example, a subject with a mean IOP of < 18 mm Hg at only one of the six study visits had a VFDS of 1.93. As with the first analysis, the overall change in VFDS for each treatment group was then determined.

RELATIONSHIP OF IOP AND LIKELIHOOD OF VISUAL FIELD DEFICIT PROGRESSION

The AGIS 7 results¹² provide a structure by which the likelihood of relative changes in visual field deficits can be evaluated. It is also crucial to assess the likelihood that a patient will develop further deficits in his or her visual field (ie, that the visual field deficits will progress). A number of recent studies have provided algorithms linking IOP and the likelihood of visual field deficit progression. We used algorithms from four recent publications (Mao and associates,²¹ Odberg,²² Shirakashi and colleagues,²³ and Stewart and coinvestigators²⁴) to evaluate the relationship between IOP and projected progression of visual field deficit. Details of these four algorithms are presented in Table I.

For each of these four algorithms, we determined the probability of visual field deficit progression based on the overall mean IOP for all time points and for each individual subject in the study. We then determined the overall likelihood of visual field deficit progression for each treatment group, and this difference was used for the cost

analysis as described in the next section. For example, with the Mao algorithm, the travoprost group has an overall likelihood of visual field deficit progression of 37.2%, compared with 55.7% for the latanoprost group, which is a difference of 18.5% points in favor of travoprost.

COST PROJECTIONS

The analysis just described provided information on the likelihood of visual field deficit progression or increase in VFDS among black subjects treated with travoprost, latanoprost, or timolol. Using this information, we made various analyses to estimate the effects of VFDS on the cost of hospitalizations and cost of outpatient glaucoma care.

Differences in visual field deficit progression were used to estimate medical care cost differences based on two sources. For an estimate of the differences in hospitalization costs, we used a study by Morse and associates.²⁵ They reported that among hospitalized subjects, those with severe visual impairment had a hospital length of stay averaging 2.4 days longer than those without severe visual impairment. The difference in length of stay was applied to the difference in the rate of visual field deficit progression to determine the incremental length of stay for hospitalized subjects (ie, the difference in rate of visual field deficit progression between subjects receiving travoprost and subjects receiving other treatments was multiplied by 2.4 hospital days). The mean num-

TABLE I: ALGORITHMS USED TO ASSESS THE RELATIONSHIP OF IOP AND LIKELIHOOD OF VISUAL FIELD DEFICIT PROGRESSION

SOURCE	ALGORITHM
Mao et al ²¹	Visual field deficit progression was based on categories of mean IOP. Subjects with mean IOP ≤ 16 mm Hg had no likelihood (0%) of progression. Those with mean IOP of 17–18 mm Hg, 19–21 mm Hg, or ≥ 22 mm Hg had likelihoods of visual field deficit progression of 29.4%, 71.4%, and 100%, respectively.
Odberg ²²	Visual field deficit progression was evaluated using a mean IOP threshold of 15 mm Hg. Subjects with mean IOP ≤ 15 had a 42% likelihood of visual field deficit progression, while those with mean IOP > 15 had an 85% likelihood.
Shirakashi et al ²³	Based on a mean IOP threshold of 15 mm Hg. Over the long term, no subjects with IOP ≤ 15 had visual field progression, while all subjects with IOP > 15 experienced progression.
Stewart et al ²⁴	Likelihood of visual field progression was stratified into several groups based on mean IOP. Subjects with mean IOP ≤ 16 mm Hg had no likelihood (0%) of progression. Those with mean IOP of 17–18 mm Hg, 19–21 mm Hg, or ≥ 22 mm Hg had likelihoods of visual field deficit progression of 15.4%, 50.0%, and 100%, respectively.

IOP, intraocular pressure.

ber of hospitalizations per year (0.183) was obtained from the 1996 National Health Interview Survey²⁶ for individuals at the median age of the patient sample (63 years). Finally, the average Medicare cost per day for hospitalization (\$1,000.36) was applied to the incremental length of stay and number of hospitalizations per year to determine the incremental hospitalization cost per year due to severe visual field deficits. As all subjects met visual field inclusion criteria (ie, none of the subjects had severe visual field loss at the time of the trial), these projections provide information on long-term cost changes (ie, these costs capture expected medical care resource utilization costs based on projected visual loss over time).

To estimate differences in outpatient costs between the various treatment groups, we used the treatment guidelines from the Preferred Practice Patterns of the American Academy of Ophthalmology.²⁷ Outpatient resource utilization rates from the guidelines and associated costs were determined for subjects with controlled IOP versus those with recent progressive damage. For controlled subjects, the mean annual rate of resource utilization was estimated as two examinations in addition to one dilated optic nerve examination and one visual field assessment. For subjects with recent progressive damage, there were approximately six examinations, two optic nerve examinations, and three visual field assessments per year. The corresponding annual costs used for controlled subjects and progressing subjects (based on 2000 Medicare reimbursement rates) were \$359 and \$818, respectively; the additional annual outpatient cost for progressing subjects is therefore assumed to be \$459. This additional cost for progressing subjects was multiplied by the difference in rate of visual field deficit progression between the three treatment groups.

DATA ANALYSIS

Comparisons of subject characteristics, VFDS, or likelihood of visual field deficit progression between the three treatment groups were made using *t* tests for continuous variables and chi-square tests for dichotomous variables. We also performed multivariate linear regression (for continuous variables) and logistic regression (for dichotomous variables) to evaluate the impact of treatment arm on visual field outcomes while controlling for age and sex. All calculations were performed using SAS software (release 8.01, Cary, North Carolina). *P* values at less than .05 were considered statistically significant. Finally, by using these algorithms we assumed that the efficacy of each drug demonstrated in the 1-year trial is representative of the performance of the drug on a longer-term basis.

RESULTS

Table II presents characteristics of study subjects. There were no statistically significant differences between the

TABLE II: CHARACTERISTICS OF SUBJECTS BY TREATMENT GROUP

CHARACTERISTICS	TRAVOPROST SUBJECTS (N=49)	LATANOPROST SUBJECTS (N=43)	TIMOLOL SUBJECTS (N=40)
Mean age, yr (SD)	62.6 (13.6)	58.6 (12.1)	62.3 (11.9)
Female	53.1%	58.1%	62.5%
Baseline mean IOP, mm Hg			
8 AM (SD)	26.8 (2.7)	27.6 (3.3)	27.2 (3.0)
1 AM (SD)	25.0 (2.7)	25.9 (3.5)	25.4 (2.8)
4 PM (SD)	24.0 (2.3)	25.2* (3.0)	24.8 (2.9)
Overall (SD)	25.3 (2.3)	26.2 (3.1)	25.8 (2.7)
Mean IOP, mm Hg			
8 AM (SD)	18.5 (2.6)	19.7* (2.4)	21.4* (3.3)
1 AM (SD)	16.6 (2.5)	18.1* (2.4)	19.9* (3.6)
4 PM (SD)	16.9 (2.8)	18.3* (3.0)	19.9* (3.7)
Overall (SD)	17.3 (2.5)	18.7* (2.4)	20.5* (3.4)

IOP, intraocular pressure.

*Statistically significant (*P* < .05) compared to travoprost.

three groups for age and sex. The difference in baseline mean IOP (before initiation of study medication) between the three groups was also not significantly different except at 4 PM between the travoprost and latanoprost groups. The mean IOP overall and throughout the day, during the 1-year study, for the travoprost group was significantly lower than that for either the latanoprost or the timolol group.

Table III presents results of changes in VFDS or likelihood of visual field deficit progression. Using either the predictive or associative AGIS analysis, the likelihood of an increase in VFDS was greater for timolol and latanoprost than for travoprost. The increase in VFDS was also greater for timolol than for latanoprost. Using both the predictive analysis (based on three categories of mean IOP) and the associative analysis (based on the percent of visits with IOP < 18 mm Hg), the differences between travoprost and the other two treatment groups were statistically significant. Similarly, the estimated proportion of subjects experiencing progression of visual field deficits was greater for timolol and latanoprost than for travoprost with each of the four algorithms used (ie, Mao and associates,²¹ Odberg,²² Shirakashi and colleagues,²³ and Stewart and coinvestigators²⁴). The direct comparisons between travoprost and the other two treatment groups were statistically significant for all four algorithms.

Differences in medical care cost projections for the three groups are presented in Tables IV and V. As described in the "Methods" section, to determine inpatient cost differences, the difference in projected rate of visual field progression between the travoprost, latanoprost, and timolol groups was applied to the annual rate of hospitalization (0.183) for this age-group and increased number of days per hospitalization (2.4) for subjects with visual impairment. This produced the

Projected Impact of Travoprost Versus Both Timolol and Latanoprost on Visual Field Deficit Progression

TABLE III: PROJECTED VISUAL FIELD CHANGE RESULTS FOR BLACK SUBJECTS

SOURCE OF IOP TO VISUAL FIELD PROGRESSION LINK	VISUAL FIELD OUTCOME	TRAVOPROST	LATANOPROST	TIMOLOL	IMPACT OF TRAVOPROST VS LATANOPROST	IMPACT OF TRAVOPROST VS TIMOLOL
AGIS, 2000 predictive	Increased VFDS based on mean IOP <14, 14-18, or ≥18 mm Hg	1.18	1.48	1.66	-25.4%*	-40.7%*
AGIS, 2000 associative	Increased VFDS based on % of visits with peak IOP <18	1.40	1.81	1.89	-29.3%*	-35.0%*
Mao et al, ²¹ 1991	Visual field progression probability based on mean IOP ≤16, 17-18, 19-21, or ≥22 mm Hg	37.2%	55.7%	72.3%	-18.5%*	-35.1%*
Odberg, ²² 1987	Visual field progression probability based on mean IOP ≤15 vs >15 mm Hg	76.2%	84.0%	83.6%	-7.8%*	-7.4%*
Shirakashi et al, ²³ 1993	Visual field progression probability based on mean IOP ≤15 vs >15 mm Hg	79.6%	97.7%	97.5%	-18.1%*	-17.9%
Stewart et al, ²⁴ 1993	Visual field progression probability based on mean IOP ≤16, 17-18, 19-21, or ≥22 mm Hg	26.9%	41.5%	56.1%	-14.7%*	-29.2%*

AGIS, Advanced Glaucoma Intervention Study; IOP, intraocular pressure; VFDS, visual field defect score.

*Statistically significant ($P<.05$) compared to travoprost.

increase in hospital days per latanoprost and timolol subject per year. For example, as shown in Table IV, patients receiving latanoprost had a 25.4% increased rate of visual field deficit progression, as compared to travoprost patients, using the first algorithm from the AGIS study. Based on this algorithm, latanoprost patients therefore had 25.4% more hospital days attributable to visual field deficits, or 25.4% times 0.183 times 2.4 (which equals 0.112) extra hospital days annually compared to travoprost patients. To determine the cost associated with this increased hospitalization, the additional hospital days (in this case, 0.112) were multiplied by the cost per day (\$1,000.36) to get the additional annual hospitalization cost (here, \$112). In Table IV, these increased costs ranged from \$34 to \$129 per latanoprost subject per year, and averaged \$83 (SD, \$34). For timolol, the increased costs ranged from \$33 to \$179 per subject per year and averaged \$121 (SD, \$55).

Tables IV and V also present similar results for outpatient medical care costs. As described in the “Methods” section, resource utilization for progressing and stable subjects was estimated by using the American Academy of Ophthalmology guidelines, and costs were assigned using Medicare 2000

reimbursement values. These costs were then applied to the differences in progression rates between travoprost, latanoprost, and timolol subjects. For example, as presented in Table V using the algorithm from Stewart and associates,²⁴ subjects receiving timolol have a 29.2% increase in the projected likelihood of visual field deficit progression. The additional outpatient cost for timolol subjects is therefore 29.2% times \$459, which equals \$133 per subject. Results are similar to those seen with increased hospital costs; the increase in annual outpatient care costs per latanoprost subject ranges from \$36 to \$134, with an average of \$87 (SD, \$35) per subject per year. For timolol subjects, the increase in annual outpatient care costs ranges from \$34 to \$186 per subject, with an average of \$126 (SD, \$57) per subject. These are conservative cost estimates, as they do not include nonphysician outpatient services and resource utilization such as systemic medications. Adding inpatient and outpatient results, the additional annual cost per latanoprost subject is projected to range from \$70 to \$263 with an average annual increase of \$170 (SD, \$69). For timolol, the range is from \$66 to \$365 with an average annual increase of \$247 (SD, \$112).

TABLE IV: COST PROJECTIONS BASED ON RATE OF VISUAL FIELD PROGRESSION: TRAVOPROST VERSUS LATANOPROST

SOURCE OF IOP TO VISUAL FIELD PROGRESSION LINK	INCREASE IN VISUAL FIELD PROGRESSION RATES, LATANOPROST VS TRAVOPROST*	INCREASE IN ANNUAL HOSPITAL DAYS PER LATANOPROST SUBJECT†	INCREASE IN ANNUAL HOSPITAL COST PER LATANOPROST SUBJECT‡	INCREASE IN ANNUAL OUTPATIENT COST PER LATANOPROST SUBJECT§	INCREASE IN ANNUAL INPATIENT PLUS OUTPATIENT COST PER LATANOPROST SUBJECT§
AGIS, predictive	25.4%	0.112	\$112	\$116	\$228
AGIS, associative	29.3%	0.129	\$129	\$134	\$263
Mao et al, ²¹ 1991	18.5%	0.081	\$81	\$85	\$166
Odberg, ²² 1987	7.8%	0.034	\$34	\$36	\$70
Shirakashi et al, ²³ 1993	18.1%	0.079	\$80	\$83	\$162
Stewart et al, ²⁴ 1993	14.6%	0.064	\$64	\$67	\$131
Average	19.0%	0.083	\$83	\$87	\$170
SD of average	7.7%	0.034	\$34	\$35	\$69

AGIS, Advanced Glaucoma Intervention Study.

*For application of the AGIS measures, the increase in visual field progression is based on the percentage increase in visual field defect score.

†Assuming an average of 0.183 annual hospitalizations per patient (National Hospital Discharge Survey) and 2.4 days of additional hospitalization for patient with visual field impairment (Morse et al,²⁵ 1999).

‡Assuming an average daily cost per hospitalization of \$1,000.36 (1995 Medicare value of \$845.62 inflated to 2000 values using the medical care component of the Consumer Price Index).

§Based on outpatient resource utilization estimates from the American Academy of Ophthalmology guidelines and Medicare reimbursement rates, as described in the "Methods" section.

TABLE V: COST PROJECTIONS BASED ON RATE OF VISUAL FIELD PROGRESSION: TRAVOPROST VERSUS TIMOLOL

SOURCE OF IOP TO VISUAL FIELD PROGRESSION LINK	INCREASE IN VISUAL FIELD PROGRESSION RATES, TIMOLOL VS TRAVOPROST*	INCREASE IN ANNUAL HOSPITAL DAYS PER TIMOLOL SUBJECT†	INCREASE IN ANNUAL HOSPITAL COST PER TIMOLOL SUBJECT‡	INCREASE IN ANNUAL OUTPATIENT COST PER TIMOLOL SUBJECT§	INCREASE IN ANNUAL INPATIENT PLUS OUTPATIENT COST PER TIMOLOL SUBJECT§
AGIS, predictive	40.7%	0.179	\$179	\$186	\$365
AGIS, associative	35.0%	0.154	\$154	\$160	\$314
Mao et al, ²¹ 1991	35.1%	0.154	\$154	\$160	\$315
Odberg, ²² 1987	7.4%	0.033	\$33	\$34	\$66
Shirakashi et al, ²³ 1993	17.9%	0.079	\$79	\$82	\$160
Stewart et al, ²⁴ 1993	29.2%	0.128	\$128	\$133	\$262
Average	27.5%	0.121	\$121	\$126	\$247
SD of average	12.5%	0.055	\$55	\$57	\$112

AGIS, Advanced Glaucoma Intervention Study.

*For application of the AGIS measures, the increase in visual field progression is based on the percentage increase in visual field defect score.

†Assuming an average of 0.183 annual hospitalizations per patient (National Hospital Discharge Survey) and 2.4 days of additional hospitalization for patient with visual field impairment (Morse et al,²⁵ 1999).

‡Assuming an average daily cost per hospitalization of \$1,000.36 (1995 Medicare value of \$845.62 inflated to 2000 values using the medical care component of the Consumer Price Index).

§Based on outpatient resource utilization estimates from the American Academy of Ophthalmology guidelines and Medicare reimbursement rates, as described in the "Methods" section.

DISCUSSION

Many studies have evaluated IOP-lowering medications and often use short-term IOP lowering as a surrogate end

point for the preservation of vision. However, in glaucoma treatment, the ultimate goal of therapy is to prevent progressive vision and visual field loss. We assumed that there is a correlation between IOP decrease and long-term

vision preservation.¹⁰⁻¹² There are possibly many other factors, such as ophthalmic blood flow, that affect the long-term preservation of the optic nerve and visual function. However, there are other potential factors that cannot be quantified.

To date, the only factor that we can reliably accomplish is IOP lowering. The AGIS¹² evaluated the long-term impact of IOP values on a visual field progression and found a relationship between both IOP lowering and consistent IOP lowering with less visual field deterioration. Other studies²¹⁻²⁴ have also used IOP as a predictive value for progression of visual field loss. We do not currently know the exact relationship between IOP and subsequent risk of progression of visual field loss. It may not necessarily be strictly linear; rather, the likelihood of visual field loss (or increases in the VFDS) may be related to thresholds or patterns of IOP values, the degree of initial field loss, the patient's age, and the eye's unique intrinsic susceptibility to damage.

There are many costs associated with glaucoma therapy. Studies have examined the number of drops per bottle, drop size, and cost per drop. We believe a better index of cost savings is the prevention of visual deficit progression. One facet of this cost is based on the responder analysis, or the percent of subjects having a sustained satisfactory IOP lowering when given a specific therapy. A medication that is most successful initially and most likely to achieve a therapeutic goal has no tachyphylaxis and no significant systemic adverse events, and it is probably far cheaper in the long term. Also, this medication, if well tolerated, has a better chance of preserving sight and would be a very cost-effective therapy.

There are many ways to lower IOP in patients with newly diagnosed glaucoma, including drug, laser, and surgical intervention.¹ Each has its own advantages and disadvantages. In newly diagnosed glaucoma, surgical therapy is most likely to lower IOP the greatest. However, surgical therapy is associated with a larger risk of cataract formation and other symptoms, such as drooping eyelids.^{10,11} Laser therapy is also a good alternative but may have a decreasing benefit with time.²⁸ All of the collaborative studies (AGIS,¹² the Collaborative Initial Glaucoma Treatment Study,¹¹ the Normal-Tension Glaucoma Study,¹⁰ and the Glaucoma Laser Trial²⁸) have not primarily used the prostaglandin analogues in their treatment algorithms, because the prostaglandin analogues are relatively new in glaucoma management. These prostaglandin analogues have a greater responder rate and better IOP lowering than all prior classes of medications. Until relatively recently, traditional initial pharmacotherapy for glaucoma has consisted of beta-adrenergic antagonists (beta blockers), alpha-adrenergic agonists (relatively specific alpha agonists), parasympathomimetic (cholinergic) agents, and carbonic anhydrase inhibitors. These medications have

generally been associated with potentially significant local and systemic adverse events.²⁹⁻³¹ Prostaglandin analogues represent a newer treatment for glaucoma and have minimal systemic and local side effects. Additionally, they more consistently lower IOP better and with fewer adverse events than other classes of medications. The responder rate among prostaglandin analogues is far superior to that of prior classes of medications.

In this study, we utilized IOP data from a recent large multicenter clinical trial comparing travoprost to latanoprost and timolol in order to project future changes in visual field loss. As presented in Table II, the short-term difference in IOP was apparent when comparing the three study groups; the mean IOP value for travoprost-treated subjects was significantly lower than that for latanoprost-treated and timolol-treated subjects (17.3 mm Hg versus 18.7 mm Hg versus 20.5 mm Hg, respectively). Further, regardless of which algorithm is used (the two algorithms from AGIS and the four from other studies), the projected long-term changes in VFDS and the proportion of subjects with progression of visual field loss were also significantly different among subjects using the three medications as shown in Table III. In particular, we projected that subjects receiving travoprost would have decreased rates of visual field deficit progression as compared to subjects receiving either latanoprost or timolol. By assigning costs to these projected differences, we are able to quantify both the short-term (from outpatient treatment changes) and longer-term (from changes in length of hospitalization resulting from multiple years of visual field deficit progression leading to severe visual impairment) economic changes.

There are a number of limitations to this study. First, data for this model and analysis are based on the results of a simple randomized and masked clinical trial. Subjects may behave differently depending on the trial design. Subjects may behave differently in a trial than they do in the real world. Also, the subjects in this study may or may not be comparable to those in the studies used to project changes in VFDS or visual field loss. Follow-up and compliance may be better or worse. Strict therapeutic regimens are followed, rather than less structured treatment protocols. Strict inclusion and exclusion criteria were used. These results may therefore not apply to those with other characteristics. Therefore, while randomized clinical trials allow for control of differences in a subject's characteristics (ie, they have a high degree of internal validity), they may not correspond as well to "real world" treatment patterns. This may affect the ability to generalize our results.

Also, any projection is associated with a level of uncertainty. In this analysis, projections of visual field loss (and associated costs) are subject to variability. However, the multiple projections used in this analysis all produced the same results (ie, lower rates of visual field loss progression

among subjects treated with travoprost). This consistency provides an increased foundation for the predicted results presented herein.

Finally, the results of this study are based on a fairly small sample of black subjects. Attempts to replicate the results should involve larger patient groups. Also, these models should involve subjects not in multicenter studies. Further, it is unknown whether these results are generalizable to groups beyond the study subject.

In addition to its economic impacts, progression of visual field loss is likely to result in decreased patient quality of life. It is often difficult to assign a relative cost to these items. Gutierrez and associates¹⁹ evaluated the impact of the AGIS-based VFDS on patient quality of life in a number of important domains. The results clearly indicate decreasing quality of life with increasing VFDS score. For example, each 1-point increase in VFDS was associated with approximately a 3-point decrease in the driving scale score (which ranged from 100 to 0). It may thus be possible to predict changes in key visual quality-of-life domains on the basis of predicted changes in visual field.

We do not assign a cost to quality-of-life issues (eg, the value of autonomy or the value of a good driving record). We do not deal with costs associated with adverse reactions to medications (ie, the cost of a hospitalization from an asthma attack while receiving a beta blocker is quite expensive compared to the value of a bottle of eyedrops). We also do not evaluate the indirect costs associated with a patient's time or the time of a family member or friend who brings the patient in for an examination. These costs of lost productivity are very important. Thus, the cost estimates presented in this manuscript are conservative and may underestimate the true economic impact of preserving vision.

SUMMARY

We have used data from a 12-month clinical trial to create a model and extrapolate changes in longer-term clinical outcomes (visual field) from intermediate outcomes (IOP). While these results will require replication, we initially can conclude that treatment with travoprost is projected to result in lower rates of visual field loss than is treatment with latanoprost or timolol. As a consequence, substantial cost savings and protection of patient quality of life may be associated with travoprost therapy. We urge that others also begin to consider the actual costs of therapy and further investigate the true costs of various interventions.

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DISCUSSION

DR M. BRUCE SHIELDS. Dr Robin and his colleagues have focused on a rather surprising finding from a previously reported multicenter trial, in which travoprost 0.004% was found to be significantly more effective in lowering intraocular pressure (IOP) among black patients than latanoprost 0.005%. What made this finding particularly surprising was the observation that travoprost 0.004% was also more effective among black patients in the clinical trial than was the same drug in the nonblack population. This is in contrast to prior studies of other topical glaucoma drugs, such as timolol, in which a higher concentration of the medication is required in eyes with darker iris pigmentation to produce the same level of pressure reduction. However, in the clinical trial cited in the present paper, travoprost 0.004% was significantly more effective than travoprost 0.0015% among black patients, which is consistent with the prior studies, and it may be that the greater affinity of travoprost for prostaglandin F receptors, as compared to latanoprost, may explain the observations in the referenced clinical trial.

In any case, it is quite appropriate that Dr Robin and his associates should pursue this question, considering the relative significance of glaucoma in the black population, in which the condition is three to four times more prevalent than in white individuals and is six times more likely to be associated with blindness. If the initial findings are correct, therefore, it would have significant implications in the treatment of black individuals with glaucoma.

Dr Robin and his colleagues have taken the IOP data within the black population of the clinical trial to estimate the long-term course of visual field progression and the economic consequences of the associated visual impairment among black patients receiving either travoprost 0.004% daily, latanoprost 0.005% daily, or timolol 0.5% twice daily. Not surprisingly, the results favor travoprost, although the magnitude of the differences is impressive.

The authors have appropriately cited limitations to their study. Specifically, two questions must be asked: How reliable is the assumed relationship between IOP data and visual field progression, and, how accurate is the IOP data upon which the assumptions are made? As the authors note, progressive visual field loss in glaucoma cannot be accurately predicted on the basis of mean IOP alone, but rather on a pattern of IOP over time. One wonders, therefore, if a 12-month study provides sufficient IOP data upon which to predict long-term visual outcome. As the authors also note, pressure is not the only factor associated with optic nerve damage and visual field loss in glaucoma, which further complicates any attempt to predict long-term visual outcome on IOP data.

Assuming for the moment, however, that the assumptions linking IOP data to visual outcome are reliable, how accurate is the IOP data on which these assumptions are based? As the authors admit, the sample size is relatively small. Furthermore, 9 of the 49 travoprost patients (18%) did not complete the study, compared to 3 of the 43 latanoprost patients (7%). It would be helpful to know the reason for the withdrawal of these patients from the study. If it were for inadequate pressure control, would this have influenced the results, since the IOP values for subjects discontinuing early were not carried forward?

As the authors correctly state, further study with a larger population of black patients and longer follow-up is first needed to confirm the IOP data in the initial clinical trial. If the findings can be confirmed, then the impact on preservation of vision, quality of life, and cost savings, as estimated by the authors, will represent a significant advance in our management of glaucoma. In any case, Dr Robin and his associates are to be complemented for focusing our attention on this important possibility and also in emphasizing the importance of considering these outcome measures in the evaluation of any glaucoma treatment.

DR ALLAN J. FLACH. The paper does involve problems of cost. The Advanced Glaucoma Intervention Study (AGIS) has recently been completed and demonstrated that intraocular pressures (IOPs) below 14 mm Hg are desirable to preserve visual function in those patients with glaucomatous visual field and disk changes. No one has disproven, however, that every individual may have his or her own susceptibility to IOP. I am alarmed by many of the individuals presenting papers in various societies that take the AGIS data and suggest that we should be striving for pressures below 15 mm Hg or 14 mm Hg in all of our patients with glaucoma. My concern that this philosophy may lead to unnecessary medical and surgical therapies.

Intraocular pressures as low as possible is a desirable goal in many, but choosing a goal pressure that is extremely low, without thinking about individual variation, may be a great financial trap.

DR ROBERT L. STAMPER. I'd like to plead that our drug and surgical studies in the future do indeed look at the primary outcome, which is, in fact, visual function and quality of life, rather than just IOP. Did you look at corneal thickness in assessing the IOP in these patients?

DR ALAN L. ROBIN. Let me address the questions in reverse order, first for Dr Stamper and then Dr Flach. I regrettably agree that many clinicians now mindlessly extrapolate from the AGIS data and create arbitrarily or artificially low IOP goals for many patients without considering the patient's age, degree of visual field and optic nerve damage, health status, or quality of life. The only way to really know of the appropriate goal for anybody is retrospectively; that is, have you preserved visual function 5 years later at the IOP level that you have chosen?

I believe that AGIS does give us some guidelines, as do the Normal Tension Glaucoma Study, Collaborative Initial Glaucoma Treatment Study (CIGTS), and the Ocular Hypertension Treatment Study (OHTS). The lessons from these studies are as follows: AGIS found that in a group of patients with advanced glaucoma, IOPs that are consistently below 18 mm Hg (averaging 12.3 mm Hg) had no net change in visual field score 6 years later. Also those

subjects whose IOPs remained below 14 mm Hg for the first 18 months after intervention had no significant change in visual function 8 years later. CIGTS found that in individuals with early glaucoma, strict IOP lowering, either medically or surgically, minimized visual field loss 5 years later, so that it occurred in less than 15% of patients. Finally the OHTS found that in subjects without glaucoma, but with elevated IOPs, a 20% decrease in IOP significantly diminished the risk of the development of glaucoma. In OHTS, corneal thickness was a significant risk factor for the development of glaucoma, as those with thinner corneas had a three times higher chance of developing the disease than those ocular hypertensives without it.

Although the results will vary from person to person and although some people are unaffected by pressure lowering, I think many ophthalmologists, regrettably, have extracted the data from AGIS and applied them to patients who don't have glaucoma or may have early glaucoma. This may be extremely inappropriate. I believe the onus and the responsibility of appropriate therapy are with the glaucoma specialists in this audience and in our society, for making sure that the right information is disseminated. We must think about the whole picture, not a "cookbook" attitude for glaucoma therapy.

Second, to answer Dr Stamper's question about pachymetry, we did not look at corneal pachymetry except for a very small number of people in this study.

Third, in response to Dr Shield's comment, there were a number of individuals, more so in the travoprost group, who were disqualified from the study. However, the disqualifications were only related to an adverse effect from Travatan in one individual. The remainder of the disqualifications were not due to either inadequate IOP lowering or drug-related adverse events. In fact, they were quite varied, including noncompliance, and car wreck.

Finally, I think that this study, in and of itself, is significant in that it finds that we should really look at therapies not only in terms of IOP lowering or visual field loss but also to analyze the cost of visual field loss preservation. The relative costs of therapy are becoming more important in choosing which therapies are most cost-efficient for our patients.