Intraocular Pressure Following Prerandomization Glaucoma Medication Washout in the HORIZON and COMPASS Trials

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• PURPOSE: To assess the effectiveness of topical ocular hypotensive medications in patients with open-angle glaucoma and to identify factors associated with postwashout intraocular pressure (IOP) elevation.

• DESIGN: Secondary analysis of prerandomization data from 2 prospective, multicenter, randomized clinical trials.

• METHODS: Fourteen hundred subjects (1,400 eyes, 781 from the HORIZON study of the Hydrus micro-stent and 619 from the COMPASS study of the Cypass micro-stent) with primary open-angle glaucoma who were using 0-4 classes of topical IOP-lowering medication underwent Goldmann applanation tonometry before and after a protocol-defined washout period.

• RESULTS: The mean (standard deviation) age was 70.7 (8.0) years and 55.6% were female. The change in IOP following washout for patients using 0 (n = 100), 1 (n = 705), 2 (n = 355), 3 (n = 214), or 4 (n = 26) medications was 0.2 (2.8), 5.7 (3.3), 6.9 (3.7), 8.8 (5.0), and 9.5 (4.1) mm Hg, respectively ($P < .001$, Kruskal-Wallis test). Postwashout IOP change was similar between the HORIZON and COMPASS cohorts. No difference in postwashout IOP change was detected among individual prostaglandin analogues in patients on monotherapy. A generalized linear model identified the following factors to be associated with greater IOP rise upon medication washout: greater number of glaucoma medications, higher unmedicated IOP, thinner central corneal thickness (CCT), lack of prior selective laser trabeculoplasty (SLT), and male sex.

• CONCLUSIONS: Cessation of glaucoma medications results in a dose-dependent IOP increase in treated open-angle glaucoma patients. Two independent clinical trial cohorts exhibit similar levels of IOP elevation upon washout, using standardized methodology to estimate real-world medication effectiveness. Thicker CCT and history of SLT may predict reduced response to IOP lowering medications. (Am J Ophthalmol 2020;216: 110–120. © 2020 Elsevier Inc. All rights reserved.)

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INTRAOCULAR PRESSURE (IOP) REDUCTION ATTENUATES glaucoma progression at all disease stages.[1–4] Despite the continual advent of new laser and surgical procedures, ocular hypotensive eye drops remain the mainstay of initial IOP-lowering therapy for most forms of glaucoma.[5–7] Physicians managing glaucoma make treatment decisions based on data comparing the relative IOP-lowering effects of various therapeutic options, including the relative potency of drug classes or different medications within a class, and the additive effects of multiple drops. Data describing glaucoma medication efficacy are primarily derived from controlled clinical trials, or meta-analyses of such trials, in which subjects are prospectively randomized to different IOP-lowering eye drops or placebo.[5,8,9]

A fundamental limitation of prospective clinical trial study designs of glaucoma medications is overestimation of drug effectiveness owing to the Hawthorn effect, in which subject behavior is altered by knowledge that he or she is being observed.[10] Moreover, clinical research subjects are incentivized and reminded to use their medication over a limited time period. Therefore, medication adherence may be particularly important in explaining lower real-world effectiveness of eye drop self-administration as compared to ideal-world efficacy. Studies of insurance and/or pharmacy claims databases have established that adherence to glaucoma eye drops is poor in real-world settings,[11–18] though prospective clinical studies[19,20] and randomized trials[21] also are subject to medication adherence deficits. A second limitation of existing data is the tendency to compare monotherapy regiments in pairwise comparison to each other or placebo. In reality, many patients under clinical care are prescribed more than 1 eye drop for lowering IOP. For instance, almost 40% of subjects in the Ocular Hypertension Treatment Study required 2 or more medicines at 5 years to achieve the study-mandated IOP reduction of 20%.[4] Nonetheless, only a few studies provide data regarding the additional IOP lowering that is conferred by adding medications to an existing glaucoma drop regimen, and most that do are retrospective and hence subject to inherent bias, or are designed to study specifically fixed-combination formulations.[22–27]

To better understand the real-world effectiveness of IOP-lowering medications, data from alternative study designs are desirable. Previously, we assessed IOP elevation

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following medication washout as a surrogate measure of IOP-lowering effect by analyzing IOP measurements from the prerandomization phase of a glaucoma surgical clinical trial.[28] The IOP during treatment was ascertained prior to formal study enrollment and therefore better reflected the real-world treatment scenario and adherence behavior than might occur in a prospective clinical trial. IOP measurement after study enrollment occurred following medication washout and so adherence was no longer a consideration. This approach in our previous work provided data regarding the stepwise increase in IOP reduction attained by adding glaucoma drops, but the limited sample size precluded within-class and between-class drug comparisons. It also remained unclear the extent to which the results were specific to the clinical trial cohort (the COMPASS trial) from which those data were drawn. In this current investigation, we have more than doubled the sample size by including data from a separate though similarly designed clinical trial (the HORIZON trial). We have replicated the major findings in an independent cohort and conducted additional analyses at a more granular level of detail, especially with regard to patients on medical monotherapy. We also provide histograms for IOP change following medication washout for a large cohort of patients with ocular hypertensive primary open-angle glaucoma, which will be valuable for planning future trials.

METHODS

PRERANDOMIZATION DATA WERE ANALYZED FROM 2 PROspective, single-masked, randomized controlled clinical trials designed to evaluate the safety and efficacy of microinvasive glaucoma surgery at the time of cataract surgery. The HORIZON trial (NCT01539239) screened 1143 subjects for eligibility and randomized 556 to cataract extraction alone vs cataract extraction with Hydrus microstent implantation into the Schlemm canal.[29] The COMPASS trial (NCT01085357) screened 897 subjects for eligibly and randomized 505 to cataract extraction alone vs cataract extraction with Cypass microstent implantation into the supraciliary space.[30] In both trials, 1 eye of each subject was randomized. Both study protocols were approved by the institutional review boards or ethics committees at all study sites and conformed to the Helsinki Declaration tenets and Health Insurance Portability and Accountability Act regulations. All patients provided written informed consent at or before the initial screening visit. Data were provided for the present analysis in de-identified form.

• **INCLUSION CRITERIA:** Both trials required diagnoses of age-related cataract with visual acuity of 20/40 or worse with or without brightness acuity testing, and mild-to-moderate primary open-angle glaucoma with automated visual field mean deviation (MD) of 0 to −12 dB. HORIZON required patients to be on 1-4 topical ocular hypotensive medications at screening and have medicated IOP ≤31 mm Hg. COMPASS included patients on 0 medications, excluded patients on >3 medications, and required medicated IOP ≤25 mm Hg or unmedicated IOP between 21 and 33 mm Hg at screening. Following washout, IOP was required to be between 22 and 34 mm Hg for randomization in HORIZON and between 21 and 33 mm Hg for randomization in COMPASS. Patients in COMPASS were ≥45 years old but there was no age criterion for HORIZON.

• **EXCLUSION CRITERIA:** Exclusion criteria for both trials included significant risk associated with medication washout, previous corneal or glaucoma surgery (except laser trabeculoplasty), clinically significant ocular pathology other than cataract and glaucoma, and angle closure or secondary open-angle glaucoma. HORIZON excluded patients with central corneal thickness (CCT) <480 or >620 μm.

• **CLINICAL MEASUREMENTS:** For both studies, patients were evaluated at 2 preoperative, prerandomization visits. A screening visit included tonometry while on medications as prescribed by the referring ophthalmologist and a second visit included diurnal tonometry following ocular hypotensive medication washout with measurements at approximately 8 AM, noon, and 4 PM. At both visits, IOP was measured using Goldmann applanation tonometry with a 2-observer protocol wherein 1 investigator applanated the subject while masked to the tonometer dial and the second investigator read the measurement from the device. IOP measurements were taken twice and if the measurement differed by 2 mm Hg or less, the mean was recorded; if IOP differed by ≥3 mm Hg or more, then a third measurement was taken, and the median was recorded. CCT was measured using ultrasonography (Sonomed Escalon, Wayne, PA, USA) or optical coherence tomography (Visante; Carl Zeiss Meditec, Dublin, CA, USA) as the average of 3 measurements. Automated perimetry was conducted using the Swedish Interactive Threshold Algorithm standard 24-2 protocol on the Humphrey perimeter (Carl Zeiss Meditec).

• **MEDICATION WASHOUT:** Washout time was 4 weeks for prostaglandin analogues (PG) and beta-adrenergic antagonists (or beta-blocker, BB); 2 weeks for alpha adrenergic agonists (AA); and 7 days for cholinergic agonists. Carbonic anhydrase inhibitors (CAI) were washed out for 5 days in COMPASS and for 14 days in HORIZON. The COMPASS trial permitted the use of brinzolamide during the washout period at the discretion of study investigators, provided it was stopped 5 days prior to the final preoperative study visit.

• **STATISTICAL ANALYSES:** Medicated IOP at screening consisted of a single-time-point IOP measurement. The

TABLE 1. Subject Characteristics

	HORIZON	COMPASS	*P* Value[a]	Combined
Subjects, n	781	619		1400
Age (years)	71.0 (7.9)	70.2 (8.2)	.044	70.7 (8.0)
Sex (% female)	56.0	55.3	.792	55.6
Eye laterality (% right eye)	50.2	51.9	.536	50.9
Race (%)				
White	78.2	83.7		80.4
Black	11.1	9.1	<.001	10.4
Asian	6.8	1.2		4.6
Other	3.8	6.0		4.7
Visual field mean deviation (dB)	−3.6 (2.5)	−3.5 (3.1)	.014	−3.6 (2.8)
Central corneal thickness (μm)	547.5 (33.3)	549.8 (35.9)	.130	548.4 (34.4)
Prior SLT (%)	14.7	22.6	<.001	17.8
Number of medications	1.7 (0.9)	1.4 (0.9)	<.001	1.5 (0.9)
Medicated IOP (mm Hg)	17.6 (3.5)	18.6 (4.0)	<.001	18.0 (3.8)

IOP = intraocular pressure; SLT = selective laser trabeculoplasty.

Data are mean (standard deviation) unless otherwise indicated.

[a]Categorical variables (sex, eye laterality, race, prior SLT) were compared between the HORIZON and COMPASS trials using Pearson χ^2 test, and means of continuous or ordinal variables (age, visual field mean deviation, central corneal thickness, number of medications, medicated IOP) were compared using Mann-Whitney *U* tests.

postwashout IOP consisted of the average of the 3 diurnal measurements. Use of the postwashout diurnal mean IOP for comparison to the medicated screening IOP has been validated previously.[28] Percent IOP increase was calculated as the difference between medicated IOP and washout IOP, divided by the medicated IOP. Percent IOP decrease was calculated as the difference between medicated IOP and washout IOP, divided by the washout IOP, based on the assumption that the washout IOP was comparable to the untreated IOP. Normality of distributions was assessed using the Shapiro-Wilk test. Categorical data were compared between clinical trial groups (HORIZON vs COMPASS) using the Pearson χ^2 test. Continuous and ordinal variables were compared between clinical trial groups using Mann-Whitney *U* tests. IOP data were compared among subjects according to the number of medications they were taking at baseline using 1-way Kruskal-Wallis tests. Pairwise comparisons of IOP change after washout according to number of medications used, specific medication classes, or specific medications were performed by Bonferroni post hoc comparisons to correct for multiple comparisons. A generalized linear model was constructed to determine the association between IOP change upon medication washout as the dependent response variable and a number of predictive variables, including study trial, eye laterality, sex, race, and history of selective laser trabeculoplasty (SLT) as categorical factors; and age, CCT, visual field MD, number of glaucoma medications, and unmedicated IOP as continuous or ordinal covariates. For race, post hoc subgroup comparisons were made with white race as the comparison group given that it had, by far, the largest sample size. Statistical significance was defined as $P < .05$. Statistical analyses were conducted using SPSS v25 (IBM Corp, Armonk, New York, USA) and data were plotted using Prism v8.0 (GraphPad Software, San Diego, CA, USA). Box plots are bounded by the 25th and 75th percentile, with median values represented by the central horizontal line. Box-plot whiskers indicate minimum and maximum data points within 1.5 times the interquartile range from the 25th or 75th percentile, respectively. Box-plot circles represent outliers at greater than 2 times the interquartile range from the mean.

RESULTS

PRERANDOMIZATION DATA WERE ANALYZED FROM 1,400 subjects who were screened for trial eligibility, and who underwent tonometry before and after washout of IOP-lowering medications. It was not necessary for patients to have met the IOP-related trial inclusion/exclusion criteria to be included in this analysis, and so the number of subjects in this analysis is greater than the number randomized to surgery in either trial. In total, 781 subjects screened from the HORIZON trial and 619 subjects from the COMPASS trial were included, and we analyzed data from 1,400 eyes of 1,400 subjects. The demographic characteristics, visual field MD, and CCT of patients from both trial cohorts are shown in Table 1. More patients had undergone SLT prior to study enrollment in COMPASS ($P < .001$, Table 1). Subjects in HORIZON had a lower IOP on medications ($P < .001$) and used more IOP-lowering medications ($P < .001$, Table 1).

TABLE 2. Numbers of Subjects Using Different Classes of Medication

	Number of Medications				
	HORIZON (N = 781 Subjects)				
Medication Class	0 (N = 0)	1 (N = 429)	2 (N = 202)	3 (N = 125)	4 (N = 25)
Prostaglandin analog	–	329 (76.7)	143 (70.8)	120 (96.0)	25 (100)
β-Adrenergic antagonist	–	38 (8.9)	151 (74.8)	113 (90.4)	25 (100)
Carbonic anhydrase inhibitor	–	37 (8.6)	57 (28.2)	49 (39.2)	24 (96.0)
α-Adrenergic agonist	–	25 (5.8)	53 (26.2)	91 (72.8)	25 (100)
Cholinergic agonist	–	0 (0)	0 (0)	2 (1.6)	1 (4.0)
	COMPASS (N = 619 Subjects)				
	0 (N = 100)	1 (N = 276)	2 (N = 153)	3 (N = 89)	4 (N = 1)
Prostaglandin analog	0 (0)	223 (80.8)	120 (78.4)	88 (98.9)	1 (100)
β-Adrenergic antagonist	0 (0)	26 (9.4)	99 (64.7)	81 (91.0)	1 (100)
Carbonic anhydrase inhibitor	0 (0)	10 (3.6)	40 (26.1)	41 (46.1)	1 (100)
α-Adrenergic agonist	0 (0)	17 (6.2)	47 (30.7)	56 (62.9)	1 (100)
Cholinergic agonist	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)
	Combined (N = 1,400 Subjects)				
	0 (N = 100)	1 (N = 705)	2 (N = 355)	3 (N = 214)	4 (N = 26)
Prostaglandin analog	0 (0)	552 (78.3)	263 (74.1)	208 (97.2)	26 (100)
β-Adrenergic antagonist	0 (0)	64 (9.1)	250 (70.4)	194 (90.7)	26 (100)
Carbonic anhydrase inhibitor	0 (0)	47 (6.7)	97 (27.3)	90 (42.1)	25 (96.2)
α-Adrenergic agonist	0 (0)	42 (6.0)	100 (28.2)	147 (68.7)	26 (100)
Cholinergic agonist	0 (0)	0 (0)	0 (0)	3 (1.4)	1 (3.8)

Data are shown as number of subjects (percent of group). Percentages for subjects taking 2, 3, and 4 medications add to 200%, 300%, and 400%, respectively.

HORIZON enrolled patients on 1-4 IOP-lowering medications and COMPASS enrolled patients on 0-3 medications. The combined dataset included 7.1% of patients on 0 medications, 50.4% on 1 medication, 25.4% on 2 medications, 15.3% on 3 medications, and 1.9% on 4 medications. PGs were used by 74.9% of subjects, BBs by 38.1%, AAs by 22.5%, and CAIs by 18.5%. In patients taking only 1 medication, PGs were by far most common (78.3%, Table 2). In patients taking 2 medications, PGs (74.1%) and BBs (70.4%) were most common (Table 2).

The mean IOP for all subjects was significantly lower on medications (18.0 ± 3.8 mm Hg) than following washout (24.1 ± 4.3 mm Hg, $P < .001$, Figure 1). The distributions of medicated IOP, washed-out IOP, and change in IOP were non-Gaussian ($P < .001$). The rise in IOP following medication washout was strongly associated with number of medications washed out ($P < .001$, Figure 2). There was no change in mean IOP between the 2 study visits for patients on 0 medications (Table 3). On average, each additional IOP medication washed out was associated with a significantly greater IOP rise except when comparing 3-4 medications. IOP rise upon medication washout ranged from 34.5% to 61.2% of the medicated IOP (Table 3). By assuming that the washed-out IOP is comparable to the untreated IOP, the corresponding decrease in IOP inferred to occur from adding medications ranged from 23.5% for 1 medication to 35.6% for 4 medications (Table 3). The medicated IOP, washed-out IOP, IOP change, percent IOP rise upon medication washout, and inferred IOP decrease upon medication addition were all significantly associated with number of medications washed out ($P < .001$, Table 3). IOP change following medication washout was strikingly similar for subjects enrolled in HORIZON and COMPASS (Table 3).

A total of 705 subjects were taking 1 IOP-lowering medication prior to washout. Among these subjects, washout of PGs produced a significantly greater IOP rise than washout of AAs, though all other pairwise comparisons between medication classes were statistically insignificant (Figure 3A). Of 552 subjects who were taking 1 PG as their only IOP lowering medication, the specific PG medication was documented for 503 subjects. Among these subjects, there was no statistically significant difference in IOP rise upon washout of the various PGs (Figure 3B).

A generalized linear model was constructed to identify factors that were associated with greater IOP rise upon medication washout. Categorical factors included clinical trial, eye laterality, sex, race, and history of SLT.

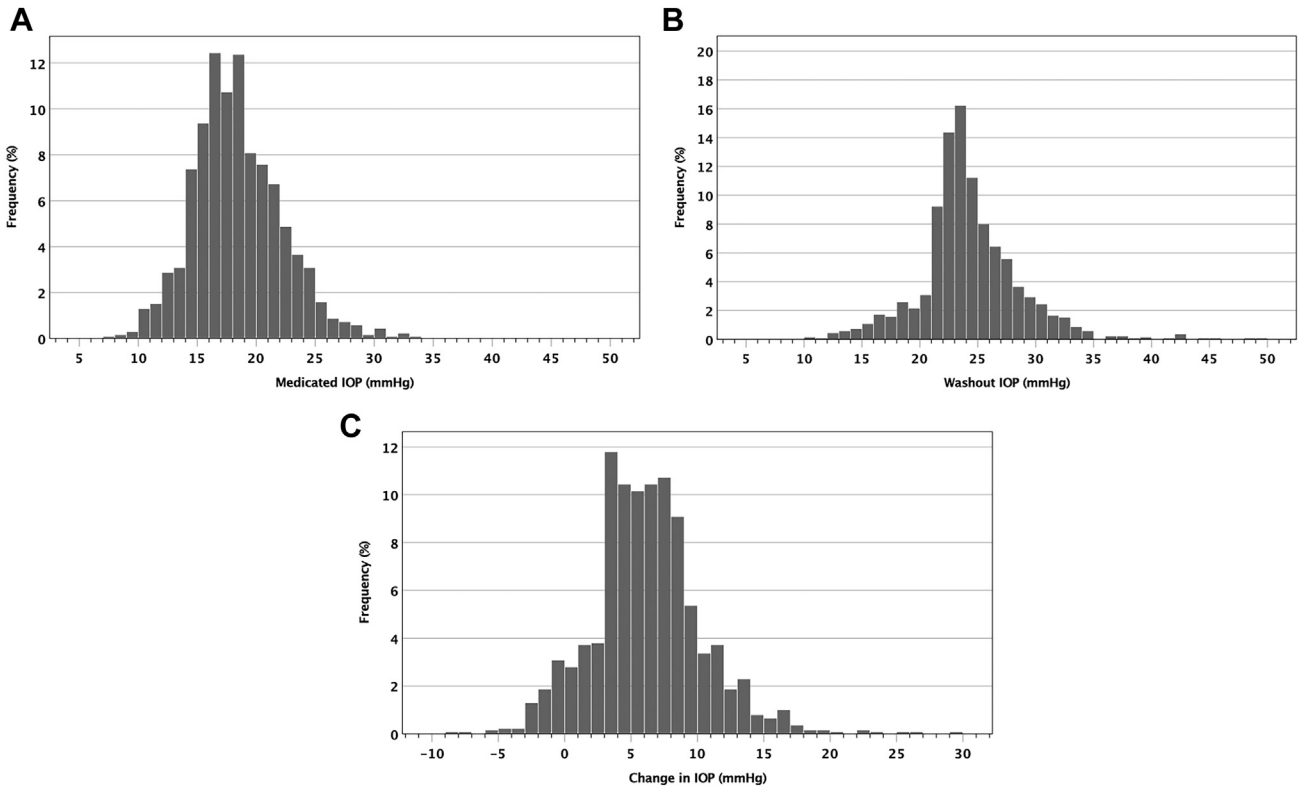

FIGURE 1. Intraocular pressure (IOP) before and after medication washout. Histograms depicting the distribution IOP on medication (A) and after medication washout (B), and the change in IOP due to washout (C), are shown. N = 1,400 eyes.

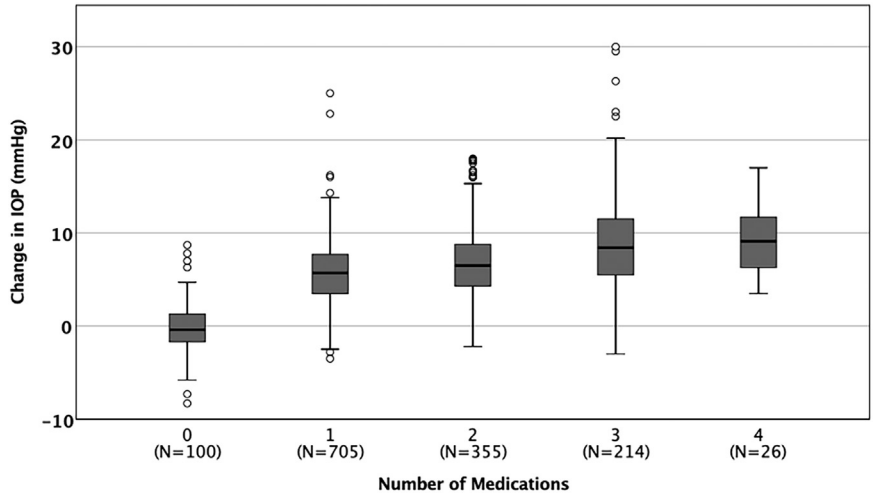

FIGURE 2. Mean intraocular pressure (IOP) change upon washout by number of medications. Change in IOP was positively associated with number of medications washed out ($P < .001$ by Kruskal-Wallis test). Pairwise comparisons for number of medications washed out: 0 vs 1, 2, 3, or 4 ($P < .001$ for each); 1 vs 2, 3, or 4 ($P < .001$ for each); 2 vs 3 ($P < .001$); 2 vs 4 ($P = .007$); 3 vs 4 ($P = 1.00$) by Bonferroni post hoc test.

Continuous and ordinal covariates included age, CCT, visual field MD, total number of drops, and washed-out IOP. Statistically significant predictors of greater change in IOP upon medication washout were greater number of medications ($\beta = 1.43$, $P < .001$), greater washed-out (unmedicated) IOP ($\beta = 0.55$, $P < .001$), thinner CCT as

TABLE 3. Intraocular Pressure Measurements by Number of Medications

No. of Medications	HORIZON (N = 781 Subjects)					
	N	Medicated IOP (mm Hg)	Washout IOP (mm Hg)[a]	IOP Change (mm Hg)[a]	% IOP Increase[a]	% IOP Decrease[a]
0	0	–	–	–	–	
1	429	17.8 (3.4)	23.6 (4.1)	5.8 (3.5)	35.3 (25.0)	−23.8 (13.1)
2	202	17.3 (3.3)	24.3 (4.5)	6.9 (3.9)	42.8 (29.0)	−27.5 (12.7)
3	125	17.5 (3.6)	26.3 (6.3)	8.8 (5.7)	52.9 (36.2)	−31.2 (15.7)
4	25	16.8 (4.2)	26.5 (5.5)	9.7 (4.1)	62.4 (33.8)	−36.1 (12.0)
	COMPASS (N = 619 Subjects)					
	N	Medicated IOP (mm Hg)[a]	Washout IOP (mm Hg)[a]	IOP Change (mm Hg)[a]	% IOP Increase[a]	% IOP Decrease[a]
0	100	24.2 (3.2)	24.0 (2.9)	−0.2 (2.8)	0.0 (11.9)	1.3 (11.6)
1	276	17.5 (3.2)	22.9 (3.4)	5.4 (3.0)	33.3 (21.2)	−23.1 (11.9)
2	153	17.4 (3.2)	24.3 (3.6)	6.8 (3.4)	41.7 (23.5)	−27.6 (11.8)
3	89	17.4 (3.2)	26.1 (4.2)	8.7 (3.9)	53.1 (26.8)	−32.6 (12.1)
4	1	18.0	23.7	5.7	31.7	−24.1
	Combined (N = 1,400 Subjects)					
	N	Medicated IOP (mm Hg)[a]	Washout IOP (mm Hg)[a]	IOP Change (mm Hg)[a]	% IOP Increase[a]	% IOP Decrease[a]
0	100	24.2 (3.2)	24.0 (2.9)	−0.2 (2.8)	0.0 (11.9)	−1.3 (11.6)
1	705	17.7 (3.4)	23.3 (3.8)	5.7 (3.3)	34.5 (23.6)	−23.5 (12.6)
2	355	17.4 (3.2)	24.2 (4.2)	6.9 (3.7)	42.4 (26.7)	−27.5 (12.3)
3	214	17.5 (3.4)	26.3 (5.5)	8.8 (5.0)	53.0 (32.6)	−31.8 (14.3)
4	26	16.8 (4.1)	26.4 (5.4)	9.5 (4.1)	61.2 (33.7)	−35.6 (12.0)

IOP = intraocular pressure.

Data are shown as mean (standard deviation). Measurement categories are defined as follows: Medicated IOP: intraocular pressure on medications; Washout IOP: intraocular pressure after washout; IOP change: washout IOP minus medicated IOP; % IOP Increase: IOP change divided by medicated IOP; % IOP Decrease: IOP change divided by washout IOP.

[a]$P < .001$ by Kruskal-Wallis test comparing group means by number of medications.

measured in micrometers ($\beta = 0.01$, $P < .001$), HORIZON as the source clinical trial ($\beta = 0.50$, $P = .004$), no prior history of SLT ($\beta = 0.48$, $P = .032$), and male sex ($\beta = 0.343$, $P = .045$). Race was a predictor of overall statistical significance ($P = .031$), but we did not identify any significant pairwise differences between race subgroups. Eye laterality ($P = .476$), age ($P = .787$), and visual field MD ($P = .285$) were not associated with IOP rise after medication washout.

DISCUSSION

THIS STUDY DEMONSTRATES A DOSE-DEPENDENT RISE IN IOP following washout of topical ocular hypotensive eye drops in patients with primary open-angle glaucoma prior to randomization in 2 surgical treatment trials. By assuming that the washout IOP is comparable to untreated IOP, we have calculated an inferred IOP reduction induced by medical glaucoma therapy. Results of prior work[28] were replicated here in an independent cohort and demonstrated a remarkable degree of similarity in the extent of IOP change per additional glaucoma drop in a multiclass regimen. It is worth noting that the relative benefit of the first glaucoma medication was relatively large in comparison to subsequent drops. The first medicine resulted in an almost 24% reduction in IOP, whereas each additional drop conferred only approximately 4% further IOP reduction. Interestingly the extent of IOP changes with each additional drop was linear from 2 to 4 drops. We did not detect a significant difference between 3 and 4 glaucoma drops, though our subject population included only 1.9% of patients taking 4 medications and therefore may have been underpowered.

• **ADDITIVE EFFECTS OF GLAUCOMA MEDICATIONS:** The additive effect of multiple glaucoma drops has previously been evaluated in prospective clinical studies. For instance, a meta-analysis of 18 trials assessing the efficacy of PGs and timolol reported that combination therapy produced a 2.2 mm Hg greater IOP lowering than timolol monotherapy, and 0.9 greater IOP lowering than PG monotherapy.[31] This decrease is comparable to the 1.2 mm Hg (4%) greater IOP reduction we found in patients taking 2 drops vs 1 drop. Several other studies of fixed-dose drop combinations

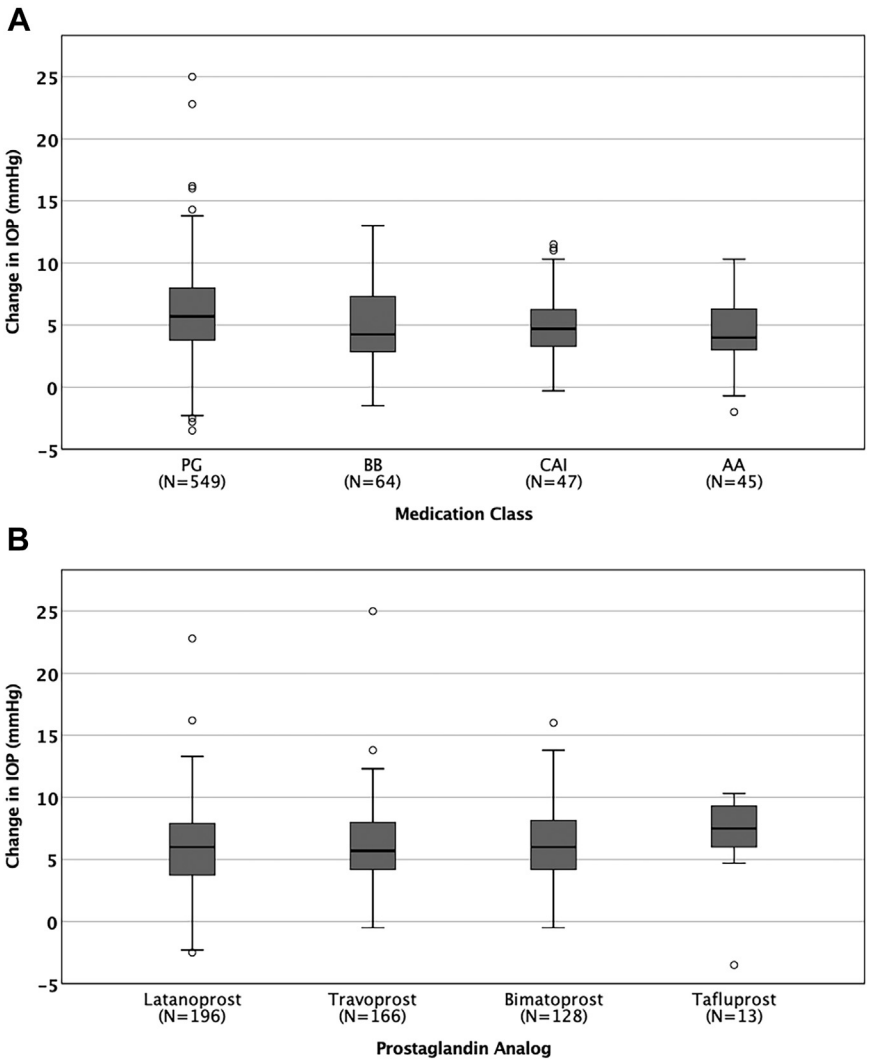

FIGURE 3. Mean intraocular pressure (IOP) change upon washout for subjects on 1 medication. (A) In subjects taking 1 IOP-lowering medication (n = 705), change in IOP differed according to the class of medication being washed out ($P = .001$ by Kruskal-Wallis test). Pairwise comparisons between medication classes were significant only for prostaglandin analogues (PG) vs alpha adrenergic agonists (AA, $P = .024$ by Bonferroni post hoc test). BB = beta-adrenergic antagonist; CAI =carbonic anhydrase inhibitor. (B) In subject taking only a PG and where the specific PG was documented (n = 503), change in IOP did not differ according to which PG was washed out ($P = .249$ by Kruskal-Wallis test).

report a range of further IOP lowering from the addition of glaucoma drops to existing medication regimens. For instance, timolol 0.5%/brimonidine 0.2%/dorzolamide 2% resulted in an IOP reduction of 9.5% more than timolol 0.5%/brimonidine 0.2% alone.[22] In patients on latanoprost with IOP >21 mm Hg, the addition of timolol further reduced IOP by 27.0% and timolol/brimonidine by 35.5%.[23] Tabet and associates[32] reviewed the additivity of various agents to PGs and reported that a second medicine reduces IOP by an additional 10%-25%. Additive effects of glaucoma medications have also been studied in retrospective fashion and report additional IOP lowering of 3-4 mm Hg or approximately 15%-25% by adding a third or fourth agent to an existing regimen.[24–27] However, potential biases of retrospective study design must be considered; for instance, 1 study excluded 28% of the study population from their analysis owing to insufficient IOP response requiring additional medications or surgery.[27]

Our data support an additive effect of multiple glaucoma agents. The relative modesty of IOP lowering conferred by the second, third, and fourth additional drop in comparison to prospective clinical studies may be explained by more realistic adherence behavior owing to the current washout study design. Of note, the present study design also may have systematically selected for patients with good responses to the medications they were taking, since the

number and identity of medicines taken by the subjects were not controlled by the study design, but rather by the referring physician. In patients for whom 1 or 2 glaucoma medications led to an insufficient IOP response, it is likely that the referring provider would have already switched classes, added a third or fourth agent, or performed a laser or surgical procedure. Prospective studies in which the response to additive glaucoma medications is unknown at baseline will likely include a greater percentage of patients who respond poorly to additional drops. It is important to consider, however, that this would have likely biased our study in favor of greater IOP change following washout, whereas our data show similar or less IOP change to many published studies.

• **DIFFERENCES IN GLAUCOMA MEDICATIONS:** Given that half of the present cohort was taking 1 glaucoma drop, we conducted analyses of patients on monotherapy in an attempt to discern differences in efficacy among drug classes and individual PGs. We found that PGs lowered IOP to a greater extent than AAs. Though IOP reduction by PGs was, on average, numerically greater than for any other drug class, we did not detect any other statistically significant between-class differences. This finding may be partially related to statistical power, as the PGs accounted for nearly 80% of the patients on monotherapy. Our results are generally in line with prior meta-analyses of patients on monotherapy, which demonstrate that PGs are the most effective IOP-lowering drug class, followed by BBs, AAs, and CAIs.[5,8,33] Though we analyzed data from 503 subjects on PG monotherapy, we did not detect any statistically significant difference in IOP reduction by individual prostaglandins. Group sizes were more evenly distributed for latanoprost, travoprost, and bimatoprost, though a dearth of subjects were using tafluoprost. According to previous meta-analyses of clinical trial data, bimatoprost may be more effective than other PGs.[5,34,35] As noted earlier, there may also have been a selection bias for patients who were already optimized on their medication regimen, which could have blunted between-group comparisons. For instance, if a patient responded poorly to latanoprost, they may have already been switched to an alternate PG or to a BB by their referring provider. By minimizing cases with poor responsivity to certain drops, bias is in favor of greater treatment responses and smaller-between group differences.

• **PREDICTORS OF RESPONSE TO THERAPY:** Using a generalized linear model, we observed several predictive factors that are associated with a greater IOP response to glaucoma medications, including thinner CCT, negative history of SLT, higher washed-out IOP, and male sex. The observation that greater untreated IOP (comparable to washed-out IOP) is correlated with greater IOP reduction induced by medical therapy is well established,[36,37] and the current data confirm that association.

Previously we reported in the COMPASS cohort alone that eyes with thicker corneas had smaller responses to IOP-lowering medications than eyes with thinner corneas,[28] and the present study replicates this result in the larger dataset that includes the HORIZON cohort. A similar inverse association between CCT and IOP reduction by topical glaucoma medications was noted in the Ocular Hypertension Treatment Study[38] and in an analysis of research records from a combined set of prospective clinical studies assessing the efficacy of various glaucoma monotherapies in patients with ocular hypertension and normotensive volunteers.[39] Lower corneal hysteresis has also been associated with greater IOP reduction following initiation of topical prostaglandins.[40] It is known that CCT systematically confounds IOP measurement by applanation and other techniques, leading to higher IOP measurements in eyes with thicker corneas.[41,42] If this measurement artifact is stronger at lower true IOP, then the apparent IOP reduction from treatment would be minimized in eyes with thicker corneas. As noted by Brandt and associates,[38] the true IOP of eyes with thicker corneas is lower than those with thinner corneas. Since baseline IOP is positively associated with the degree of IOP reduction, the effect of CCT on true baseline IOP may also partially explain this observation. The overall effect of CCT on IOP reduction by topical glaucoma eye drops is small, and it seems unwarranted that an individual patient's CCT should influence the choice of pharmacotherapy, though our data do suggest that patients with thicker CCT who are being treated may have a slightly smaller measured response to eye drops than subjects with thinner CCT. It is interesting to consider that PG therapy has been associated with CCT thinning over time.[43,44] Including whether subjects were taking PGs in our generalized linear model did not alter the association between CCT and change in IOP with washout (not shown), suggesting that thinner CCT is not simply a confounder associated with both presence of PG use and lower IOP after washout.

We found that history of previous SLT predicted less IOP elevation upon medication washout. Laser trabeculoplasty is 1 potential first-line treatment for primary open-angle glaucoma, and its utilization will likely increase following the publication of the LiGHT trial results.[45] As new protocols, such as that of the Glaucoma Intensive Treatment Study,[46] randomize patients to intensive glaucoma treatments that include SLT plus multiple eye drops, understanding the interactions between these treatment modalities becomes more important. SLT increases outflow facility without altering aqueous production, and has only modest effects on uveoscleral outflow.[47,48] It is possible that prior SLT blunted the IOP rise that otherwise would have occurred following medication washout. We are unaware of prior studies that demonstrate a differential effect of glaucoma medications based on having undergone prior SLT. It would be of interest to determine whether other glaucoma interventions—such as trabecular bypass

shunts, goniotomy, trabeculotomy, and/or canaloplasty—are similarly affected by having undergone prior SLT preoperatively.

We noted a small but statistically significant effect of biological sex on IOP change, in favor of men having a greater rise in IOP following medication washout. Possible explanations for this include a stronger IOP-lowering effect of medications in male subjects (though we are unaware of evidence for this to be the case) or better adherence in male subjects. Prior work assessing adherence to glaucoma eye drops in a wide range of study populations has found disparate associations with biological sex,[11,49–55] and without having directly assessed adherence in this study, it is not possible to know whether adherence played a role here. Although hormonal influences on IOP have been demonstrated,[56] it seems unlikely that these would systematically account for within-subject changes in IOP before and after medication washout. The influence of sex on glaucoma should continue to undergo careful examination.[57]

Of note, we found that the clinical trial for which a subject was screened (HORIZON vs COMPASS) also predicted the IOP response to medication washout. This may be related to the differential inclusion criteria between the 2 studies, which also resulted in subjects within HORIZON having a lower IOP and being on more medications. HORIZON required patients to be taking at least 1 glaucoma medication at baseline to be considered for enrollment, whereas COMPASS permitted untreated ocular hypertensive patients to be enrolled, provided their baseline IOP was ≥21 mm Hg. Therefore, 100 (16.2%) of the patients from COMPASS exhibited no mean change in IOP following washout, owing to the fact that zero medications were washed out.

• **FUTURE CONSIDERATIONS:** As clinical trials for new glaucoma therapies are developed and conducted, understanding the expected IOP elevation following medication washout for participating subjects will increase the efficiency of planning and recruitment. The World Glaucoma Association has stated that "pre- and postoperative washout (off medication) IOP curves are a robust method to define the IOP-lowering effects associated with a procedure, while avoiding confounding effects from medication use" and recommends that washed-out IOP be measured and reported when safe and ethical to do so.[58] Indeed, the United States Food and Drug Administration has provided guidance for premarket studies of implantable minimally invasive glaucoma surgical devices that recommends that effectiveness endpoints be based on IOP measured following medication washout.[59] The pre- and postwashout histograms of IOP provided here can be useful in estimating the percentage of screened patients who will meet inclusion criteria based on a variety of IOP thresholds. As new glaucoma medications including nitric oxide donors and rho kinase inhibitors have only recently been introduced to the market, the present data do not provide information to understand how these drops affect washout IOP. Future studies could certainly be performed on analogous datasets from upcoming clinical trials to obtain that information.

CONCLUSIONS

CESSATION OF GLAUCOMA MEDICATIONS RESULTS IN A dose-dependent IOP increase in treated open-angle glaucoma patients. Two independent clinical trial cohorts exhibit similar levels of IOP elevation upon washout, using standardized methodology to estimate real-world medication effectiveness. Washout of PGs results in a greater rise in IOP than washout of AAs, whereas washout of individual medications within the PG class results in comparable IOP elevation. Thicker CCT and history of SLT are associated with reduced IOP elevation following glaucoma medication washout.

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