# Lower Limits of Intraocular Pressure in Glaucoma Clinical Trials

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**Purpose:** To determine the association of the lower limit of intraocular pressure (IOP) specified in the inclusion criteria to baseline and active treatment visit IOPs for monotherapy treatments.

**Methods:** A review of clinical trial articles evaluating currently used topical glaucoma medicines. Articles were published between January 1995 and December 2011.

**Results:** This study included 37 monotherapy treatment arms from 15 studies. There were 18 prostaglandin analogs, 8 β-blockers, 8 carbonic anhydrase inhibitors, 2 α-agonists, and 1 unoprostone. For all studies included generally there was a stepwise increase in the baseline 8 AM and diurnal IOP of approximately 1 mm Hg for each 1 mm Hg increase in entry criteria. This was true for all treatment arms together, with or without a PM entry criterion ($P < 0.0001$). However, the inclusion of an afternoon entry criterion time point did not seem to affect average IOP at baseline for the 8 AM and diurnal IOP. The treated reductions from baseline were not statistically different based on morning or afternoon entry criteria for either the 8 AM or diurnal IOPs ($P \geq 0.07$).

**Conclusions:** Progressively higher 8 AM entry criteria IOPs at untreated baseline may influence, depending on design, in a linear manner the 8 AM and diurnal baseline IOPs of glaucoma studies at baseline. However, this effect was not observed in the treated reductions from baseline. Further, the addition of an afternoon entry criterion time point does not seem to change baseline 8 AM and diurnal IOPs.

**Key Words:** lower limit, intraocular pressure, baseline, active treatment visit, glaucoma, clinical trial

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The parallel, randomized, double-masked, active-controlled trial is generally regarded as the most rigorous and unbiased design that most adequately compares 2 glaucoma medicines.[1,2] Important to this design are the intraocular pressure (IOP) entry criteria for a study. The lower limit of IOP is usually set at ≥21 mm Hg to help assure that the study population has the appropriate diagnosis (ocular hypertension or primary open-angle glaucoma).[1,2]

However, higher inclusion values are often considered for baseline pressures to potentially allow for a greater reduction in IOPs with treatment.[3] Further, there is some belief that a larger drop in IOP might better differentiate the ocular hypotensive efficacy between 2 products. Unfortunately, there is little evidence as yet to support this hypothesis. Further, few data are available that examine the impact of the lower limit on the IOP results of clinical trials.

The purpose of this study was to review past parallel, randomized, active-controlled, single-masked, or double-masked monotherapy glaucoma trials to determine the association of the lower limit of IOP specified in the entry criteria to the baseline and active treatment pressures.

## MATERIALS AND METHODS

### Inclusion Criteria

Articles evaluated in this review, published between January 1995 and December 2011, were found through the PubMed database (http://www.pubmed.gov) using search terms: primary open-angle glaucoma, ocular hypertension, IOP, diurnal, monotherapy, baseline, reduction, beta-blockers (timolol, betaxolol), carbonic anhydrase inhibitors (dorzolamide, brinzolamide), alpha-adrenergic agonists (brimonidine), prostaglandins (latanoprost, travoprost, bimatoprost), and unoprostone. Brand names of single-agent glaucoma preparations currently available also were used as search terms.

Complete articles were retrieved for more details and studies were accepted into the analysis based on the inclusion criteria of: randomized, prospective, controlled, parallel, single-masked, or double-masked trial with a treatment period of ≥6 weeks and at least 70 patients per treatment arm. This criterion limiting the sample size was used to assure that individual trials were large enough to assure a minimally sufficient statistical power from which to draw clinically meaningful conclusions. Only trials with ocular hypertension or primary open-angle glaucoma were included. Trials with exfoliation and pigment dispersion glaucoma patients were included if they comprised <10% of the total patient sample size.

Studies must have had both baseline and treated diurnal curve pressure measurements consisting of at least 3 time points. The morning IOP must have been measured between 08:00 and 09:00 and at least 1 time point measured in the afternoon. No more than 6 hours should have separated any 2 measurements.

The baseline IOP between 08:00 and 09:00 should have been ≥22 mm Hg. If an afternoon pressure criterion was set, it should have been ≥18 mm Hg between 16:00 and 18:00. IOPs must have been measured with Goldmann applanation tonometry. Each article was evaluated independently (G.N.M.) to assure that it met the inclusion criteria specified above. All articles meeting the above

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criteria were used in the analysis. No specific exclusion criteria were defined for the study.

Once the articles meeting the inclusion criteria were identified, data were collected regarding the IOP at each time point in the diurnal curve. The primary variable assessed was reduction of IOP from baseline to the last visit. The data from the articles was recorded in an Excel spreadsheet and the baseline and active treatment visit IOPs were analyzed.

## Statistics

PRN Pharmaceutical Research Network, LLC, analyzed the data. The level to declare significance was 0.05 and all analyses were 2-way. Mean IOP values for the morning pressure and diurnal curve were analyzed for the reduction in pressure from baseline, and the differences between each treatment arm and various IOP levels, by an ANOVA test.[4] A modified Bonferroni correction of $\alpha/3$ was used to adjust the *P*-value due to multiple questions.

# RESULTS

## Study Inclusion

This study included 37 monotherapy treatment arms from 15 studies that included untreated baseline pressures. There were 18 prostaglandin analogs, 8 β-blockers, 8 carbonic anhydrase inhibitors, 2 α-agonists, and 1 unoprostone. The total number of subjects included was 5572. The results are shown in the Table 1.

## Baseline Pressures

For all included treatment arms generally there was a stepwise increase in the untreated baseline 8 AM and diurnal pressures of approximately 1 mm Hg for each 1 mm Hg increase in entry criteria. This was true for all treatment arms together, with or without a PM entry criterion ($P < 0.0001$).

However, the inclusion of any PM IOP entry criterion time point (n = 19) did not affect the pressure at baseline for the 8 AM (26.3 vs. 25.7 mm Hg, $P = 0.16$) or diurnal pressures (25.3 vs. 24.5 mm Hg, $P = 0.05$) compared with studies without a PM time point (n = 18).

Further, a stepwise increase in the entry value required by a PM time point, associated with any level of the 8 AM entry criterion, was not associated with a progressive increase in entry pressure for both the 8 AM and diurnal baseline pressures, although a nonprogressive difference was observed between PM entry pressures for the 8 AM baseline pressure ($P = 0.01$).

## Treated Pressures

Similar to the baseline pressures for the absolute treated pressures, there was a stepwise increase in the baseline 8 AM and diurnal pressures of approximately 1 mm Hg for each 1 mm Hg increase in entry criteria. This was true for all treatment arms together and for treatment arms without a PM entry criterion ($P \leq 0.0052$).

However, after a modified Bonferroni correction, for the absolute treated pressures with any PM time point or a progressive increase in the PM time point as well as the reductions from untreated baseline, at 8 AM and for the diurnal pressure, there were no statistical differences in treatment pressures based on entry criteria ($P \geq 0.07$).

Further, for the prostaglandin study arms (most numerous medicine class available to compare reductions across study), the addition of an afternoon time point did not change the treated decrease in pressure for the 8 AM (6.9 vs. 7.7 mm Hg, $P = 0.13$) or diurnal curve (6.6 vs.

**TABLE 1.** Untreated Baseline As Well As Active Treatment Absolute and Reduction of Intraocular Pressures (mm Hg ± SD)

| | | Untreated Baseline | | Absolute Treated | | Treated Reduction | |
|---|---|---|---|---|---|---|---|
| **IOP Entry 8 AM** | **N** | **AM** | **Diurnal** | **AM** | **Diurnal** | **AM** | **Diurnal** |
| Entry IOPs | | | | | | | |
| ≤24-all | 10 | 24.4 ± 0.3 | 23.4 ± 0.4 | 18.5 ± 1.4 | 17.8 ± 1.0 | 5.9 ± 1.2 | 5.6 ± 0.9 |
| 25-all | 9 | 25.5 ± 0.3 | 24.4 ± 0.2 | 18.5 ± 1.8 | 17.9 ± 1.5 | 7.2 ± 1.4 | 6.6 ± 1.3 |
| 26-all | 3 | 26.5 ± 0.4 | 25.4 ± 0.4 | 20.0 ± 1.5 | 19.3 ± 1.2 | 6.1 ± 1.2 | 5.7 ± 0.6 |
| ≥27-all | 15 | 27.3 ± 0.2 | 26.2 ± 0.3 | 20.8 ± 1.4 | 20.2 ± 1.5 | 6.3 ± 1.5 | 5.9 ± 1.4 |
| *P* | | < 0.0001* | < 0.0001* | 0.0009* | 0.0001* | 0.28 | 0.62 |
| Without any PM time point | | | | | | | |
| 24-no PM time point | 5 | 24.4 ± 0.4 | 23.4 ± 0.4 | 17.4 ± 1.2 | 17.4 ± 1.2 | 6.4 ± 1.3 | 6.0 ± 1.0 |
| 25-no PM time point | 7 | 25.5 ± 0.4 | 24.3 ± 0.3 | 17.8 ± 0.9 | 17.4 ± 1.0 | 7.7 ± 1.0 | 7.0 ± 1.1 |
| 26-no PM time point | 1 | 26.1 | 24.9 | 18.9 | 18.7 | 7.2 | 6.3 |
| 27-no PM time point | 5 | 27.2 ± 0.1 | 25.9 ± 0.2 | 20.2 ± 1.2 | 19.6 ± 1.3 | 7.0 ± 1.1 | 6.2 ± 1.4 |
| *P* | | < 0.0001* | < 0.0001* | 0.0052* | 0.0041* | 0.18 | 0.48 |
| With any PM time point | | | | | | | |
| 24-any PM time point | 5 | 24.4 ± 0.2 | 23.4 ± 0.4 | 18.8 ± 1.1 | 18.1 ± 0.9 | 5.6 ± 1.1 | 5.3 ± 0.7 |
| 25-any PM time point | 2 | 25.4 ± 0.1 | 24.7 ± 0.2 | 21.2 ± 2.2 | 19.9 ± 1.6 | 5.3 ± 1.4 | 5.1 ± 0.7 |
| 26-any PM time point | 2 | 26.7 ± 0.1 | 25.5 ± 0.3 | 20.4 ± 1.6 | 20.3 ± 1.3 | 5.6 ± 1.5 | 5.3 ± 1.2 |
| 27-any PM time point | 10 | 27.3 ± 0.3 | 26.3 ± 0.3 | 21.1 ± 1.5 | 20.5 ± 1.5 | 5.9 ± 1.6 | 5.7 ± 1.5 |
| *P* | | < 0.0001* | < 0.0001* | 0.07 | 0.04 | 0.83 | 0.83 |
| With specific PM time point | | | | | | | |
| Any PM time point 21 | 10 | 26.6 ± 1.0 | 25.4 ± 1.2 | 20.2 ± 1.7 | 19.4 ± 1.4 | 6.3 ± 1.4 | 6.0 ± 1.3 |
| Any PM time point 22 | 3 | 24.3 ± 0.2 | 23.7 ± 0.2 | 19.3 ± 1.0 | 18.6 ± 0.7 | 5.0 ± 0.9 | 5.1 ± 0.8 |
| Any PM time point >22 | 6 | 26.9 ± 1.1 | 25.9 ± 1.0 | 21.6 ± 1.2 | 21.1 ± 1.3 | 5.2 ± 0.9 | 4.8 ± 0.7 |
| *P* | | 0.0064* | 0.03 | 0.08 | 0.02 | 0.08 | 0.07 |

*Statistical after Bonferroni correction.
AM indicates morning; IOP, intraocular pressure; PM, afternoon.

7.1 mm Hg, $P = 0.31$) time points compared with treatment arms without a PM time point.

## DISCUSSION

This study showed for baseline IOPs generally there was a stepwise increase in the baseline 8 AM and diurnal pressures of approximately 1 mm Hg for each 1 mm Hg increase in entry criteria. This was true for all treatment arms together, with or without a PM entry criterion. However, a stepwise increase of a PM time point did not demonstrate a progressive increase in entry pressure for both the 8 AM and diurnal baseline pressures. Further, the inclusion of an afternoon entry criterion time point did not alter the average inclusion pressures at 8 AM or for the diurnal curve compared with studies that did not include such a criterion.

Similar to the baseline pressures for the absolute treated pressures, there was a stepwise increase in the baseline 8 AM and diurnal pressures of approximately 1 mm Hg for each 1 mm Hg increase in entry criteria. This was true for all for all treatment arms together and for treatment arms without a PM entry criteria.

However, for the absolute treated pressures for treatment arms with a PM time point entry criterion, or for all treatment arms regarding the reduction from untreated baseline, there were no statistical differences in treatment pressures based on entry criteria. Further, the addition of an afternoon entry criterion did not change the average treated absolute level of pressure compared with treatment arms without an afternoon entry criterion for prostaglandin treatment arms.

These data were not consistent with data by Heijl et al,[3] who showed a greater reduction in pressure based on higher entry pressures. The common belief that higher pressures at baseline would help differentiate 2 competing products because a greater reduction would tend to widen any potential differences has not yet been proved.

The results of this study are important because they can help guide sponsors of large pharmaceutical trials in their development of a protocol design by realizing that admitting patients with higher IOPs will not necessarily produce greater decreases in pressures. Further, the addition of an afternoon time point will not assist in providing higher baseline pressures. The avoidance of both of these inclusion criteria might theoretically speed subject recruiting. This study suggests that progressively higher 8 AM entry criteria pressures at untreated baseline may influence, depending on design, in a linear manner the 8 AM and diurnal baseline pressures of glaucoma studies at baseline. However, this effect was not observed in the treated reductions from baseline. Further, the addition of an afternoon entry criterion time point does not seem to change baseline 8 AM and diurnal pressures.

The results of this study are limited by the relatively small number of phase III/IV trials available. In addition after treatment, despite the paired comparisons, the different treatment classes could have distorted the results. More research is needed to fully understand the influence of differences in entry criteria on baseline and active treatment visit pressures as well as the influence of baseline pressures on differentiating between 2 products.

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