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Comparative effectiveness of generic latanoprost versus branded prostaglandin analogs for primary open angle glaucoma

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Abstract

Purpose: To determine the comparative effectiveness of generic latanoprost (GL) to its branded (BL) counterpart and other brand-name prostaglandin analogs (bPGAs) in preventing the need for additional therapy in the treatment of primary open angle glaucoma (POAG).

Methods: Retrospective cohort study using U.S. commercial medical claims data. All new POAG patients from 2000–2015 who initiated treatment with either GL or BL were included. Exclusion occurred for having less than 2 years of time in the plan prior to diagnosis, previous use of glaucoma medications or any diagnosis of glaucoma other than POAG at any time. Analyses compared GL to BL and also to those who received any branded PGA after 2011 (when the generic became available). Cox proportional hazard regression was used to assess the hazards of filling a prescription for a second IOP-lowering medication or having surgical intervention, individually and either outcome combined.

Results: 6,317 and 4,150 POAG patients were treated with GL and BL, respectively. After 2010, 6,317 GL and 3,703 bPGA POAG patients met criteria for inclusion. After adjustment, compared to BL, the GL conferred a reduced hazard of having a glaucoma procedure performed (HR=0.72, 95% CI:0.62–0.84, $p<0.001$) and the combined outcome (HR=0.90, 95% CI:0.83–0.97, $p=0.006$), but was not associated with having a second IOP medication (HR=0.95, 95% CI:0.87–1.03,

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Conflicts of Interest:

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p=0.18). Compared to the bPGAs, however, GL conferred a reduced hazard in each comparison (2nd IOP medication HR=0.87, 95% CI: 0.81–0.94, p<0.001; surgery HR=0.70, 95% CI: 0.61–0.81, p<0.001; combined HR=0.85, 95% CI: 0.79–0.92, p<0.001). Sensitivity analyses confirmed these findings.

Conclusions: Generic latanoprost was no less and possibly more effective in preventing the need for additional intervention than branded PGAs.

Keywords

glaucoma; prostaglandin analog; latanoprost; generic

Introduction

Glaucoma is a progressive optic neuropathy and the second leading cause of blindness worldwide. Although the etiology of glaucoma remains poorly understood, numerous studies have shown that intraocular pressure reduction slows the onset and progression of the disease. Glaucoma encompasses a group of diseases with primary open angle glaucoma (POAG) being the second most common cause of blindness in the United States. At the present time, initial intraocular pressure reduction in POAG is typically accomplished through medical therapy.

Prostaglandin analogs (PGAs) are the most common first-line treatment for lowering intraocular pressure in POAG due to their potent ocular hypotensive action, limited systemic side effects and once-daily dosing regimen. Among PGAs, latanoprost is the most frequently prescribed, having both a branded (Xalatan®, Pfizer, New York, NY) and generic versions available. Latanoprost has been shown to be one of the most effective glaucoma medications for IOP reduction.

Since its introduction, generic latanoprost has generated significant research interest, likely in part due to its savings of nearly \$50 per month over its branded PGA counterparts. Studies have included evaluations of dose equivalency and the number of drops offered by each formulation. Additionally, the reduced cost of generic latanoprost has been associated with an improved rate of medication adherence. Despite these advantages, several small clinical studies have suggested that generic latanoprost has less IOP reduction potential than the branded medication. Contradicting these reports, however, are other studies that have shown no difference in efficacy between the two formulations. All of these reports, however, have almost uniformly been limited by short follow up (<3 months) and small sample sizes (<35 patients).

Given the considerable financial difference between generic and branded PGAs and the progressive aging of the population, a dramatic increase in usage of the generic form is likely to occur over the coming years. It is important that additional evidence be gathered to inform this decision. The lower cost and subsequent lower profit margin of generic latanoprost make it unlikely a generic pharmaceutical company will ever fund a large scale randomized trial to assess its efficacy. The only alternative is to assess its efficacy through observational data, despite the concerns over unmeasured confounding this method confers.

Fortunately, epidemiologists have developed tools to reduce bias and confounding in these situations. Using techniques inspired by these methods, this study aims to examine the relative comparative effectiveness of generic latanoprost versus its branded counterparts.

Methods

Database

Retrospective cohort studies were performed using administrative medical claims and prescription claims data from the Clinformatics™ Data Mart Database (OptumInsight, Eden Prairie, MN), which derives its data from a large, national U.S. insurer. The data used for this project encompassed the time period from January 1st, 2000 through September 30th, 2015. Due to the de-identified nature of the data, The University of Pennsylvania's Institutional Review Board deemed this study exempt from review.

Cohorts

Patients who received a new ICD9 code for POAG and filled a prescription within 30 days of diagnosis for either one of the generic or branded PGAs, were included. (Please see Supplemental Table 1 for full list of ICD9 and CPT codes used during this study). The date of incident POAG diagnosis was considered the index date. Patients were excluded for having less than two consecutive years of time in the plan prior to diagnosis, any use of glaucoma medication prior to the index date, or any other form of glaucoma diagnosis before or after the index date. The initial analysis strictly compared generic latanoprost to only its direct branded equivalent (Xalatan). The secondary analyses expanded PGA cohort to include all new POAG patients started on branded PGAs (latanoprost, bimatoprost, latanoprost, tafluprost, and travoprost) after January 1st, 2011. Any patient who filled a prescription for more than one type of IOP medication on the index date, was excluded.

Effectiveness Studies

To investigate the comparative effectiveness of generic latanoprost, numerous analyses were conducted, each with unique criteria as noted here. The primary analysis was analogous to an "intention-to-treat" study: any newly diagnosed POAG patient initiated on generic or branded latanoprost was included, regardless of the duration of the patient's medication use post-diagnosis. A sensitivity analysis was also performed in which both generic and branded users were required to have 120 days of prescription medication coverage during the first 180 days after the date of diagnosis. Next, due to potential imbalances in baseline characteristics (age, sex, race, *etc.*) between generic latanoprost and branded users, a sensitivity analysis was performed using cohorts created from a 1:1 matched propensity score based on each patient's propensity for initiating branded latanoprost (vs. the generic form) at the index date.

Finally, after observing the data for these studies, it was noted that once the generic latanoprost was released to the market (2011), very few patients were initiated on the branded form of latanoprost. To better address differences in POAG care that might have occurred over the total 16-year observation period, each of the above outlined analyses were repeated for a restricted cohort that included only patients diagnosed after January 1st, 2011

and the branded group was expanded to include users of all possible branded PGAs. Lastly, to reduce the concern that physicians could “pick and choose” by giving one version of the medication to one type of patient and the other to healthier (or sicker) patients, an analysis was run in which patients were only included if their physician had prescribed only one category of medication or the other at least 80% of the time. We called this analysis the physician preference analysis. Again, due to physicians not having a choice other than branded latanoprost prior to 2011, this analysis was only run on the latanoprost vs. all branded PGA cohorts. We could not conduct an instrumental variable analysis using the physician as the instrumental variable due to the fact it would have created collinearity with each of drug covariates and potentially induced bias. In total, seven different analyses were run.

Outcomes of Interest

Three main outcomes of interest were measured as indicators of clinical efficacy. The first outcome measured was the initiation of a second IOP-lowering medication, defined as filling a prescription for a second class of IOP-lowering medication after the index date. The second outcome was having a surgical intervention, defined as having a claim for a glaucoma laser or other surgical procedure after the index date. Lastly, a combined outcome was created and considered to have occurred if either of the above outcomes happened. Covariates of interest included age, gender, race, education level, yearly income, history of diabetes, region of the country and, as a potential surrogate marker for severity of glaucoma at the time of index, the number of Humphrey visual fields (HVF) performed on the patient in the two years preceding the index date (i.e. someone with numerous HVFs prior to diagnosis, likely had less obvious/severe glaucoma at the time of initial diagnosis). Lastly, in all of the generic latanoprost vs. all branded PGA analyses, the year the patient was diagnosed was also included. This was not done for the generic vs. branded latanoprost analyses because of collinearity between drug group and cohort years.

Statistical Analysis

Cox proportional hazard models were used to calculate crude and covariate-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for comparing medication and procedure outcomes in the generic and branded drug cohorts. Censoring occurred if the patient was outcome event-free for two years post-index date, if the patient left the insurance plan, or if a prescription for the comparison cohort of medication was given. For the analysis that required the 120-day coverage, the patient was censored at anytime after the index date, even if an event occurred prior to the date the 120-day coverage mandate was filled. The proportional hazards assumption was tested for each variable and found to not be violated. Due to the numerous statistical comparisons made, a Bonferroni correction was applied lowering the level required to meet statistical significance to $p < 0.007$ (not $p < 0.05$). Statistical analysis was performed using SAS (version 9.4; SAS Institute Inc., Cary, NC).

Results

Generic vs. Branded Latanoprost

In the primary analysis of generic latanoprost versus the branded medication a total of 10,467 patients met inclusion/exclusion criteria with 6,317 in the generic group and 4,150 in the branded group (Figure 1). Baseline characteristics between the two cohorts differed significantly in all covariates except gender (Table 2). Among patients in the generic group, 1658 (26.2%) had a second class of IOP-lowering medication filled, 435(6.9%) had a glaucoma procedure and 1,847(29.2%) had one of the combined outcomes. The branded cohort had 1,095(26.4%) patients receiving a second IOP-lowering medication, 361(8.7%) had a glaucoma procedure and 1,272(30.7%) had one of the combined outcomes.

Univariate Cox proportional hazards analysis (HR < 1 meaning outcomes were better in the generic group) revealed no differences in the hazard of requiring a second IOP-lowering medication(HR=0.99, 95% CI:0.91–1.06, p=0.72) or the combined outcome(HR=0.94, 95% CI:0.87–1.01, p=0.08), but generic latanoprost had a lower hazard for a glaucoma procedure(HR=0.78, 95% CI:0.68–0.90, p<0.001)(Table 4). After controlling for baseline covariates, the generic cohort was not associated with having a second IOP-lowering medication (HR=0.95, 95% CI: 0.87–1.03, p=0.18) or having the combined outcome(HR=0.90, 95% CI:0.83–0.97, p=0.006), but had a 28% decreased hazard of having a glaucoma procedure performed compared to the branded cohort (HR=0.72, 95% CI:0.62–0.84, p<0.001)(Table 5).

Our first sensitivity analysis examined only patients that met a prescription drug coverage criterion of 120 days coverage out of the initial 180 days after the index date. This reduced the cohort sizes to 2,965 in the generic group and 1,171 in the branded group(Table 4). None of the outcomes were associated with a difference in hazard (2nd IOP med: HR=1.02, 95% CI:0.89–1.17, p=0.77; glaucoma procedure: HR=0.74, 95%CI:0.57–0.95, p=0.02; combined outcome: HR=0.96, 95% CI:0.84–1.09, p=0.53)(Table 5).

Matched propensity score analysis limited each cohort to 3,274 individuals, but balanced all baseline covariates much better than in the primary analysis(Table 3). The multivariate analyses also found no differences in the hazards between the generic and branded cohorts for any of the outcomes (2nd IOP med: HR=0.94, 95% CI:0.86–1.04, p=0.22; glaucoma procedure: HR=0.83, 95% CI:0.71–0.99, p=0.03; combined outcome: HR=0.92, 95% CI: 0.84–1.00, p=0.06)(Table 5).

Generic Latanoprost vs. All Branded PGAs

In our second set of analyses (Figure 1), the generic latanoprost cohort was unchanged in totals or numbers of outcomes (all patients already occurred after 2010). The branded PGAs cohort had 3,703 patients in our primary, intention-to-treat analysis. Of these, 1,077(29.1%) started a second IOP-lowering medication, 364(9.8%) had a glaucoma procedure and 1,228(33.2%) had one of the combined outcomes. In this analysis, the baseline covariates were significantly different by age, race, yearly income, number of HVFs, geographic location and index year (p<0.05 for all comparisons)(Table 2).

After adjusting for covariates, cox proportional hazard analysis revealed that generic latanoprost users had decreased hazard of requiring a second IOP-lowering medication (HR=0.87, 95% CI:0.81–0.94, $p<0.001$), having a glaucoma procedure (HR=0.70, 95% CI: 0.61–0.81, $p<0.001$) and the combined outcome (HR=0.85, 95% CI:0.79–0.92, $p<0.001$) as compared to the branded group (Table 5).

The analysis mandating 120-day coverage of medication reduced the cohorts to 2,965 generic latanoprost patients and 1,164 branded PGA patients (Table 4). Again, the risk of outcomes for those using the generic form was lower for each comparison (second IOP med: HR=0.81, 95% CI: 0.71–0.92, $p<0.001$ and combined outcome: HR=0.80, 95% CI:0.71–0.90, $p<0.001$), but did not meet significance for in procedure comparison (HR=0.74, 95% CI: 0.59–0.94, $p=0.01$). The propensity score multivariate analysis demonstrated similar results in that generic latanoprost was associated with reduced hazard of filling a secondary IOP-lowering medication (HR=0.89, 95% CI: 0.81–0.97, $p<0.001$), having a glaucoma procedure (HR=0.70, 95% CI: 0.59–0.82, $p<0.001$) and the combined outcome (HR=0.86, 95% CI:0.79–0.94, $p<0.001$) (Table 5). The physician preference analysis that removed all patients who were not treated by a doctor who gave at least 80% of their patients one category of medication or the other had 5,495 patients in the generic latanoprost cohort and 2,987 in the all branded PGA cohort. Again, the generic cohort was favored in all comparisons (2nd IOP med: HR=0.87, 95% CI: 0.80–0.95, $p<0.001$; glaucoma procedure: HR=0.72, 95% CI:0.61–0.83, $p=0.002$; combined outcome: HR=0.85, 95% CI:0.79–0.93, $p<0.001$) (Table 5).

Discussion

For new drug approval, the FDA requires phase three clinical trials to test clinical efficacy within the context of highly specific patient populations under ideal settings. Although this is the standard for branded medications, generic versions of drugs do not require the same rigorous clinical trials for FDA approval. Instead, the generic version is approved after it is demonstrated to have similar chemical bioavailability to its branded counterpart. Thus, questions into the real clinical effectiveness (defined as patients in a real-world setting, as compared to clinical efficacy which is defined by a clinical trial setting) of latanoprost have considerable relevance to the treatment of POAG.

Our study offers effectiveness markers that are different from most glaucoma trials which typically focus solely on IOP reduction. We used prescription of a second pressure lowering medication and performance of laser or surgical interventions as clinically relevant indicators that the initially prescribed medication was not providing sufficient control of IOP. The decision to add a medication or to undertake surgery is based not only on observed reduction in IOP, but also on stability or progression of disease as evidenced by visual field loss, thinning of the retinal nerve fiber layer, or increasing cup-to-disc ratio. These actions reflect a more comprehensive assessment of the effectiveness of the initial medication in preventing disease progression.

Our findings show that generic latanoprost was no worse than its branded counterpart in any of the analyses performed. Compared to the broader group of all branded PGAs, the results

in favor of generic latanoprost were even more striking, with significantly reduced hazards seen in each of the three measured outcomes for generic latanoprost. These results were consistent over multiple iterations of sensitivity testing, and no evidence was found to suggest that generic latanoprost was less effective than branded PGAs. Several of our analyses would have been significant under conventional significance standards, however, due to the large number of analyses performed, we were concerned about committing a type I (or alpha) error. To address this, a Bonferroni correction was applied, reducing the p-value that can be considered significant to $P < 0.007$.

Comparative effectiveness studies using observational data such as this have long had to deal with unmeasured confounding. Numerous methods have been developed specially to address this issue, two of which inspired analyses in this study. Propensity scores are used as a way to better equalize baseline covariates throughout the cohorts, as evidenced when contrasting Table 2 and Table 3. After propensity score matching, nearly all differences in baseline covariates were resolved. In our study, controlling for the “type” (generic vs. branded) of physician would be one way of using an instrumental variable. We attempted to do this but were unable to due to strong overlap and collinearity between the physician and drug groups (as noted in Table 4, few patients were lost in the physician preference analysis). In an instrumental analysis, a variable is chosen that in theory should only have a direct effect on the independent variable being studied. If the instrumental variable also has an association with the dependent variable, then unmeasured confounding exists in the study that should be addressed. Since we could not perform an instrumental variable analysis, instead, we chose to remove those patients who were treated by a physician who did not use one medication over the other at least 80% of the time. In this manner, the physician preference analysis should reduce the effect of physicians picking and choosing which patients should receive which medication and its impact outcomes. One of the most significant potential critiques this study would be that generic latanoprost appeared better because physicians would save the “more effective” branded-medication for sicker patients, causing the branded version to perform worse. Seeing that the results were essentially unchanged in this analysis, eases this concern, and further supports the argument that for most physicians, initial treatment preference depends less on patient risk factors (i.e. disease severity) and more on their own preferences and health care system characteristics.

One interpretation of our results would be that the generic form is a “better” drug. In this comparison, we do not believe this to be the case. For one, multiple formulations of the generic version comprised the generic cohort. It would seem unlikely that several companies independently identified a “better” version of latanoprost and improved its clinical efficacy over all other branded PGAs. Instead, it is more likely factors ancillary to the clinical efficacy of the branded PGAs impacted their clinical effectiveness and may have led to our findings. One recent study showed that users of generic latanoprost are 25% more adherent to regular medication regimen, likely due in large part to affordability. Our sensitivity analysis mandating 120-day medication coverage may have partially addressed this issue, however, it is also possible that 120-day coverage out of 180 days (or medication usage only two out of every three days) may not have been strict enough to identify those truly adherent from those that were not. Nor would it have identified those patients that became non-adherent after the first 180 days.

An additional explanation for our results may be related to relative differences in patient tolerability between PGAs. One study showed that corneal toxicity was a much larger issue with the branded latanoprost compared to generic, due to its use of 0.02% benzalkonium chloride preservative. This may in part explain our findings of the generic to have a decreased hazard for receiving a second class of IOP medication. One limitation in this outcome measurement is that those patients that switched to a second class of IOP-lowering medication may have done so as a replacement of a PGA for tolerability purposes, and not as a true “failure” to reach a target IOP goal. Despite this possibility, it should also be noted that this issue would not have impacted the need for procedural outcome results. Any decrease in use due to intolerance, financial reasons, or both, could cause patients to use branded medications less often and would make the generic more clinically effective.

A final possible explanation may reside within differences between the physicians themselves. The decision to add a second IOP-lowering medication or proceed with laser or surgery was based solely on physician judgment, creating the potential for different standards for the different forms of the medications. This could have impacted the results through several avenues. The first is that physicians could have been biased against the effectiveness of the branded PGAs, which seems unlikely. A second avenue would be for physicians who use branded medications to collectively treat disease more aggressively. Unfortunately, no evidence to support (or refute) this theory currently exists in the literature, as no studies to the authors’ knowledge have assessed a physician’s overall therapeutic aggressiveness and compared it to the likelihood they would prescribe a branded medication over a generic. While the authors believe the results are more easily explained as the manifestation of the differential in adherence noted above, we cannot exclude this possibility.

An important subset of this theory would also argue physician-related financial considerations can be used to explain our results. Again, while possible, a couple of additional assertions would need to be true for this to have affected the study. One, that physicians who prescribed branded medications also perform more surgeries, and two, given the hundreds of providers who contributed data to this study, a significant proportion of our profession, not just one or two, would need to prioritize their own financial benefit of performing surgery. Currently no evidence exists in the literature to support either assertion, nor is there a financial incentive that would explain the difference in prescribing a second medication, but we also cannot rule out this possibility that these issues impacted our study either.

The current literature contrasting the IOP-lowering effect of branded versus generic latanoprost is quite mixed. Several studies have shown no significant difference between the IOP effects of the two versions of latanoprost,²⁷ while others observed greater IOP-lowering efficacy with branded latanoprost (typically in the range of 1mmHG).²⁸ In comparison to our results, these studies were limited by small sample sizes, short follow-up time and in some cases, both. Of these studies, the largest only had 35 patients, and the longest only followed patients for three months, which may not have been long enough to account for financial differences or gradual patient intolerance due to symptomatic eye irritation.

Other limitations to our study need to be noted when evaluating our results. First, this study is based on administrative claims billing data, and therefore does not have access to chart level data like IOP measurement or visual field loss. Differences in disease severity may thus exist between the cohorts that may not have been fully accounted for in the analysis. Furthermore, despite the creation of ICD9 codes for glaucoma severity in October 2011, these codes were used sparingly between October 2011 and October 2015 (when ICD10 was introduced) with less than 5% of our included patients being assigned one of these severity codes, preventing its usefulness in any type of modeling. Similarly, we were unable to directly measure disease progression via field loss or lack of IOP response to medication. Instead we defined outcomes within the framework of the available data that only allowed for indirect measures of effectiveness. Despite this, our rate of outcomes were consistent with a 2010 randomized trial that directly measured IOP and found 33–35% of branded latanoprost patients needed additional treatment at 24 months (compared to 28.6–32.9% of branded PGA patients in our studies).

Lastly, we attempted to control for differences in treatment thresholds that may have changed over the course of the study by controlling for year of diagnosis where statistically possible. In the generic versus branded latanoprost analysis, this was not possible as it would have introduced collinearity issues with the drug cohorts since the variables would have had near perfect overlap. This allows for the possibility that treatment decisions over time could have impacted the results, especially in the generic vs. branded latanoprost study.

Our study suggests that generic latanoprost is no less effective in preventing the need for a second IOP-lowering medication or procedural intervention than its branded counterparts. Given the low profit margin and the US Food and Drug Administration's mere bioequivalence mandate for approval of generic medications, it is unlikely a generic form of medication will ever be tested in formal large randomized clinical trials. Well-designed retrospective studies performed on secondary data can aid in better understanding the utility of generic medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Number of patients included/excluded for each criteria used to create the primary cohorts:

Table 2:

Baseline demographic information for “intention-to-treat” analysis in A) generic v. the branded form of latanoprost and B) generic latanoprost v. all branded PGAs in POAG patients initiated on treatment after 2010:

		A. Generic v. Branded Latanoprost			B. Generic Latanoprost v. All PGAs		
Characteristic		Generic (n = 6317)	Branded (n = 4150)	P-value	Generic (n = 6317)	All PGAs (n = 3703)	P-value
Age	Mean age in years (SD)	68.8 (12.6)	62.3 (12.8)	<0.001	68.8 (12.6)	67.6 (13.3)	<0.001
Gender	Female	3256 (51.4%)	2113 (50.9%)	0.42	3256 (51.4%)	1831 (49.4%)	0.08
Race	White	3962 (62.7%)	2636 (63.5%)	<0.001	3962 (62.7%)	2214 (59.8%)	0.004
	Asian	276 (4.4%)	155 (3.7%)		276 (4.4%)	138 (3.7%)	
	Black	1118 (17.7%)	681 (16.4%)		1118 (17.7%)	744 (20.1%)	
	Hispanic	634 (10.0%)	353 (8.5%)		634 (10.0%)	412 (11.1%)	
	Unknown	327 (5.2%)	325 (7.8%)		327 (5.2%)	195 (5.3%)	
Education	High School or Less	2207 (34.9%)	1275 (30.7%)	<0.001	2207 (34.9%)	1314 (35.5%)	0.81
	<Bach Degree	3181 (50.4%)	2027 (48.8%)		3181 (50.4%)	1833 (49.5%)	
	Bach Degree +	753 (11.9%)	655 (15.8%)		753 (11.9%)	458 (12.4%)	
	Unknown	176 (2.8%)	193 (4.7%)		176 (2.8%)	98 (2.6%)	
Net Worth	<\$40K	1965 (31.1%)	719 (17.3%)	<0.001	1965 (31.1%)	1080 (29.2%)	0.049
	\$40K–\$49K	534 (8.5%)	213 (5.1%)		534 (8.5%)	318 (8.6%)	
	\$50K–\$59K	498 (7.9%)	233 (5.6%)		498 (7.9%)	286 (7.7%)	
	\$60K–\$74K	610 (9.7%)	265 (6.4%)		610 (9.7%)	341 (9.2%)	
	\$75K–\$99K	710 (11.2%)	371 (8.9%)		710 (11.2%)	438 (11.8%)	
	\$100K+	1195 (18.9%)	846 (20.4%)		1195 (18.9%)	794 (21.4%)	
	Unknown	805 (12.7%)	1503 (36.2%)		805 (12.7%)	446 (12.0%)	
Diabetes	Yes	2313 (36.6%)	1099 (26.5%)	<0.001	2313 (36.6%)	1294 (34.9%)	0.09
Number of HVF	0	2720 (43.1%)	1678 (40.4%)	0.03	2720 (43.1%)	1460 (39.4%)	0.002
	1	3084 (48.8%)	2112 (50.9%)		3084 (48.8%)	1919 (51.8%)	
	2	513 (8.1%)	360 (8.7%)		513 (8.1%)	324 (8.7%)	
Geo-graphic Region	New England	242 (3.8%)	121 (2.9%)	<0.001	242 (3.8%)	130 (3.5%)	<0.001
	North Central	1300 (20.6%)	953 (23.0%)		1300 (20.6%)	614 (16.6%)	
	South Central	1046 (16.6%)	880 (21.2%)		1046 (16.6%)	691 (18.7%)	
	Mid-Atlantic	431 (6.8%)	287 (6.9%)		431 (6.8%)	306 (8.3%)	
	Mountain	582 (9.2%)	200 (4.8%)		582 (9.2%)	382 (10.3%)	
	Pacific	1012 (16.0%)	445 (10.7%)		1012 (16.0%)	492 (13.3%)	
	South Atlantic	1661 (26.3%)	1245 (30.0%)		1661 (26.3%)	1074 (29.0%)	
	Unknown	43 (0.7%)	19 (0.5%)		43 (0.7%)	14 (0.4%)	
Diagnosis Year	2002	0	153 (3.7%)	<0.001	0	0	<0.001
	2003	0	346 (8.3%)		0	0	
	2004	0	405 (9.8%)		0	0	

		A. Generic v. Branded Latanoprost			B. Generic Latanoprost v. All PGAs		
Characteristic		Generic (n = 6317)	Branded (n = 4150)	P-value	Generic (n = 6317)	All PGAs (n = 3703)	P-value
	2005	0	753 (18.1%)		0	0	
	2006	0	571 (13.8%)		0	0	
	2007	0	474 (11.4%)		0	0	
	2008	0	494 (11.9%)		0	0	
	2009	0	472 (11.4%)		0	0	
	2010	0	368 (8.9%)		0	0	
	2011	684 (10.8%)	90 (2.2%)		684 (10.8%)	817 (22.1%)	
	2012	1251 (19.8%)	11 (0.3%)		1251 (19.8%)	748 (20.2%)	
	2013	1496 (23.7%)	6 (0.1%)		1496 (23.7%)	894 (24.1%)	
	2014	1607 (25.4%)	5 (0.1%)		1607 (25.4%)	742 (20.0%)	
	2015	1279 (20.2%)	2 (0.0%)		1279 (20.2%)	502 (20.2%)	

Table 3:

Baseline demographic information after propensity score matching:

		A. Generic v. Branded Latanoprost			B. Generic Latanoprost v. All PGAs		
Characteristic		Generic (n = 3243)	Branded (n = 3243)	P-value	Generic (n = 3702)	All PGAs (n = 3702)	P-value
Age	Mean age in years (SD)	64.1 (13.0)	63.4 (12.6)	0.03	67.7 (13.4)	67.6 (13.3)	0.70
Gender	Female	1671 (51.5%)	1653 (51.0%)	0.65	1827 (49.4%)	1831 (49.5%)	0.93
Race	White	2076 (64.0%)	2063 (63.6%)	0.79	2210 (59.7%)	2214 (59.8%)	0.60
	Asian	121 (3.7%)	140 (4.3%)		135 (3.6%)	137 (3.7%)	
	Black	567 (17.5%)	560 (17.3%)		789 (21.3%)	744 (20.1%)	
	Hispanic	272 (8.4%)	280 (8.6%)		391 (10.6%)	412 (11.1%)	
	Unknown	207 (6.4%)	200 (6.2%)		177 (4.8%)	195 (5.3%)	
Education	High School or Less	1015 (31.3%)	974 (30.1%)	0.64	1335 (36.1%)	1314 (35.5%)	0.82
	<Bachelor Degree	990 (30.5%)	956 (29.5%)		1843 (49.8%)	1833 (49.5%)	
	Bachelor Degree +	1625 (50.1%)	1655 (51.0%)		439 (11.9%)	457 (12.3%)	
	Unknown	477 (14.7%)	495 (15.3%)		85 (2.3%)	98 (2.6%)	
Net Worth	<\$40K	740 (22.8%)	715 (22.0%)	0.42	1103 (29.8%)	1080 (29.2%)	0.99
	\$40K–\$49K	210 (6.5%)	213 (6.6%)		324 (8.8%)	318 (8.6%)	
	\$50K–\$59K	221 (6.8%)	231 (7.1%)		290 (7.8%)	286 (7.7%)	
	\$60K–\$74K	271 (8.4%)	264 (8.1%)		341 (9.2%)	341 (9.2%)	
	\$75K–\$99K	369 (11.4%)	369 (11.4%)		422 (11.4%)	438 (11.8%)	
	\$100K+	768 (23.7%)	839 (25.9%)		787 (21.3%)	793 (21.4%)	
	Unknown	664 (20.5%)	612 (18.9%)		435 (11.8%)	446 (12.0%)	
Diabetes	Yes	948 (29.2%)	931 (28.7%)	0.64	1292 (34.9%)	1294 (35.0%)	0.96
Number of HVF	0	1308 (40.3%)	1309 (40.4%)	0.63	1471 (39.7%)	1459 (39.4%)	0.85
	1	1650 (50.9%)	1670 (51.5%)		1920 (51.9%)	1919 (51.8%)	
	2	285 (8.8%)	264 (8.1%)		311 (8.4%)	324 (8.8%)	
Geo-graphic Region	New England	96 (3.0%)	100 (3.1%)	0.95	128 (3.5%)	130 (3.5%)	0.98
	North Central	726 (22.4%)	695 (21.4%)		640 (17.3%)	614 (16.6%)	
	South Central	661 (20.4%)	672 (20.7%)		676 (18.3%)	691 (18.7%)	
	Mid-Atlantic	205 (6.3%)	221 (6.8%)		305 (8.2%)	306 (8.3%)	
	Mountain	178 (5.5%)	179 (5.5%)		364 (9.8%)	382 (10.3%)	
	Pacific	388 (12.0%)	375 (11.6%)		482 (13.0%)	492 (13.3%)	
	South Atlantic	974 (30.0%)	982 (30.3%)		1093 (29.5%)	1073 (29.0%)	
	Unknown	15 (0.5%)	19 (0.6%)		14 (0.4%)	14 (0.4%)	

Table 4:

Event rates and unadjusted hazard ratios for all analyses

		A. Generic v. Branded				B. Generic v. All PGAs					
		Generic	Branded	Hazard Ratio	95% CI	P-Value	Generic	All PGAs	Hazard Ratio	95% CI	P-Value
"Intention-to-treat" Analysis											
n	6317	4150*					6317	3703*			
2nd IOP Medication	1658 (26.2%)	1095 (26.4%)	0.99	(0.95, 1.18)	0.72	1658 (26.2%)	1077 (29.1%)	0.88	(0.79, 0.91)	<0.001	
Surgical Intervention	435 (6.9%)	361 (8.7%)	0.78	(0.68, 1.06)	<0.001	435 (6.9%)	364 (9.8%)	0.69	(0.60, 0.79)	<0.001	
Any Outcome Event	1847 (29.2%)	1272 (30.7%)	0.94	(0.87, 1.01)	0.08	1847 (29.2%)	1228 (33.2%)	0.85	(0.79, 0.91)	<0.001	
120-day Prescription Coverage Mandate Analysis											
n	2965	1171*					2965	1164*			
2nd IOP Medication	826 (27.9%)	314 (26.8%)	1.05	(0.92, 1.19)	0.50	826 (27.9%)	376 (32.3%)	0.83	(0.73, 0.94)	0.003	
Surgical Intervention	205 (6.9%)	103 (8.8%)	0.79	(0.62, 1.00)	0.05	205 (6.9%)	109 (9.4%)	0.72	(0.57, 0.91)	0.006	
Any Outcome Event	907 (30.6%)	362 (30.9%)	0.99	(0.88, 1.12)	0.88	907 (30.6%)	418 (35.9%)	0.81	(0.72, 0.91)	<0.001	
Propensity Score Matched Analysis											
n	3243	3243*					3702	3702*			
2nd IOP Medication	811 (25.0%)	877 (27.0%)	0.94	(0.85, 1.03)	0.21	948 (25.6%)	1076 (29.1%)	0.86	(0.79, 0.94)	<0.001	
Surgical Intervention	209 (6.4%)	299 (9.2%)	0.72	(0.60, 0.86)	0.01	263 (7.1%)	363 (9.8%)	0.71	(0.61, 0.84)	<0.001	
Any Outcome Event	903 (27.8%)	1019 (31.4%)	0.89	(0.82, 0.98)	0.01	1061 (28.7%)	1227 (33.1%)	0.84	(0.77, 0.91)	<0.001	
Physician Preference Analysis											
					n		5495	2987*			
					2nd IOP Medication		1460 (26.6%)	869 (29.1%)	0.89	(0.81, 0.96)	0.005
					Surgical Intervention		385 (7.0%)	296 (9.9%)	0.69	(0.59, 0.80)	<0.001
					Any Outcome Event		1630 (29.7%)	993 (33.2%)	0.86	(0.79, 0.93)	<0.001

Table 5:

Adjusted hazard ratios for all analyses after controlling for age, gender, race, education level, net-worth, diabetes, number of HVE, geographic region of the country and for the Generic vs. All PGA analyses, the year of diagnosis.

	Generic v. Branded			Generic v. All PGAs		
	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value
“Intention-to-treat” Analysis						
2nd IOP Medication	0.95	(0.87, 1.03)	0.18	0.87	(0.81, 0.94)	<0.001
Surgical Intervention	0.72	(0.62, 0.84)	<0.001	0.70	(0.61, 0.81)	<0.001
Any Outcome Event	0.90	(0.83, 0.97)	0.006	0.85	(0.79, 0.92)	<0.001
120-day Prescription Coverage Mandate Analysis						
2nd IOP Medication	1.02	(0.89, 1.17)	0.77	0.81	(0.71, 0.90)	<0.001
Surgical Intervention	0.74	(0.57, 0.95)	0.02	0.74	(0.59, 0.92)	0.01
Any Outcome Event	0.96	(0.84, 1.09)	0.53	0.80	(0.71, 0.90)	<0.001
Propensity Score Matched Analysis						
2nd IOP Medication	0.94	(0.86, 1.04)	0.22	0.89	(0.81, 0.97)	0.007
Surgical Intervention	0.83	(0.71, 0.99)	0.03	0.70	(0.59, 0.82)	<0.001
Any Outcome Event	0.92	(0.84, 1.00)	0.06	0.86	(0.79, 0.94)	<0.001
Physician Preference Analysis						
			2nd IOP Medication	0.87	(0.80, 0.95)	<0.001
			Surgical Intervention	0.72	(0.61, 0.83)	0.002
			Any Outcome Event	0.85	(0.79, 0.93)	<0.001