Using diurnal intraocular pressure fluctuation to assess the efficacy of fixed-combination latanoprost/timolol versus latanoprost or timolol monotherapy

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ABSTRACT
Aim: To evaluate differences in diurnal intraocular pressure (IOP) fluctuation in glaucoma/ocular hypertension patients treated with once-daily fixed-combination latanoprost/timolol, once-daily latanoprost, or twice-daily timolol.
Methods: In two 6-month, double-masked, parallel-group studies, patients received run-in timolol (2-4 weeks) and randomised (1:1:1) to therapy. IOP was measured three times/day at baseline and weeks 2, 13, 26. In post-hoc analyses, diurnal IOP fluctuation = highest daily IOP–lowest daily IOP at baseline and week 26. Fluctuation also was dichotomised: high (>6mmHg), low (≤6 mmHg).
Results: 854 patients were randomised (fixed combination=278; latanoprost=287; timolol=289). Diurnal fluctuation was significantly reduced from baseline to week 26 with the fixed combination (p=0.002) but not with latanoprost or timolol monotherapy (p=0.601; p=0.097). Relative to baseline, the percentage with high diurnal IOP fluctuation at week 26 was reduced by 48% with fixed combination but increased 13% with latanoprost and 48% with timolol. Changes in IOP fluctuation and in mean IOP were significantly correlated for the monotherapies but not the fixed combination.
Conclusions: Fixed-combination latanoprost/timolol results in lower diurnal IOP fluctuation and significantly fewer patients with high fluctuation than treatment with latanoprost or timolol monotherapy. The fixed combination may have an independent effect on reducing IOP fluctuation in addition to lowering IOP.
Although aggressive lowering of intraocular pressure (IOP) levels has been shown to slow or prevent glaucomatous progression, other IOP-related factors such as fluctuation also may be associated with progression. Whether or not IOP fluctuation is a risk factor for progression of glaucoma is controversial. This ongoing lack of clarity may be explained, at least in part, by differences among studies in the methods used to measure fluctuation. For example, some studies studied the possible correlation between fluctuation and progression using baseline IOP data while others assessed IOP fluctuation across follow-up visits; some evaluated short-term IOP fluctuation (over hours or days) while others assessed long-term fluctuation (over months or years); some studied progression of ocular hypertension to glaucoma while others investigated progression from mild to advanced glaucoma; and some relied on measures of central tendency such as the IOP mean while others used the standard deviation or inter-visit IOP range to reflect dispersion.

Two recent studies of the relationship between mean IOP and IOP fluctuation in surgically treated patients found that greater fluctuation was significantly related to visual field progression despite low mean IOP levels. In both studies, concomitant IOP-lowering therapy was used but analyses stratified by therapy were not performed. Musch et al noted that the range of IOP levels over six baseline measurements (median = 6.5 mm Hg) in the Collaborative Initial Glaucoma Treatment Study (CIGTS) was related to subsequent visual field loss. Trabeculectomy and aggressive medical treatment (target 35% IOP reduction) appeared to have similar effects on halting progression in the CIGTS, but again relationships between specific medical therapies and either fluctuation or progression were not evaluated.

Because little is known about the impact of specific medical therapies on long-term IOP fluctuation, we evaluated differences in diurnal IOP fluctuation over a 6-month period in patients treated with fixed-combination latanoprost/timolol or monotherapy with either latanoprost or timolol. In addition, although others have found IOP fluctuation to be directly proportional to mean IOP, it is not known whether this relationship varies across ocular hypotensive agents. We therefore assessed the relationship between change in diurnal IOP fluctuation and change in mean IOP to determine whether latanoprost, timolol, or the fixed combination of latanoprost and timolol reduce fluctuation independent of changes in IOP levels.

**MATERIALS AND METHODS**

**Clinical trial designs**

Two 6-month, randomised, double-masked, parallel-group studies of fixed-combination latanoprost/timolol administered once daily versus monotherapy with either latanoprost once daily or timolol twice daily were conducted at 38 sites in the United States (NCT00800267) and at 37 centres in Germany (NCT00856622). Ethics approval was provided by the institutional review board or ethics committee of each participating centre before study initiation, and both studies were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient prior to study enrollment.

Patients were evaluated for eligibility at a screening visit during the 2 to 4 weeks preceding the start of each study. In brief, men and women 18 years of age or older with unilateral or bilateral primary open-angle, pigmentary, or pseudoexfoliation glaucoma, or
with ocular hypertension were eligible if the prestudy IOP was ≥30 mmHg without ocular hypotensive medication or ≥25 mmHg with prior therapy.

Eligible patients discontinued current therapy and had 2 to 4 weeks of “run-in” treatment with one drop of 0.5% timolol instilled twice daily. At the baseline visit (following timolol run-in), patients were randomised (1:1:1) to receive: (a) fixed-combination latanoprost/timolol once daily in the morning and placebo in the evening; (b) latanoprost once daily in the morning and placebo in the evening in Germany20 or latanoprost once daily in the evening and placebo in the morning in the United States19; or (c) timolol twice daily in the morning and evening. Three postbaseline visits at which IOP was measured in triplicate in each eye at 08:00, 10:00, and 16:00 were scheduled at weeks 2, 13, and 26. In both studies, the morning dose of medication was administered immediately after the 8 AM IOP measurement. The primary efficacy outcome was the difference between the fixed-combination therapy and the two monotherapy groups in mean IOP reduction through 6 months of treatment.

**Post hoc analysis of diurnal intraocular pressure fluctuation**

This post hoc analysis compared fixed-combination latanoprost/timolol and its components as monotherapy with regard to change in diurnal IOP fluctuation from baseline to week 26. Diurnal IOP fluctuation at baseline was defined as the highest IOP minus the lowest IOP of three measurements taken at the baseline visit. Diurnal IOP fluctuation at week 26 was calculated as the highest IOP minus the lowest IOP of three measurements taken at the week 26 visit. Change in diurnal IOP fluctuation at week 26 was the difference between baseline and week 26 measurements. Mean IOP levels at baseline and week 26 were the averages of the three IOP measurements at the respective time points; change in IOP at week 26 was the difference between baseline and week 26 measurements.

For continuous demographic and ocular variables, the *t* test was used for pairwise comparisons and analysis of variance (ANOVA) for overall comparisons; for categorical variables, pairwise and overall comparisons were made using the Pearson chi-square test. The effect of treatment on diurnal IOP fluctuation was evaluated by calculating the least square means for each treatment. The overall and pair-wise treatment comparisons were performed using ANOVA. For the within-treatment group comparisons, the paired *t* test was used to compare the postbaseline diurnal IOP fluctuation versus baseline. In addition, diurnal IOP fluctuation was dichotomised as “high” (>6 mmHg) versus “low” (≤6 mmHg).21-23 Baseline pairwise comparisons were made using the chi-square test; at week 26, the chi-square test adjusted for dichotomised baseline IOP fluctuation was used to evaluate between-group differences, and the overall p value was estimated using the Type III Wald test adjusted for dichotomised baseline IOP fluctuation. The McNemar test was used to compare dichotomised diurnal IOP fluctuation at each visit against baseline within each treatment group to account for matched individual subjects at each visit. For each therapy, the strength of the relationship between change in diurnal IOP fluctuation at week 26 and change in mean IOP at week 26 was assessed using a correlation coefficient.

**RESULTS**

In all, 854 patients were included in the post hoc analysis: fixed-combination latanoprost/timolol, *n* = 278; latanoprost, *n* = 287; timolol, *n* = 289). Treatment groups
generally were similar with regard to pretreatment characteristics (Table 1). Although baseline mean IOP was statistically significantly higher among those randomised to treatment with timolol versus fixed-combination latanoprost/timolol (p = 0.030), the 0.7 mmHg difference was not clinically significant.

<p>| Table 1 Characteristics of patients included in the post hoc analysis by treatment group* |
|--------------------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Fixed-combination latanoprost/timolol n = 278</th>
<th>Latanoprost monotherapy n = 287</th>
<th>Timolol monotherapy n = 289</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean ± SD 62.3 ± 12.8</td>
<td>63.2 ± 12.2</td>
<td>63.8 ± 11.6</td>
</tr>
<tr>
<td>Gender, male</td>
<td>134 (48.2)</td>
<td>145 (50.5)</td>
<td>132 (45.7)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>229 (82.4)</td>
<td>242 (84.3)</td>
<td>239 (82.7)</td>
</tr>
<tr>
<td>African American</td>
<td>38 (13.7)</td>
<td>37 (12.9)</td>
<td>35 (12.1)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (4.0)</td>
<td>8 (2.8)</td>
<td>15 (5.2)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary open-angle glaucoma</td>
<td>200 (71.9)</td>
<td>201 (70.0)</td>
<td>213 (73.7)</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>63 (22.7)</td>
<td>56 (19.5)</td>
<td>54 (18.7)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (5.4)</td>
<td>30 (10.5)</td>
<td>22 (7.6)</td>
</tr>
<tr>
<td>Duration of condition (months)</td>
<td>Mean ± SD 81.0 ± 80.7</td>
<td>76.6 ± 72.1</td>
<td>78.6 ± 72.2</td>
</tr>
<tr>
<td>Positive family history</td>
<td>83 (29.9)</td>
<td>91 (31.7)</td>
<td>81 (28.0)</td>
</tr>
<tr>
<td>Prior IOP reduction medication within 3 months</td>
<td>244 (87.8)</td>
<td>255 (88.9)</td>
<td>253 (87.5)</td>
</tr>
<tr>
<td>Baseline IOP (mmHg)</td>
<td>Mean ± SD 22.4 ± 3.9</td>
<td>22.7 ± 4.0</td>
<td>23.1 ± 4.1</td>
</tr>
<tr>
<td>Baseline IOP fluctuation (mmHg)</td>
<td>Mean ± SD 3.7 ± 2.5</td>
<td>3.5 ± 2.6</td>
<td>3.4 ± 2.3</td>
</tr>
</tbody>
</table>

IOP, intraocular pressure; SD, standard deviation.
Condition-related data refer to the study eye.
*n (%), unless otherwise specified. Unless otherwise noted, between-group differences were not significant (p > 0.09) for any variable.
†p = 0.030 for the difference between fixed-combination latanoprost/timolol vs timolol.

Treatment with the fixed combination of latanoprost and timolol resulted in a significant reduction in diurnal IOP fluctuation from baseline to week 26 (p = 0.002; Table 2). During that period, diurnal IOP fluctuation was increased but did not change significantly among those treated with either latanoprost or timolol monotherapy (p = 0.601 and 0.097, respectively). The between-treatment difference of the change in diurnal IOP fluctuation from baseline to week 26 was statistically significant between the fixed-combination group and both monotherapy groups (p≤0.010 for each comparison).
<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Fixed-combination latanoprost/timolol n = 278</th>
<th>Latanoprost monotherapy n = 287</th>
<th>Timolol monotherapy n = 289</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diurnal IOP fluctuation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean ± SD (mmHg)</td>
<td>3.7 ± 2.5</td>
<td>3.5 ± 2.6</td>
<td>3.4 ± 2.3</td>
</tr>
<tr>
<td>Week 26 Mean ± SD (mmHg)</td>
<td>3.0 ± 2.1</td>
<td>3.7 ± 3.1</td>
<td>3.7 ± 3.2</td>
</tr>
<tr>
<td>Change: baseline versus week 26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least square mean ± SEM (mmHg)*</td>
<td>-0.68 ± 0.22</td>
<td>0.11 ± 0.22</td>
<td>0.36 ± 0.22</td>
</tr>
<tr>
<td>Within-treatment p values</td>
<td>0.002</td>
<td>0.601</td>
<td>0.097</td>
</tr>
</tbody>
</table>

IOP, intraocular pressure; SD, standard deviation; SEM, standard error of the mean. *Between-treatment p value for change in mean diurnal IOP fluctuation from baseline to week 26: fixed-combination latanoprost/timolol vs latanoprost, p = 0.010; fixed-combination latanoprost/timolol vs timolol, p < 0.001; latanoprost vs timolol, p = 0.423. Overall three-way comparison, p = 0.002.

Distributions of patients with high versus low diurnal IOP fluctuation also were similar across treatment groups at baseline (table 3). At week 26, however, significantly fewer patients in the fixed-combination group than in either monotherapy group had high diurnal IOP fluctuation (p = 0.003 for each comparison). The absolute percentage of patients with high diurnal IOP fluctuation was reduced by nearly half from baseline to week 26 in the fixed-combination latanoprost/timolol group (13.3% at baseline vs 6.9% at week 26; p = 0.004). In contrast, approximately one-half more patients in the timolol monotherapy group had high diurnal IOP fluctuation at week 26 compared with baseline (9.7% at baseline vs 14.4% at week 26; p = 0.080), and approximately 10% more in the latanoprost monotherapy group had higher diurnal IOP fluctuation at final follow-up (13.2% at baseline vs 14.9% at week 26; p = 0.633). Relative to baseline, the percentage of patients with high diurnal IOP fluctuation at week 26 was reduced by nearly 50% in the fixed-combination group but increased by nearly 50% and 13% among those treated with timolol or latanoprost monotherapy, respectively.
Table 3  Patients with high (>6 mmHg) versus low (≤6 mmHg) diurnal IOP fluctuation at baseline and week 26 by treatment group, n (%)

<table>
<thead>
<tr>
<th>Diurnal IOP fluctuation</th>
<th>Fixed-combination latanoprost/timolol n = 278</th>
<th>Latanoprost monotherapy n = 287</th>
<th>Timolol monotherapy n = 289</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>37 (13.3)</td>
<td>38 (13.2)</td>
<td>28 (9.7)</td>
</tr>
<tr>
<td>Low</td>
<td>241 (86.7)</td>
<td>249 (86.8)</td>
<td>261 (90.3)</td>
</tr>
<tr>
<td>Week 26†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>19 (6.9)</td>
<td>42 (14.9)</td>
<td>41 (14.4)</td>
</tr>
<tr>
<td>Low</td>
<td>256 (93.1)</td>
<td>239 (85.1)</td>
<td>243 (85.6)</td>
</tr>
<tr>
<td>Change in % high:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline versus week 26</td>
<td>-6.4%</td>
<td>+1.7%</td>
<td>+4.7%</td>
</tr>
<tr>
<td>Within-treatment p values</td>
<td>0.004</td>
<td>0.633</td>
<td>0.080</td>
</tr>
<tr>
<td>Relative % change from baseline in patients with high fluctuation</td>
<td>-48.1%</td>
<td>+12.9%</td>
<td>+48.4%</td>
</tr>
</tbody>
</table>

IOP, intraocular pressure.
*Between-treatment p value: fixed-combination latanoprost/timolol vs latanoprost, p = 0.981; fixed-combination latanoprost/timolol vs timolol, p = 0.178; latanoprost vs timolol, p = 0.182. Overall three-way comparison, p = 0.317.
†Between-treatment p value: fixed-combination latanoprost/timolol vs latanoprost, p = 0.003; fixed-combination latanoprost/timolol vs timolol, p = 0.003; latanoprost vs timolol, p = 0.977. Overall three-way comparison, p = 0.005.

At week 26, the mean diurnal IOP level was significantly lower in the fixed combination group compared with each monotherapy group and in the latanoprost versus timolol monotherapy groups (fixed combination: 19.4 ± 3.5 mmHg; latanoprost: 20.6 ± 4.8 mmHg; timolol: 22.4 ± 5.5 mmHg; p<0.01 for each two-way comparison); changes from baseline to week 26 in mean IOP levels were greatest in the fixed combination group (-2.9 ± 3.2 mmHg; -2.1 ± 4.1 mmHg, and -0.7 ± 3.6 mmHg, respectively; p<0.01 for each two-way comparison). However, correlations between change in IOP fluctuation and change in mean IOP at week 26 were significant for the two monotherapy groups but not for the fixed-combination latanoprost/timolol group (fig). Correlation coefficients (r values) were 0.27 (p<0.001) for both monotherapy groups versus 0.07 (p = 0.276) for the fixed-combination group.

DISCUSSION
In this post-hoc analysis of data from two randomised, double-masked trials,19,20 significantly fewer patients treated with fixed-combination latanoprost/timolol had high diurnal IOP fluctuation after 6 months compared with those receiving either latanoprost or timolol monotherapy. Moreover, the nearly 50% relative reduction from baseline in the percentage of patients with high diurnal IOP fluctuation in the fixed combination...
group contrasted with an increase of similar magnitude in this percentage in the timolol monotherapy group and with the 13% increase in the latanoprost monotherapy group. The extent to which the somewhat lower mean baseline IOP level and larger mean baseline IOP fluctuation in the fixed combination group contributed to these differences is unknown.

The fixed combination was statistically significantly superior to both monotherapies with regard to reducing diurnal IOP fluctuation, but differences between the latanoprost and timolol monotherapies were not statistically significant. Thus, mean diurnal IOP fluctuation increased to 3.7 mmHg at week 26 in the latanoprost and timolol groups from baselines of 3.5 mmHg and 3.4 mmHg, respectively (p = 0.423). The fact that patients received 2 to 4 weeks of “run-in” treatment with timolol probably blunted its impact on fluctuation. The reason for the relatively low effect of latanoprost alone on fluctuation requires additional study.

Lower IOP levels have been associated with lower IOP fluctuation.\(^7\)\(^{18}\) In the present research, however, this relationship was observed among those treated with latanoprost or timolol monotherapy but not in patients receiving fixed-combination latanoprost/timolol. The nature of IOP lowering with the fixed combination appears to be different than that achieved with latanoprost or timolol alone.

The impact of various ocular hypotensive medications on IOP fluctuation and ultimately on glaucomatous progression requires additional clarification. Hong \(et\ al\)\(^{10}\) assessed progressive visual field deterioration in glaucoma patients after phacoemulsification, posterior chamber intraocular lens implantation, and trabeculectomy. After 13 years, progressive visual field deterioration was noted in more patients with postoperative IOP standard deviations >2 than in those with standard deviations ≤2. Although patients were treated with an average of >1 topical ocular hypotensive during follow-up, outcomes were not assessed with regard to postsurgical medication(s) prescribed. It is plausible to hypothesise, however, that differences among medications may account, at least in part, for the long-term variability in IOP levels reflected in the standard deviations. We have previously demonstrated differences between topical medications with regard to their ability to reduce the intervisit IOP range despite similar effects on lowering mean IOP levels.\(^{23}\) It is therefore reasonable for ophthalmologists to consider not only the magnitude of IOP lowering but also the nature or quality of IOP lowering. Fluctuation of IOP is emerging as a potentially important element that may be taken into account when medically managing patients with glaucoma. That significant differences may exist among therapeutic choices otherwise thought to be equally effective may be a new factor to consider.

The current study is limited by the fact that it was a post hoc analysis; the impact of reducing high diurnal IOP fluctuation on progressive glaucomatous damage requires additional investigation in prospectively designed studies. Further research is necessary to clarify the benefit of lowering the peak or diurnal IOP relative to reducing high diurnal IOP fluctuation. In addition, future research should compare reductions in diurnal IOP fluctuation among patients treated with a wider variety of ocular hypotensive agents and should include IOP measurements reflecting the full 24-hour period.

In conclusion, we found that treatment with fixed-combination latanoprost/timolol results in significantly fewer patients with high diurnal IOP fluctuation than does treatment with either latanoprost or timolol monotherapy. Moreover, the fixed
combination may have an independent effect on reducing IOP fluctuation in addition to reducing IOP levels. If it is confirmed that either short- or long-term IOP fluctuation is a risk factor for glaucomatous progression, it will be important to evaluate potential differences among ocular hypotensives in their abilities to reduce fluctuation and to determine whether or not differences are clinically relevant.
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**Competing interest:** Dr. Varma and Mr. Bean are consultants to Pfizer Inc. Drs. Hwang and Grunden are employees of Pfizer Inc. Editorial support, including contributing to the first draft of the manuscript, revising the paper based on author feedback, and styling the paper for journal submission, was provided by Jane G. Murphy, PhD, of Zola Associates and was funded by Pfizer Inc.

**Ethics approval:** Ethics approval was provided by the institutional review board or ethics committee of each participating centre before study initiation. Both studies were conducted in accordance with the Declaration of Helsinki.

**Patient consent:** Obtained.

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**Figure legend:**

**Figure.** Change in intraocular pressure (IOP) fluctuation vs change in mean IOP at week 26 by treatment group.
REFERENCES


**Figure.** Change in intraocular pressure (IOP) fluctuation vs change in mean IOP at week 26 by treatment group.

- **Fixed-combination latanoprost/timolol:**
  - IOP Fluctuation Change = 0.059 x IOP Change -0.504
  - $r = 0.07$ (p-value = 0.2755)

- **Timolol:**
  - IOP Fluctuation Change = 0.291 x IOP Change +0.574
  - $r = 0.27$ (p-value < 0.0001)

- **Latanoprost:**
  - IOP Fluctuation Change = 0.263 x IOP Change +0.676
  - $r = 0.27$ (p-value < 0.0001)