

Patient Persistency With Topical Ocular Hypotensive Therapy in a Managed Care Population

GREGORY REARDON, PhD, RPH, GAIL F. SCHWARTZ, MD, AND
ESSY MOZAFFARI, PHARM D, MPH

- **PURPOSE:** To evaluate persistency with topical ocular hypotensive therapies in patients new to pharmacological management of elevated intraocular pressure (IOP).
- **DESIGN:** Retrospective, cohort study; Protocare Sciences managed care database; approximately 3 million members in commercial health maintenance organizations and preferred provider organizations and in Medicare risk plans.
- **METHODS:** Patients were at least 20 years of age initiating therapy between July 1, 1996, and June 30, 2002, with betaxolol, bimatoprost, brimonidine, dorzolamide, latanoprost, timolol, or travoprost as monotherapy. Patients must have been continuously enrolled and not have received glaucoma surgery in the 180 days before the index prescription fill. Prescription refill records for all ocular hypotensive drugs were extracted through June 30, 2002. Outcome measures were (1) discontinuation of index drug, and (2) either discontinuation or change in index drug. Changing therapy was defined as switching to or adding another ocular hypotensive. Rates of discontinuation and discontinuation/change were compared using Cox regression models.
- **RESULTS:** In all, 28,741 patients met the inclusion criteria. Compared with latanoprost, those treated with other drugs were from 37% (timolol) to 72% (bimatoprost) more likely to discontinue and from 20% (timolol) to 58% (dorzolamide) more likely to discontinue/change therapy ($P < .001$ for all comparisons). At 12 months,

33% of patients treated with latanoprost and 19% of those receiving other ocular hypotensives had not discontinued therapy; 23% and 13%, respectively, had not discontinued or changed therapy. Compared with latanoprost, significantly higher percentages of patients treated with each alternate agent had only one fill of their index drugs ($P < .001$).

- **CONCLUSIONS:** Although persistency rates were low across agents, latanoprost-treated patients demonstrated significantly greater persistency than did those treated with other topical ocular hypotensive therapies. (Am J Ophthalmol 2004;137:S3-S12. © 2004 by Elsevier Inc. All rights reserved.)

PHARMACOLOGIC THERAPY FOR ANY CONDITION CAN be effective only if patients fill their prescriptions (persistency) and take their medications as directed (compliance). In principle, medication compliance is not possible without persistency because patients must fill prescriptions before using them. Over time, patients who do not fill their prescriptions do not receive adequate treatment, making lack of persistency equivalent to withdrawal of therapy.

For patients with ocular hypertension or open-angle glaucoma, therapy focuses on reducing intraocular pressure (IOP) levels in order to delay or prevent the progression of ocular hypertension to glaucoma¹ and to slow disease progression in glaucoma patients.²⁻⁴ First-line treatment usually consists of monotherapy with a topical ocular hypotensive. Persistency with these agents apparently reflects many factors including patient satisfaction with medication tolerability and physician satisfaction with IOP control,⁵ medication costs,⁶ and patient understanding of the importance of taking their medication over the long term.⁷ Persistency is important for patients with these conditions because those who do not continue therapy risk developing elevated IOP levels and, over time, progressing to blindness.

Results of recent research using natural history, cohort designs and survival analyses suggest that persistency with

Accepted for publication Oct 13, 2003.

From Informagenics LLC, Worthington, Ohio (G.R.); Glaucoma Consultants, Greater Baltimore Medical Center, Wilmer Eye Institute, Johns Hopkins University, and the University of Maryland, Baltimore, Maryland (G.F.S.); and Pfizer Inc, New York, New York (E.M.).

Doctor Reardon was a consultant to Pharmacia Corporation. Doctor Schwartz has received research support from Pharmacia Corporation. Doctor Mozaffari currently is an employee of Pfizer Inc but was an employee of Pharmacia Corporation at the time the research was conducted and completed.

Inquiries to Gregory Reardon, PhD, RPh, Informagenics, LLC, 500 W. Wilson Bridge Rd, Suite 115, Worthington, OH 43085; phone: (614) 847-1900; fax: (614) 573-7129; e-mail: greardon@informagenics.com

ocular hypotensives varies across medications.⁸⁻¹² These methods are well suited to evaluating persistency. In particular, survival analyses control for unequal durations of follow-up among patients and also account for patient loss due to the occurrence either of "censoring" events that prevent the clinical outcome from being observed (for example, leaving the health insurance plan or reaching the end of the study period) or from experiencing the clinical event under study. The present study used a natural history design and survival analysis to evaluate persistency with a wide range of commonly used topical ocular hypotensive therapies in patients new to pharmacologic management of glaucoma or ocular hypertension.

METHODS

CLAIMS RECORDS FROM THE PROTOCARE SCIENCES MANAGED care database (United States) were used in this population-based, retrospective, cohort study. This database includes information for approximately 3 million members of commercial preferred provider organizations (PPOs), health maintenance organizations (HMOs), and Medicare risk plans. The database is "de-identified" by Protocare Sciences in accordance with privacy regulations promulgated by the US Department of Health and Human Services, pursuant to the Health Insurance Portability and Accountability Act (HIPAA), and includes encrypted patient and physician identifiers and appropriately modified age and zip code formats.

To ensure that complete medical and pharmacy utilization was obtained for all eligible patients, those with Medicare supplemental coverage were excluded from the analysis. Remaining patients were members in medical plans with both medical and pharmacy benefit coverage. The population included patients 20 years of age and older who began therapy between July 1, 1996, and June 30, 2002; with betaxolol, bimatoprost, brimonidine, dorzolamide, latanoprost, timolol, or travoprost as monotherapy (index drugs). Patients were excluded from further analyses if on the initial medication dispensing date (index date) they had received more than one ocular hypotensive agent. Patients also were excluded if, in the 180 days preceding the index date, they had received a prescription for any topical ocular hypotensive (that is, were not naive to therapy), had not been continuously enrolled in the insurance plan, or had glaucoma-related surgery (CPT codes 65805, 65855, 66170, 66172, 66180, or 66250). Prescription refill records for all ocular hypotensive agents were extracted through June 30, 2002. By focusing on actual patient fill data, the model accounted for variation in drops per bottle and in patterns of patient use.

Because glaucoma patients are sometimes dispensed more than one bottle of the same product by the pharmacy, our persistency model had different assumptions concerning single and multiple bottles of the same medi-

cation dispensed on the same date. In the primary analysis, discontinuation of therapy (discontinuation date) was defined as no further index drug refill 90 days (if dispensed one bottle) or 180 days (if dispensed more than one bottle) after the last prescription fill. These time frames were selected because a separate analysis showed that most patients receiving one bottle of an ocular hypotensive refilled the prescription within 40 to 75 days.¹³ The 90-day and 180-day intervals allowed for some degree of noncompliance or variation in prescription dosing within patients (for example, skipping doses or using medication every other day). The discontinuation date minus the index date was used to calculate the number of days of therapy on the index drug before discontinuation. Therapy change was defined as switching to or adding any ocular hypotensive medication. The change date minus the index date was used to calculate the number of days of therapy on the index drug before changing. Drug persistency was calculated as the number of days from the index date to (1) the discontinuation date (discontinuation event) and to (2) the earlier of either the discontinuation or change date (discontinuation/change event). Discontinuation of therapy is patient driven as it reflects the patient's decision not to refill a prescription. Discontinuation/change of therapy is both patient and physician driven as it may reflect either the patient's decision not to refill a prescription or the physician's decision to prescribe a different therapeutic regimen.

To develop the primary persistency model, Cox regression was used to estimate rate ratios of discontinuation and discontinuation/change across treatment groups with latanoprost as the reference group. Kaplan-Meier plots provided comparisons of the probability of remaining persistent with drugs over time. Data for patients who were not followed up long enough to observe a drug discontinuation or change event were treated as censored either upon termination of insurance coverage or at the end of study period.¹⁴ SPSS software version 11.0 (SPSS, Chicago, Illinois, USA) was used to perform all statistical analyses.

The stability of the primary persistency model described above was tested in a less restrictive, expanded patient cohort that included both those who received the index drug as monotherapy and those who received cotherapy with the index drug and another ocular hypotensive agent within the 180 days preceding the index date. In this stability analysis, any new glaucoma agent, other than the index drug or the alternative cotherapy, was a potential change agent. The sensitivity of the primary persistency model to variation in the time permitted between refills prior to identification of a discontinuation or discontinuation/change event was tested by applying two alternative refill time frames to the patient cohort: a 60-day (1 bottle)/120-day (>1 bottle) time frame and a 120-day (1 bottle)/180-day (>1 bottle) time frame.

The percentage of patients who did not refill their index drug within the 90-day/180-day time frames after the index date was calculated for each index drug; patients were included in this analysis only if they maintained continuous enrollment until the end of the 90-day/180-day period. To determine whether financial considerations might be the source of a selection bias, copayment amounts for the index drug and each subsequent refill dispensed to patients were analyzed; all fills during the period from the index date to the earlier of termination of insurance coverage or the end of the study period were included.

We also compared patient persistency with ocular hypotensives with persistency with therapy for another asymptomatic condition, elevated cholesterol levels. Using the patient cohort included in the primary persistency model, persistency was evaluated for the subset of patients who received concurrent therapy with any hydroxymethylglutaryl-CoA reductase inhibitor (statin). For each eligible patient, prescription records were screened for any statin dispensed on or after the index date of the ocular hypotensive medication through June 30, 2002. The earliest statin product dispensed for a patient was identified as the statin index drug, and the dispensing date of the statin was the statin index date. Patients were identified as discontinuing statin therapy if they had no further statin index drug refills within a period of 1.5 times the days' supply (allowing for some degree of noncompliance) reported on the last prescription fill record. Days of therapy on the statin index drug before discontinuation or discontinuation/change were calculated as described above with regard to ocular hypotensive medications. Patient data were censored if termination of insurance coverage or the end of the study period occurred before a discontinuation or discontinuation/change event was observed.

RESULTS

OVERALL, 72,125 PATIENTS WERE PRESCRIBED EITHER BETAXOLOL, BIMATOPROST, BRIMONIDINE, DORZOLAMIDE, LATANOPROST, TIMOLOL, OR TRAVOPROST DURING THE STUDY PERIOD; 28,741 patients met all additional inclusion criteria (Table 1). The three most frequently prescribed drugs were timolol (prescribed for 43% of patients), latanoprost (33%), and brimonidine (18%); relatively few patients were prescribed either travoprost or bimatoprost (1% of patients for each).

Demographic and ocular characteristics are summarized in Table 2. Nearly 60% of patients were women; almost three quarters were 65 years of age or older. About half of those for whom a diagnosis was recorded had primary open-angle glaucoma; a specific diagnosis was not documented in the medical claims database for the 55% of patients with no glaucoma-related visit during the 180 days before and including the index date.

TABLE 1. Application of Exclusion Criteria to Patient Population*

Application of Exclusion Criteria	Number Excluded	Number Included
Patient prescribed one of the selected topical ocular hypotensives between July 1, 1996, and June 30, 2002	—	72,125
Patient prescribed multiple ocular hypotensive therapies on the index date	12,604	59,521
Patient prescribed an ocular hypotensive within 180 days preceding the index date, ie, was not new to therapy	6,614	52,907
Patient <20 years of age on the index date	376	52,531
Patient did not have continuous drug benefit enrollment for 180 days preceding the index date	23,670	28,861
Patient had glaucoma-related surgery within 180 days preceding the index date	120	28,741

*The analysis included patients taking a single topical ocular hypotensive drug; the index drug was identified by the first prescription fill for the topical ocular hypotensive medication.

Cox regression model statistics for discontinuation in the primary persistency model are shown in Table 3. Patients treated with any other ocular hypotensive therapy were significantly ($P < .001$) more likely to discontinue their index drug than were patients treated with latanoprost. Compared with latanoprost-treated patients, patients treated with timolol or dorzolamide were 37% and 41%, respectively, more likely to discontinue therapy, and patients receiving travoprost and bimatoprost were 58% and 72%, respectively, more likely to discontinue ($P < .001$ for each comparison). Figure 1 provides corresponding Kaplan-Meier plots for these ocular hypotensive therapies, showing that latanoprost-treated patients demonstrated the greatest persistency with therapy over time. Note that the plots are flat for the first 90 days after the index date because by definition patients could not discontinue their therapy during that time. At 12 months, 33% of patients treated with latanoprost and 19% of those treated with other ocular hypotensives had not discontinued therapy. Adjusting for age and sex did not appreciably change the magnitude of increased risks of discontinuation in any treatment group (data not shown).

Compared with latanoprost, those treated with an alternative ocular hypotensive also were significantly ($P < .001$) more likely to discontinue/change therapy (Table 4), with increased risks of discontinuation/change ranging from 20% in patients treated with timolol to 58% in

TABLE 2. Patient Demographics and Ocular Characteristics*

	Ocular Hypotensive Therapy						
	Timolol	Latanoprost	Brimonidine	Betaxolol	Dorzolamide	Travoprost	Bimatoprost
Patient, n (%)	12,298 (43)	6,772 (24)	5,057 (18)	2,458 (9)	1,344 (5)	408 (1)	404 (1)
Age (years) [†]							
20 to 34	171 (1)	87 (1)	79 (2)	18 (1)	15 (1)	8 (2)	6 (1)
35 to 49	998 (8)	517 (8)	366 (7)	154 (6)	76 (6)	30 (7)	28 (7)
50 to 64	2,307 (19)	1,286 (19)	812 (16)	427 (17)	221 (16)	87 (21)	103 (26)
65 to 79	6,484 (53)	3,509 (52)	2,642 (52)	1,285 (52)	723 (54)	223 (55)	197 (49)
>79	2,338 (19)	1,373 (20)	1,158 (23)	574 (23)	309 (23)	60 (15)	70 (17)
Sex [‡]							
Male	5,362 (44)	2,859 (42)	2,086 (41)	995 (40)	595 (44)	171 (42)	177 (44)
Type of glaucoma [†]							
Open angle	2,657 (22)	1,682 (25)	949 (19)	482 (20)	289 (22)	127 (31)	117 (29)
Suspect	1,520 (12)	923 (14)	655 (13)	266 (11)	128 (10)	69 (17)	56 (14)
Other	1,329 (11)	707 (10)	476 (9)	270 (11)	209 (16)	32 (8)	37 (9)
Not documented	6,792 (55)	3,460 (51)	2,977 (59)	1,440 (59)	718 (53)	180 (44)	194 (48)
Frequency of glaucoma-related visits [†]							
0	6,792 (55)	3,460 (51)	2,977 (59)	1,440 (59)	718 (53)	180 (44)	194 (48)
1	2,876 (23)	1,639 (24)	993 (20)	549 (22)	300 (22)	73 (18)	90 (22)
>1	2,630 (21)	1,673 (25)	1,087 (21)	469 (19)	326 (24)	155 (38)	120 (30)

*Based on data from the medical claims database for the period 180 days prior to the index date.

[†]P < .001 for difference among treatment groups (chi-square).

[‡]P = .016 for difference among treatment groups (chi-square).

TABLE 3. Rate Ratios and 95% Confidence Intervals for Discontinuation of Initial Ocular Hypotensive Therapies Using a Cox Regression Model: Primary Persistency Model*

	RR	95% CI	P Value
Discontinuation of therapy			
Latanoprost [†]	1.00		
Timolol	1.37	1.31, 1.42	<.001
Brimonidine	1.45	1.38, 1.52	<.001
Betaxolol	1.42	1.34, 1.51	<.001
Dorzolamide	1.41	1.30, 1.53	<.001
Travoprost	1.58	1.36, 1.83	<.001
Bimatoprost	1.72	1.50, 1.97	<.001

*Hazard rate ratios (RR) and 95% confidence intervals (CI) from Cox regression models.

[†]Reference group.

patients receiving dorzolamide ($P < .001$ for each comparison). Figure 2 presents Kaplan-Meier plots for discontinuing or changing therapy for the drugs; declines in these plots before 90 days reflect changes in initial therapy. At 12 months, 23% of latanoprost-treated patients and 13% of patients treated with other ocular hypotensives had neither discontinued nor changed therapy. Adjusting for

age and sex did not change the size of the increased risks of discontinuation/change in patients treated with alternate therapies compared to those receiving latanoprost (data not shown).

The relative relationships between latanoprost and alternate ocular hypotensive therapies demonstrated in these primary persistency models were stable in the cohort of patients permitted to receive cotherapy with any ocular hypotensive agent in the 180 days preceding the index date ($n = 34,010$) and were not sensitive to changes in assumptions concerning refill time frames (Figures 3 and 4). The percentage of patients who were continuously enrolled until the end of the first fill period (90 or 180 days) and who did not refill their index drug ranged from 34% for latanoprost to 54% for bimatoprost (Table 5); compared with latanoprost, the percentages of patients who had only one fill of their index drugs were significantly higher ($P < .001$) for each of the other ocular hypotensive agents. Mean copayments for index drugs are shown in Table 6. For five of the index drugs that were commercially available before 2001 (betaxolol, brimonidine, dorzolamide, latanoprost, and timolol), mean copayments between July 1, 1996, and June 30, 2002, ranged from \$7.46 for timolol to \$11.38 for brimonidine. We also examined differences in copayments for a narrower time frame, July 1, 2001, through June 30, 2002, that includes data for the more recently available ocular hypotensives, travoprost

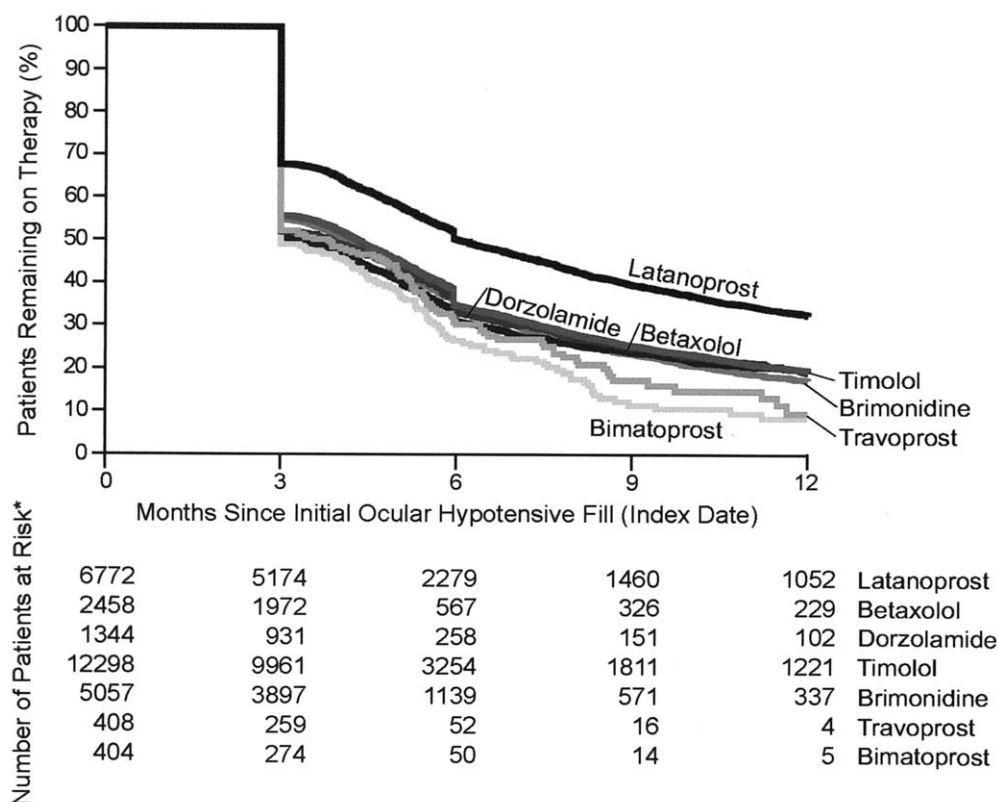


FIGURE 1. Kaplan-Meier plot for time to discontinuation of ocular hypotensive therapies. *The numbers of patients at risk are those who had not discontinued therapy or been censored by the start of each 3-month period.

TABLE 4. Rate Ratios and 95% Confidence Intervals for Discontinuation of or Change in Initial Ocular Hypotensive Therapies Using a Cox Regression Model: *Primary Persistency Model**

	RR	95% CI	P Value
Discontinuation of or change in therapy			
Latanoprost†	1.00		
Timolol	1.20	1.16, 1.24	<.001
Brimonidine	1.41	1.35, 1.47	<.001
Betaxolol	1.29	1.23, 1.36	<.001
Dorzolamide	1.58	1.48, 1.68	<.001
Travoprost	1.36	1.20, 1.55	<.001
Bimatoprost	1.46	1.29, 1.65	<.001

*Hazard rate ratios (RR) and 95% confidence intervals (CI) from Cox regression models.

†Reference group.

and bimatoprost; average copayments for all drugs were higher during this period than during the broader time frame and ranged from \$8.92 for timolol to \$18.30 for dorzolamide.

In all, 7,055 patients (25%) were treated concurrently with an ocular hypotensive drug and a statin. A comparison of Kaplan-Meier plots of time on therapy until either discontinuation or discontinuation/change across the ocular hypotensive drugs studied and for statins showed similar steep rates of decline during the first year of treatment as well as similar absolute rates of persistency (Figures 5 and 6). At 12 months, persistency with statins was slightly greater than persistency with ocular hypotensive drugs overall (no discontinuation: 23% vs 22%, respectively; no discontinuation or change: 20% vs 15%, respectively).

DISCUSSION

ALTHOUGH THE PERCENTAGES OF PATIENTS WHO HAD not continuously persisted with therapy over a year were low across agents, patients receiving betaxolol, bimatoprost, brimonidine, dorzolamide, timolol, or travoprost were significantly ($P < .001$) more likely to discontinue or discontinue/change their index therapy during the study period and less likely to fill a second prescription than were latanoprost-treated patients. The present survival analysis results confirm those of previous research using similar methodologies. For example, three retrospective, cohort studies,^{8,11,12} each including more than 1,000 patients less

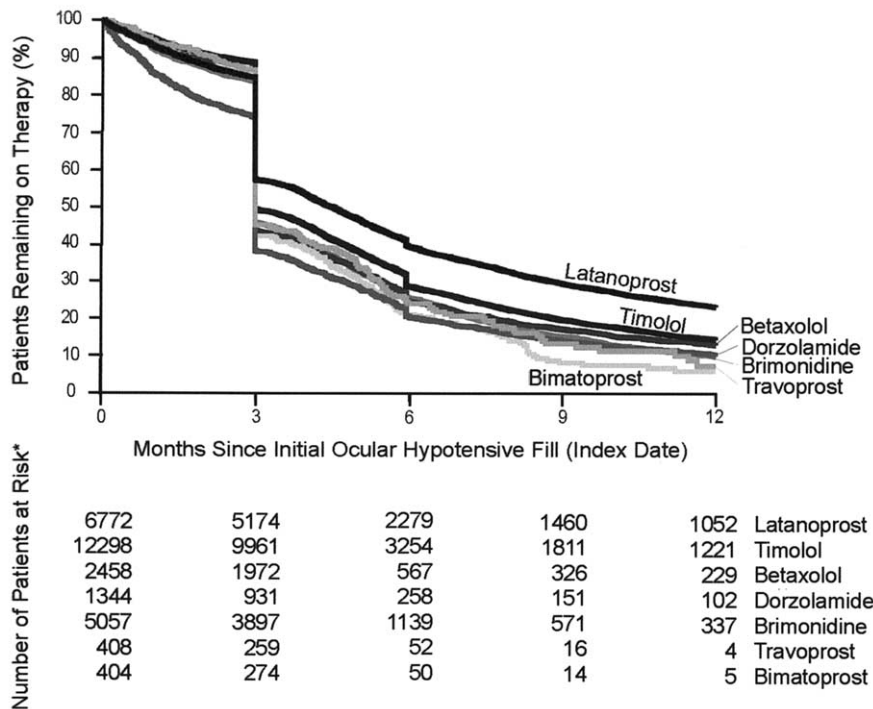


FIGURE 2. Kaplan-Meier plot for time to discontinuation of or change in ocular hypotensive therapies. *The numbers of patients at risk are those who had not discontinued or changed therapy or been censored by the start of each 3-month period.

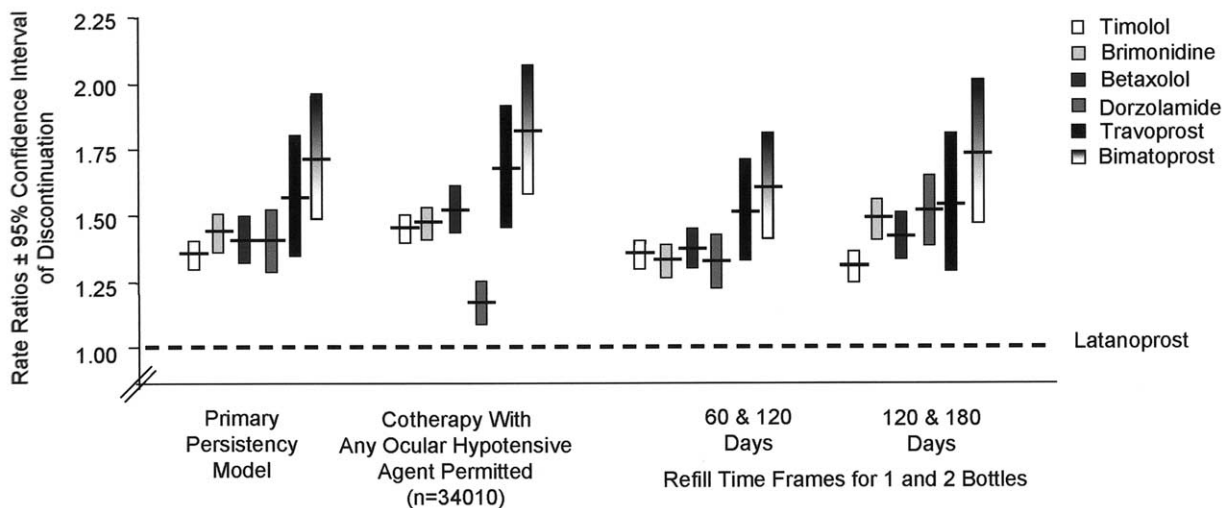


FIGURE 3. Rate ratios of discontinuation of ocular hypotensive therapies: sensitivity and stability analyses.

than 65 years of age, compared medication persistency over 18 to 30 months in patients treated with beta-blockers, brimonidine, carbonic anhydrase inhibitors, or latanoprost; patients treated initially with latanoprost monotherapy remained on therapy significantly ($P < .001$ to $P < .05$) longer than patients treated with comparator drugs. A study of 2,850 patients 20 years of age or more followed up for 21 months found that patients receiving latanoprost were significantly ($P < .05$) less likely to

discontinue or discontinue/change the index therapy than those treated with betaxolol, brimonidine, dorzolamide, or timolol.¹⁰ Finally, research that included 4,356 patients 20 years of age or more followed up for 15 months compared persistency across three prostaglandin analogs; patients treated with latanoprost were significantly ($P < .001$) more persistent than those receiving either bimatoprost or travoprost.⁹ As in previous reports,⁸⁻¹² long-term persistency with all ocular hypotensive therapies was poor.

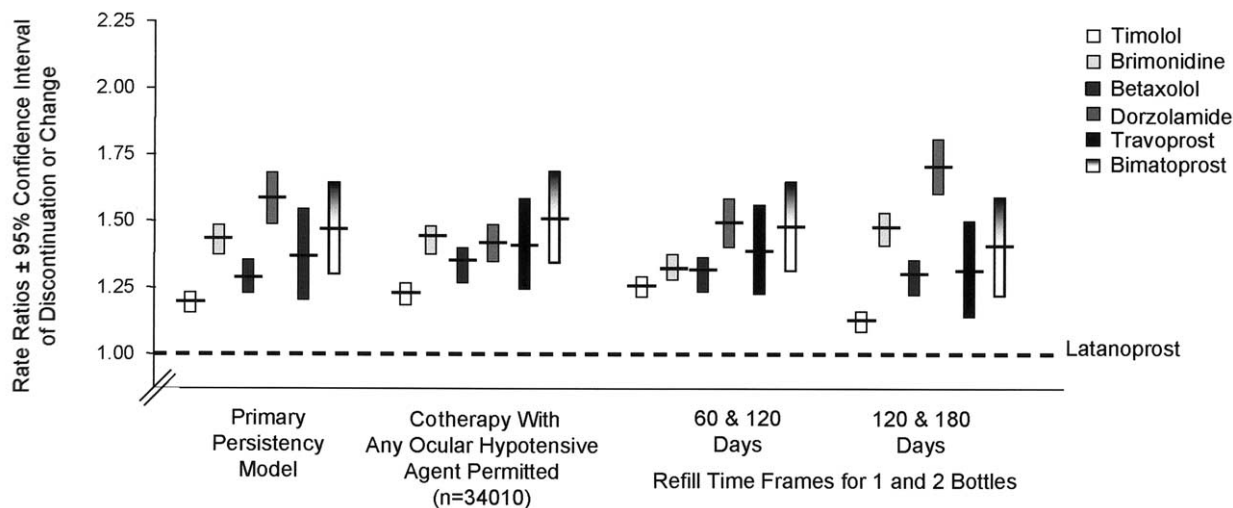


FIGURE 4. Rate ratios of discontinuation of or change in ocular hypotensive therapies: sensitivity and stability analyses.

TABLE 5. Percentages of Patients Having Only One Fill of Index Drug

	n*	Percent Having Only One Fill	P Value†
Latanoprost‡	6086	34	
Timolol	11,110	48	<.001
Brimonidine	4,614	46	<.001
Betaxolol	2,261	52	<.001
Dorzolamide	1,249	48	<.001
Travoprost	294	50	<.001
Bimatoprost	312	54	<.001

*Includes patients continuously enrolled from index date through end of initial 90-day/180-day period.

†For difference in percentages compared with reference group (latanoprost) using Z-test for independent proportions.

‡Reference group.

The fact that persistency dropped off steeply in the first 90 to 180 days for all therapies parallels the finding that 37% of 89 patients newly diagnosed with asymptomatic elevation of IOP were lost to follow-up over a 12-month to 20-month follow-up period and that most of these were lost within 1 month of the initial diagnosis.¹⁵ Low persistency rates are a general problem with chronic disease pharmacotherapies, especially for asymptomatic conditions. Herein, patients treated concurrently with an ocular hypotensive and a statin demonstrated parallel steep decreases in therapeutic persistency during the first year of treatment, suggesting that the progressive decline in persistency may cross pharmacotherapeutic classes. Studies have documented poor long-term persistency in patients receiving antihypertensive therapies,^{16–19} especially in those new to treatment.¹⁷ Variability in persistency rates across antihypertensives has been hypothesized to be

TABLE 6. Mean (SD) Copayments by Index Drug

	n*	Mean (SD)
July 1, 1996–June 30, 2002		
Latanoprost	53,776	\$11.21 (8.59)
Timolol	80,917	\$7.46 (5.99)
Brimonidine	24,364	\$11.38 (8.57)
Betaxolol	13,954	\$10.58 (9.00)
Dorzolamide	8,022	\$10.36 (8.17)
July 1, 2001–June 30, 2002		
Latanoprost	10,022	\$15.49 (9.24)
Timolol	13,639	\$8.92 (5.93)
Brimonidine	4,258	\$15.52 (9.27)
Betaxolol	1,549	\$16.06 (9.64)
Dorzolamide	416	\$18.30 (9.65)
Travoprost†	903	\$15.29 (8.97)
Bimatoprost‡	843	\$15.73 (8.61)

*Number of prescriptions filled.

†Became commercially available in March 2001.

SD = standard deviation.

related to differences in medication effectiveness and tolerability,^{16,18,19} and such differences may be reflected in the greater persistency demonstrated in the current study by latanoprost-treated patients. With respect to effectiveness, clinical studies have shown that latanoprost reduces IOP levels more effectively when compared with brimonidine,^{20–22} dorzolamide,²³ or timolol,^{24–26} whereas latanoprost, bimatoprost, and travoprost are comparable in their IOP-lowering abilities.²⁷ Systemic side effects occur less frequently with latanoprost than with brimonidine²² or timolol,²⁶ and hyperemia occurs more frequently with either bimatoprost^{27–29} or travoprost^{27,30,31} than with latanoprost. Hyperemia may lead to decreased ocular tolerability and may negatively affect persistency.

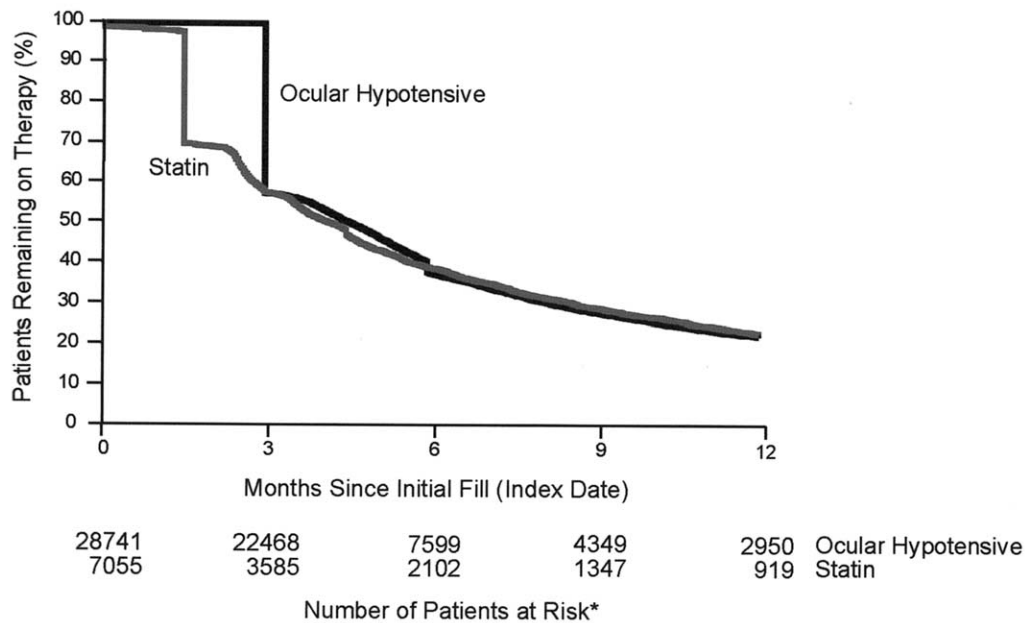


FIGURE 5. Kaplan-Meier plot for time to discontinuation of ocular hypotensive and HMG-CoA reductase inhibitor (statin) therapies. *The numbers of patients at risk are those who had not discontinued therapy or been censored by the start of each 3-month period.

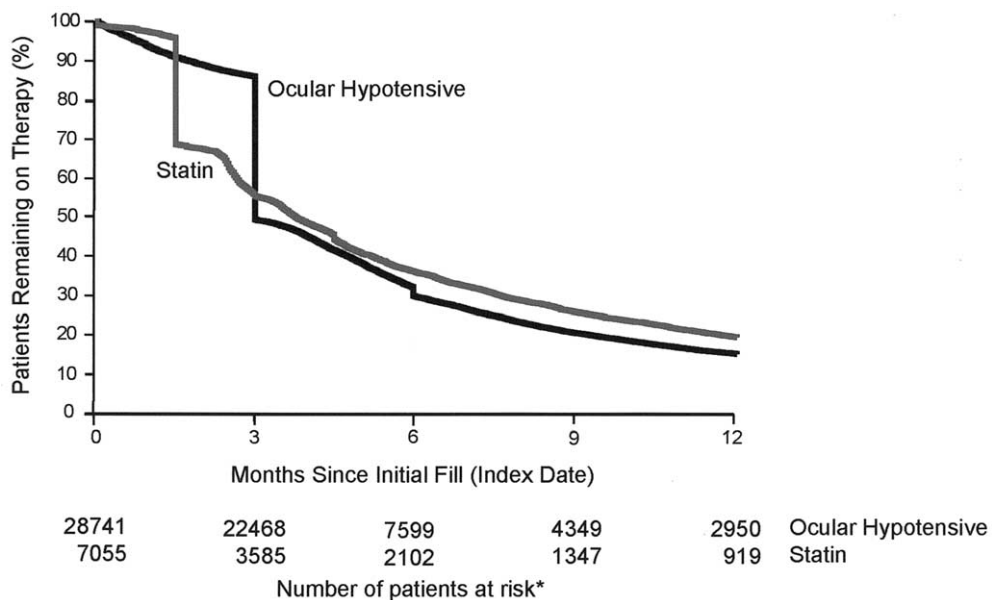


FIGURE 6. Kaplan-Meier plot for time to discontinuation of or change in ocular hypotensive and HMG-CoA reductase inhibitor (statin) therapies. *The numbers of patients at risk are those who had not discontinued or changed therapy or been censored by the start of each 3-month period.

It is worth noting that although methods used in the present study identify a patient as not persistent based on a single discontinuation event, we have found in unpublished work that some patients return to therapy after a large gap between refills; results of these analyses will be published in the near future. Actual absolute persistency

rates over the long term may be considerably higher than those reported in this and other persistency studies.

The current research has both strengths and weaknesses. The large sample afforded by a managed care claims database allows effect sizes to be estimated more precisely.³² In addition, claims data better reflect community

practice than do data from controlled clinical trials, where protocols or clinician monitoring of medication persistency and compliance may reduce the generalizability of results. The potential effect of bias due to differences in copayment levels was evaluated, and no association between copayments and persistency was apparent.

The results may have been biased, however, owing to differences in severity of disease among patients taking different study medications or by the effects of potential confounders, other than sex and age, that could not be controlled.³² Although patients were not required to have a diagnosis of elevated IOP for inclusion, most patients prescribed a topical ocular hypotensive have been found to have a diagnosis of elevated IOP.³³ The use of retrospective claims data also did not allow an assessment of patient or physician reasons for discontinuing or changing therapy while incomplete prescription records or physician dispensing of product samples could have affected results. Factors that can affect compliance or persistency, including cost of therapy, patient understanding of the seriousness of the disease, and the quality of the physician-patient relationship,¹⁵ could not be evaluated. Finally, the design of the present study did not support an evaluation of the effects of persistency on other clinical outcomes or costs although pharmacotherapeutic changes have been associated with increased costs in patients with hypertension³⁴ and with glaucoma.³⁵

This research provides a window into variability in patient persistency with medical therapy, an important issue because physicians frequently see patients who have been prescribed ocular hypotensive therapy but who nevertheless exhibit elevated IOP levels or visual field changes. In these cases, the ophthalmologist must determine whether the prescribed drug is not effective—making more aggressive treatment warranted—or whether the patient is not taking the medication as directed.¹⁵ To minimize instances in which lack of persistency leads to poor clinical outcomes, physicians may wish to use information concerning long-term use, as reflected in prescription refill analyses, when selecting from among pharmacotherapeutic options.

CONCLUSIONS

ALTHOUGH PERSISTENCY RATES WERE LOW ACROSS agents, latanoprost-treated patients demonstrated significantly greater persistency than did patients treated with alternative topical ocular hypotensive therapies. Future trials should evaluate the reasons for such variation and assess the impact of reduced persistency on short-term, targeted IOP control and long-term disease progression.

REFERENCES

1. 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.
2. 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.
3. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2003;121:48–56.
4. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002;120:1268–1279.
5. Schwartz GF. Measuring persistency with drug therapy in glaucoma management. *Am J Manag Care* 2002;8(Suppl):S237–S239.
6. Daily Health Policy Report. Prescription drugs—study looks at effect of cost on California seniors' prescription drug practices (Nov 1, 2002). Available at: http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=3&DR_ID=14385. (Accessed on October 7, 2003).
7. Weinreb RN. Compliance with medical treatment of glaucoma. *J Glaucoma* 1992;1:134–136.
8. Dasgupta S, Oates V, Bookhart BK, Vaziri B, Schwartz GF, Mozaffari E. Population-based persistency rates for topical glaucoma medications measured with pharmacy claims data. *Am J Manag Care* 2002;8(Suppl):S255–S261.
9. Reardon G, Schwartz GF, Mozaffari E. Patient persistency with topical prostaglandin therapy in the management of glaucoma. *Clin Ther* 2003;25:1172–1185.
10. Reardon G, Schwartz GF, Mozaffari E. Patient persistency with pharmacotherapy in the management of glaucoma. *Eur J Ophthalmol* 2003;13(Suppl 4):S44–S53.
11. Shaya FT, Mullins CD, Wong W, Cho J. Discontinuation rates of topical glaucoma medications in a managed care population. *Am J Manag Care* 2002;8(Suppl):S271–S277.
12. Spooner JJ, Bullano MF, Ikeda LI, et al. Rates of discontinuation and change of glaucoma therapy in a managed care setting. *Am J Manag Care* 2002;8(Suppl):S262–S270.
13. Platt R, Reardon G, Mozaffari E. Observed time between prescription refills for newer ocular hypotensive agents: the effect of bottle size. *Am J Ophthalmol* 2004;137(Suppl):S17–S23.
14. Bland JM, Altman DG. Survival probabilities (the Kaplan-Meier method). *BMJ* 1998;371:1572.
15. Bigger JF. A comparison of patient compliance in treated vs untreated ocular hypertension. *Trans Am Acad Ophthalmol Otolaryngol* 1976;81:277–285.
16. Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. *Clin Ther* 1998;20:671–681.
17. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. *Can Med Assoc J* 1999;160:31–37.
18. Degli Esposti E, Sturani A, Di Martino A, et al. Long-term persistence with antihypertensive drugs in new patients. *J Hum Hypertens* 2002;16:439–444.
19. Degli Esposti L, Degli Esposti E, Valpiani G, et al. A retrospective, population-based analysis of persistence with antihypertensive drug therapy in primary care practice in Italy. *Clin Ther* 2002;24:1347–1357.
20. Stewart WC, Day DG, Stewart JA, et al. Therapeutic success of latanoprost 0.005% compared to brimonidine 0.2% in patients with open-angle glaucoma or ocular hypertension. *J Ocul Pharmacol Ther* 2000;16:557–564.
21. Stewart WC, Day DG, Stewart JA, Schuhr J, Latham KE. The efficacy and safety of latanoprost 0.005% once daily

- versus brimonidine 0.2% twice daily in open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2001;131:631–635.
22. Kampik A, Arias-Puente A, O'Brart DPS, Vuori M-L, and the European Latanoprost Study Group. Intraocular pressure-lowering effects of latanoprost and brimonidine therapy in patients with open-angle glaucoma or ocular hypertension: a randomized observer-masked multicenter study. *J Glaucoma* 2002;11:90–96.
 23. O'Donoghue EP and the UK and Ireland Latanoprost Study Group. A comparison of latanoprost and dorzolamide in patients with glaucoma and ocular hypertension: a 3-month, randomised study. *Br J Ophthalmol* 2000;84:579–582.
 24. Alm A, Stjernschantz J, the Scandinavian Latanoprost Study Group. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning: a comparison with timolol. *Ophthalmology* 1995;102:1743–1752.
 25. Camras CB, the United States Latanoprost Study Group. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma. A six-month, masked, multicenter trial in the United States. *Ophthalmology* 1996;103:138–147.
 26. Watson P, Stjernschantz J, the Latanoprost Study Group. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. *Ophthalmology* 1996;103:126–137.
 27. Parrish RK, Palmberg P, Sheu W-P, for the XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator, multicenter study. *Am J Ophthalmol* 2003;135:688–703.
 28. Gandolfi S, Simmons ST, Sturm R, Chen K, VanDenburgh AM, for the Bimatoprost Study Group 3. Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. *Adv Ther* 2001;18:110–121.
 29. Noecker RS, Dirks MS, Choplin NT, et al. A six-month randomized clinical trial comparing the IOP-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. *Am J Ophthalmol* 2003;135:55–63.
 30. Stewart WC, Kolkler AE, Stewart JA, Leech J, Jackson AL. Conjunctival hyperemia in healthy subjects after short-term dosing with latanoprost, bimatoprost, and travoprost. *Am J Ophthalmol* 2003;135:314–320.
 31. Netland PA, Landry T, Sullivan EK, et al. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2001;132:472–484.
 32. Coleman AL, Morgenstern H. Use of insurance claims databases to evaluate the outcomes of ophthalmic surgery. *Surv Ophthalmol* 1997;42:271–278.
 33. Bohn RL, Gurwitz JH, Yeomans SM, et al. Which patients are treated for glaucoma? An observational analysis. *J Glaucoma* 2000;9:38–44.
 34. McCombs JS, Nichol MB, Newman CM, Sclar DA. The costs of interrupting antihypertensive drug therapy in a Medicaid population. *Med Care* 1994;32:214–226.
 35. Rouland J-F, Hågå A, Bengtsson S, Hedman K, Kobelt G. What triggers change of therapy? In: Jonsson B, Krieglstein G, editors. *Primary open-angle glaucoma: differences in international treatment patterns and costs*. Oxford, UK: Isis Medical Media, 1999:163–169.