

# Intraocular Pressure–Lowering Effects of All Commonly Used Glaucoma Drugs

## A Meta-analysis of Randomized Clinical Trials

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**Objective:** To estimate the intraocular pressure (IOP) reduction achieved by the most frequently prescribed glaucoma drugs and a placebo in a meta-analysis of randomized clinical trials.

**Design:** Meta-analysis of randomized clinical trials.

**Participants:** Twenty-seven articles reporting on 28 randomized clinical trials. These articles reported 6953 participants for the trough and 6841 for the peak.

**Methods:** Articles published up to December 2003 were identified in the following data sources: Medline, Embase, and the Cochrane Controlled Trials Register, and references from relevant articles. Over 85% of the patients had to be diagnosed with primary open-angle glaucoma (POAG) or ocular hypertension (OH), and articles had to be written in English, German, French, or Dutch. Quality of trials was assessed by a Delphi list with additions. The pooled 1-month IOP-lowering effect from baseline at peak and trough was calculated by performing meta-analysis using the random effects model.

**Main Outcome Measures:** Absolute and relative change in IOP from baseline, for peak and trough moments.

**Results:** Relative IOP reductions from baseline [mean (95% confidence interval)] were –23% (–25% to –22%) for a peak and –20% (–23% to –17%) for a trough for 0.5% betaxolol; peak, –27% (–29% to –25%), and trough, –26% (–28% to –25%), for 0.5% timolol; peak, –22% (–24% to –20%), and trough, –17% (–19% to –15%), for 2.0% dorzolamide; peak, –17% (–19% to –15%), and trough, –17% (–19% to –15%) for 1.0% brinzolamide; peak, –25% (–28% to –22%), and trough, –18% (–21% to –14%) for 0.2% brimonidine; peak, –31% (–33% to –29%), and trough, –28% (–30% to –26%) for 0.005% latanoprost; peak, –31% (–32% to –29%), and trough, –29% (–32% to –25%) for 0.004% travoprost; peak, –33% (–35% to –31%), and trough, –28% (–29% to –27%) for 0.03% bimatoprost; and peak, –5% (–9% to –1%), and trough, –5% (–10% to –0%) for the placebo. The difference in absolute IOP reduction from baseline between timolol and prostaglandin analogs or prostamide varied from –0.4 to 0.1 mmHg at trough and from 1.0 to 1.5 mmHg at peak. Quality scores of included studies were generally high, a mean of 14.2 on a scale from 0 to 20 (interquartile range, 13–16).

**Conclusion:** This meta-analysis suggests that bimatoprost, travoprost, latanoprost, and timolol are the most effective intraocular pressure–reducing agents in POAG and OH patients. *Ophthalmology* 2005;112:1177–1185 © 2005 by the American Academy of Ophthalmology.

Glaucoma is the third largest cause of worldwide blindness. It is estimated that, in 2000, 67 million people worldwide had primary glaucoma, with 6.7 million suffering from bilateral blindness.<sup>1</sup> In Caucasians, approximately 70% of glaucoma patients have primary open-angle glaucoma

(POAG). The treatment of glaucoma focuses mainly on the reduction of intraocular pressure (IOP) with drugs, laser, or surgery.

In the last decade, several new drugs to lower IOP were introduced. Because these drugs have mechanisms of action

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Table 1. Drugs Included in the Meta-analysis with the Most Commonly Prescribed Regimen and Moment Chosen for Peak and Trough Measurements

Drug	Concentration (%)	Dosing Frequency	Moment of Administration	Peak	Trough
Timolol	0.5	Twice daily	Morning evening	2 hrs after morning administration	12 hrs after evening administration
Betaxolol	0.5	Twice daily	Morning, evening	2 hrs after morning administration	12 hrs after evening administration
Brimonidine	0.2	Twice daily	Morning evening	2 hrs after morning administration	12 hrs after evening administration
Dorzolamide	2.0	Twice or thrice daily	Morning, (afternoon), evening	2 hrs after morning administration	12 hrs after evening administration
Brinzolamide	1.0	Thrice daily	Morning, afternoon, evening	2 hrs after morning administration	12 hrs after evening administration
Latanoprost	0.005	Once daily	Evening	12 hrs after evening administration	24 hrs after evening administration
Travoprost	0.004	Once daily	Evening	12 hrs after evening administration	24 hrs after evening administration
Bimatoprost	0.03	Once daily	Evening	12 hrs after evening administration	24 hrs after evening administration

and contraindications that are different from the more classic drugs ( $\beta$ -blockers), the number of treatment options has increased substantially. However, there is controversy as to the degree of reduction of IOP that can be achieved with different drugs. This controversy is fueled by the preferred citation of studies with a favorable result for certain new drugs and the absence of a recent and adequate systematic review that summarizes the results of the individual clinical trials.

In contrast to the statement that "meta-analysis is not available for any of the drugs used for glaucoma treatment with the exception of beta-blockers,"<sup>2</sup> we found 2 recently published meta-analyses.<sup>3,4</sup> These reported on latanoprost versus timolol and latanoprost or brimonidine versus timolol or betaxolol. In these meta-analyses, the mean of morning, noon, and evening IOPs was calculated, but the calculated summary statistics did not give insight into possible differences between peak and trough effects. This latter issue could be important in clinical practice, because some of the new medications are administered only once daily. Thus, the differences in effect on IOP between the new drugs and  $\beta$ -blockers could diverge at peak and trough. Finally, several new studies have been published since these 2 meta-analyses.

Hence, we conducted a meta-analysis of all frequently prescribed drugs for glaucoma, including the prostamide bimatoprost and the prostaglandin analog travoprost. To improve homogeneity, we used strict eligibility criteria. Moreover, we estimated peak and trough IOP reductions of every drug separately.

## Materials and Methods

Articles were identified through a computerized search in Medline, Embase, and the Cochrane Controlled Trials Register. The search strategy, as advised by the Cochrane Collaboration, was used to identify randomized clinical trials.<sup>5-7</sup> The keywords for medication were *betaxolol*, *timolol*, *dorzolamide*, *brinzolamide*, *brimonidine*, *latanoprost*, *travoprost*, and *bimatoprost* and their commercial names. The keywords for the disease were *ocul\** and *hypert\**, explode *Ocular-hypertension/all* subheadings, *glaucom\**, and explode *Glaucoma/all* subheadings. Relevant publications were examined for references until no further studies were found.

Potentially eligible for inclusion in our meta-analysis were randomized clinical trials on IOP-lowering drugs, written in En-

glish, French, German, or Dutch and published up to December 2003. After completion of the searches, title, abstract, and medical subject heading (MeSH) words of the obtained publications were used for a rough judgment of an article's eligibility. This was done by one researcher (JSAGS). Of the remaining identified publications, the complete articles were printed or photocopied to judge whether they reported randomized clinical trials. The remaining potentially eligible trials were distributed to 1 of 2 researchers (CABW and RvdV) using a computerized list of random numbers. The observers were blinded to the names of the authors and their institutions, the names of the journals, sources of funding, and acknowledgments, as well as the financier of the study.<sup>6,8</sup>

Trials were excluded if they did not include one of the medications listed in Table 1 or a placebo in  $\geq 2$  of their study arms.

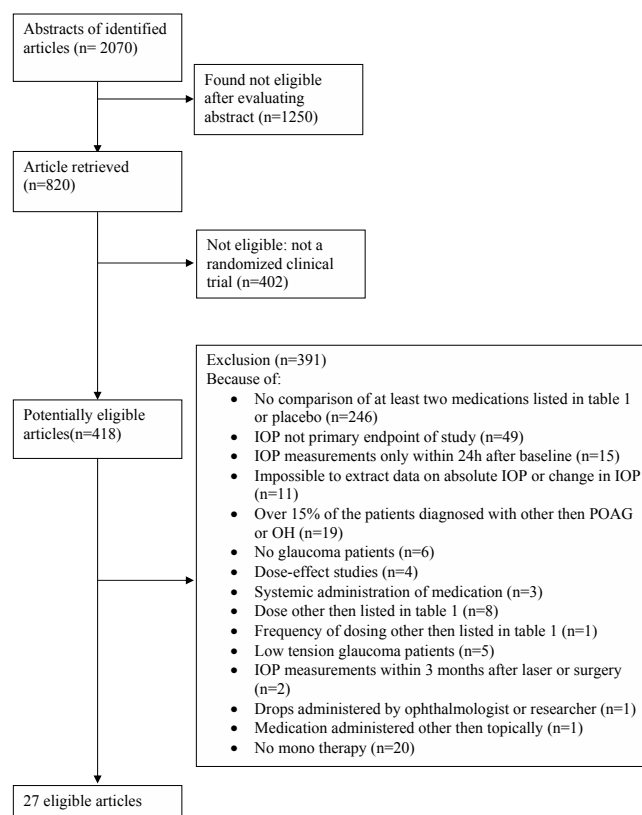


Figure 1. Flowchart of selection of studies. IOP = intraocular pressure; OH = ocular hypertension; POAG = primary open-angle glaucoma.

Table 2. Quality Items Included for Quality Assessment, Source from Which the Quality Item Was Obtained, and Number of Publications That Had a Positive Quality Score, per Quality Item

Item Code	Source*	Quality Item	No. of Publications Scored "Yes"
A	Delphi list	Was a method of randomization used?	27
B	Added by authors <sup>†</sup>	Is the period of outcome measurements equal for all groups?	27
C	Considered for Delphi list	Is it unlikely that compliance may explain differences between groups?	27
D	Added by authors	Are side effects reported?	26
E	Added by authors	Were short- and long-term follow-up IOP measurements performed?	26
F	Added by authors	Are times of IOP measurements equal for all-groups?	26
G	Delphi list <sup>‡</sup>	Were inclusion criteria specified?	25
H	Delphi list <sup>‡</sup>	Were exclusion criteria specified?	25
I	Considered for Delphi list	Are the interventions described explicitly?	25
J	Delphi list	Were the groups similar at baseline regarding the most important prognostic indicators?	22
K	Delphi list	Were point estimates and measures of variability presented for the primary outcome measures?	21
L	Added by authors	Is information about the method of IOP measurement presented?	20
M	Added by authors	Are times between applying the eyedrop and IOP measurement equal for all groups?	20
N	Considered for Delphi list	Was comedication avoided or standardized?	19
O	Delphi list	Was the patient masked to the treatment?	16
P	Considered for Delphi list	Was calculation of statistical power reported after allocation to the treatment?	16
Q	Delphi list	Was an intention-to-treat analysis performed?	15
R	Delphi list	Was the treatment allocation concealed?	0
S	Delphi list	Was the outcome assessor blinded?	0
T	Delphi list	Was the care provider blinded?	0

IOP = intraocular pressure.

\*Verhagen AP, de Vet HC, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;51:1235–41.

<sup>†</sup>The authors added items specifically important for interpreting IOP measurements.

<sup>‡</sup>Item split into inclusion and exclusion criteria.

Other exclusion criteria are listed in [Figure 1](#).

The reason for exclusion was recorded on a standard form. In case more than one reason for exclusion was present, only the first reason encountered was listed in [Figure 1](#). Excluded publications were reassessed to make sure all eligible publications were included. At the start of this selection process, there were common meetings with a third researcher (JSAGS). After this, 25 articles were judged by 2 researchers independently to evaluate agreement in judgment of inclusion or noninclusion, and yielded a  $\kappa$  of 1.0.

Included articles' data were extracted using a standard form. Operationalization of the items on this form was achieved by consensus meetings of the 3 researchers (JSAGS, CABW, RvdV) before the the process of data abstraction began. The 3 researchers met on a regular basis to discuss any ambiguity.

### Quality Assessment

Methodological quality was evaluated using the Delphi list<sup>9</sup> with additional items. Items specifically important for interpreting IOP measurements were also added ([Table 2](#)). Each item in this quality list had the same weight. For each publication, a quality score was calculated, where "yes" was scored as 1 point for a certain quality item and "no" and "do not know" were scored as 0 points. For scoring quality items on masking, allocation concealment, and intention-to-treat analysis, we used suggestions from Berger et al.<sup>10–13</sup>

### Outcome Measure

The outcome measure was the change in IOP from baseline at 1 month. In case the measurement at 1 month was not present, the

first measurement after 1 month was accepted, with a maximum of 6 months. In absence of an IOP value reported in a table or text, the IOP was measured when presented in a figure. If no IOP at 1 month from baseline was reported in a figure, the value was measured at another point in time, using the earlier mentioned sequence. In case of a crossover design, data were extracted only from the period before crossing over of therapies. Figures used to extract data were electronically scanned and viewed at full screen size (1400×1050 pixels). A digital ruler was used to measure the number of pixels corresponding with the IOP baseline value, and the value corresponding to change in IOP was measured. All figures were read by the same researcher (CABW).

Original data were obtained from the articles as much as possible; data that could not be obtained were to be calculated when necessary. When the number of patients at a relevant point in time was not reported, this number was calculated using the number of patients lost to follow-up. In case the moment of loss to follow-up was unclear, the overall number of patients lost to follow-up was used to calculate the number of patients at the relevant time point. In case no data on the number of patients lost to follow-up were present, the number of patients at baseline was used as an estimate.

Peak and trough measurements were noted ([Table 1](#)). Peak and trough moments for each medication were as advised by the American Academy of Ophthalmology.<sup>14</sup> In case dorzolamide monotherapy was administrated 3 times daily, morning measurements were included in the analysis.

Three publications did not report peak or trough moments, just means of measurements over the day. These means were used in the calculation of peak and trough values.<sup>15–17</sup> If a study appeared in

Table 3. Baseline Characteristics

Trial	Medication	Country	End Point Measurement	No. of Patients at Baseline	Withdrawals (%)
Rusk et al <sup>†</sup>	Betaxolol vs. dorzolamide	USA	1 mo	311	5.1
Strahlman et al <sup>26</sup>	Betaxolol vs. dorzolamide vs. timolol	USA	1 mo	568	9.9
Nordmann et al <sup>  </sup>	Betaxolol vs. timolol	France	3 mos	278	5.0
Stewart et al <sup>16</sup>	Betaxolol vs. timolol	USA	1 mo <sup>¶</sup>	29	0.0
Collignon-Brach <sup>#</sup>	Betaxolol vs. timolol	Belgium	3 mos	20	NR
Noecker et al <sup>21</sup>	Bimatoprost vs. latanoprost	USA	1 mo <sup>**</sup>	269	7.4
Gandolfi et al <sup>††</sup>	Bimatoprost vs. latanoprost	Italy	3 mos	232	7.8
DuBiner et al <sup>24</sup>	Bimatoprost vs. latanoprost vs. placebo	USA	1 mo	64	7.8
Parrish et al <sup>23</sup>	Bimatoprost vs. latanoprost vs. travoprost	USA	3 mos	410	6.8
Brandt et al <sup>19</sup>	Bimatoprost vs. timolol	USA	3 mos <sup>**</sup>	353	5.1
Whitcup et al <sup>20</sup>	Bimatoprost vs. timolol	USA	3 mos <sup>**</sup>	362	5.0
Higginbotham et al <sup>18</sup>	Bimatoprost vs. timolol	Australia	6 wks	715	16.0
Noecker et al <sup>§§</sup>	Bimatoprost vs. travoprost	USA	1 mo	31	6.5
Kampik et al <sup>15</sup>	Brimonidine vs. latanoprost	Germany	6 mos <sup>¶¶</sup>	379	12.6
DuBiner et al <sup>   </sup>	Brimonidine vs. latanoprost	USA	1 mo	127	5.5
Schuman <sup>¶¶¶</sup>	Brimonidine vs. timolol	USA	1 mo	926 <sup>###</sup>	9.6
Sall et al <sup>9</sup>	Brinzolamide vs. dorzolamide vs. placebo	USA	1 mo	294	6.8
O'Donoghue et al <sup>***</sup>	Dorzolamide vs. latanoprost	United Kingdom	3 mos	224	4.9
Wilkerson et al <sup>†††</sup>	Dorzolamide vs. placebo	USA	1 mo	48	8.3
Boyle et al <sup>25</sup>	Dorzolamide vs. timolol	USA	1 mo	221	2.2
Alm et al <sup>§§§</sup>	Latanoprost vs. timolol	Scandinavia	3 mos	178	NR
Camras et al <sup>¶¶¶¶</sup>	Latanoprost vs. timolol	USA	6 mos <sup>**</sup>	268	7.5
Aquino and Lat-Luna <sup>17</sup>	Latanoprost vs. timolol	Philippines	6 wks <sup>¶¶</sup>	60	5.0
Watson et al <sup>####</sup>	Latanoprost vs. timolol	United Kingdom	6 mos (peak), 6 wks (trough)	294	8.8
Netland et al <sup>22</sup>	Latanoprost vs. timolol vs. travoprost	USA	6 wks	585	1.9
Fellman et al <sup>****</sup>	Timolol vs. travoprost	USA	6 wks	396	2.7
Goldberg <sup>††††</sup>	Timolol vs. travoprost	USA	6 wks (8 AM and 10 AM), 3 mos (4 PM)	382	NR

Publications cited in this table with superscript numbers can be found in "References."

NR = not reported; OH = ocular hypertension; POAG = primary open-angle glaucoma; SD = standard deviation.

\*Pooled value, measurements closest to 8 AM.

<sup>†</sup>Rusk C, Sharpe E, Laurence J, et al. Dorzolamide Comparison Study Group. Comparison of the efficacy and safety of 2% dorzolamide and 0.5% betaxolol

<sup>‡</sup>Open-angle glaucoma or ocular hypertension.

<sup>§</sup>Open-angle glaucoma.

<sup>||</sup>Nordmann JP, Mertz B, Yannoulis NC, et al. Unoprostone Monotherapy Study Group-EU. A double-masked randomized comparison of the efficacy and hypertension. 6 month data. *Am J Ophthalmol* 2002;133:1-10.

<sup>¶</sup>Mean of peak and trough.

<sup>#</sup>Collignon-Brach J. Long-term effect of ophthalmic beta-adrenoceptor antagonists on intraocular pressure and retinal sensitivity in primary open-angle

<sup>\*\*</sup>Data measured out of figures.

<sup>††</sup>Gandolfi S, Simmons ST, Sturm R, et al. Bimatoprost Study Group 3. Three-month comparison of bimatoprost and latanoprost in patients with

<sup>‡‡</sup>Chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridectomy, pseudoexfoliative glaucoma, or pigmentary glaucoma.

<sup>§§</sup>Noecker RJ, Earl ML, Mundorf T, et al. Bimatoprost 0.03% versus travoprost 0.004% in black Americans with glaucoma or ocular hypertension. *Adv*

<sup>|||</sup>DuBiner HB, Mroz M, Shapiro AM, et al. Brimonidine vs. Latanoprost Study Group. A comparison of the efficacy and tolerability of brimonidine and Ther 2001;23:1969-83.

<sup>¶¶¶</sup>Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. *Surv Ophthalmol* 1996;41(suppl):

<sup>###</sup>Two studies reported in the same publication; demographics presented only for per protocol analysis (n = 837).

<sup>\*\*\*</sup>O'Donoghue EP, UK and Ireland Latanoprost Study Group. A comparison of latanoprost and dorzolamide in patients with glaucoma and ocular

<sup>†††</sup>Wilkerson M, Cyrlin M, Lippa EA, et al. Four-week safety and efficacy study of dorzolamide, a novel, active topical carbonic anhydrase inhibitor. *Arch*

<sup>¶¶¶</sup>Primary open-angle glaucoma or ocular hypertension.

<sup>§§§</sup>Alm A, Widengard I, Kjellgren D, et al. Latanoprost administered once daily caused a maintained reduction of intraocular pressure in glaucoma

<sup>|||</sup>Primary open-angle glaucoma, ocular hypertension, capsular glaucoma, or pigmentary glaucoma.

<sup>¶¶¶¶</sup>Camras CB, United States Latanoprost Study Group. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a

<sup>####</sup>Watson P, Stjernschantz J, Latanoprost Study Group. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle

<sup>\*\*\*\*</sup>Fellman RL, Sullivan EK, Ratliff M, et al. Travoprost Study Group. Comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients

<sup>††††</sup>Goldberg I, Cunha-Vaz J, Jakobsen JE, et al. Comparison of tropical travoprost eye drops given once daily and timolol 0.5% given twice daily in

more than one publication, the most recent results with complementary data from previous articles were used for statistical analysis. In one article, results from earlier studies were combined with new data. However, in this publication trough values were not presented.<sup>18</sup> Therefore, these values were extracted from 2 earlier studies.<sup>19,20</sup>

## Statistical Analysis

Absent absolute values were calculated by use of the baseline value and the difference from baseline. In case standard deviation (SD) could not be obtained from the publication, it was calculated

of Included Publications

Gender (Male/Female)	Mean Age (yrs)	Types of Glaucoma			Baseline IOP (mm Hg) [mean (SD)]*	Quality Score	Quality Criteria Not Fulfilled
		POAG	OH	Others			
138/173	64	NR <sup>‡</sup>	NR <sup>‡</sup>	NR <sup>‡</sup>	24.8 (4.7)	14	l, n, o, r, s, t
243/280	62	371 <sup>§</sup>	197	NR <sup>§</sup>	26.8 (4.9)	17	r, s, t
150/128	63	135	128	15	24.4 (2.7)	16	o, r, s, t
12/17	65	11	18	0	28.3 (2.9)	14	n, p, q, r, s, t
NR	60	20	0	0	24.3 (3.8)	5	d, f, g, h, i, j, l, m, n, o, p, q, r, s, t
103/166	61	155	93	21	24.9 (2.7)	18	r, s, t
87/145	62	138	81	13	25.7 (3.8)	16	o, r, s, t
29/35	66	29	35	0	25.5 (2.6)	15	o, q, r, s, t
172/238	65	309	95	6	25.6 (2.9)	16	o, r, s, t
145/208	63	227 <sup>**</sup>	126	NR <sup>**</sup>	26.0 (3.3)	18	r, s, t
162/200	60	186 <sup>**</sup>	176	NR <sup>**</sup>	25.9 (3.1)	15	k, m, o, r, s, t
307/408	62	413 <sup>**</sup>	302	NR <sup>**</sup>	25.9 (3.1)	14	k, l, n, r, s, t
11/20	65	28	3	0	26.0 (1.6)	13	k, l, p, q, r, s, t
154/225	65	284	64	31	22.8 (3.0)	13	j, m, o, p, r, s, t
52/75	61	93	34	0	24.3 (2.1)	15	p, q, r, s, t
421/416	62	513	324	0	24.8 (3.2)	13	l, o, p, q, r, s, t
131/163	64	217	70	7	26.5 (2.4)	16	q, r, s, t
130/94	67	120	88	16	27.7 (3.6)	12	m, n, o, p, q, r, s, t
23/25	63	NR <sup>***</sup>	NR <sup>***</sup>	0	27.1 (3.7)	11	e, j, n, o, p, q, r, s, t
117/104	62	NR <sup>‡</sup>	NR <sup>‡</sup>	NR <sup>‡</sup>	28.0 (4.6)	17	l, r, s, t
43% male	66	NR <sup>    </sup>	NR <sup>    </sup>	NR <sup>    </sup>	24.5 (3.2)	8	g, h, i, j, l, m, n, p, q, r, s, t
152/154	62	84	170	14	25.3 (4.1)	17	p, r, s, t
38/22	57	55	4	1	29.3 (9.1)	13	j, o, p, q, r, s, t
191/103	65	121	148	25	26.3 (3.8)	17	q, r, s, t
296/289	NR	396	181	8	26.9 (3.8)	17	k, r, s, t
188/208	64	251	132	13	27.3 (5.4)	16	k, m, r, s, t
192/190	63	208	147	27	27.3 (2.9)	16	k, m, r, s, t

in the treatment of elevated intraocular pressure. Clin Ther 1998;20:454–66.

safety of unoprostone with timolol and betaxolol in patients with primary open-angle glaucoma including pseudoexfoliation glaucoma or ocular

glaucoma. Curr Eye Res 1992;11:1–3.

glaucoma and ocular hypertension. Adv Ther 2001;18:110–21.

Ther 2003;20:121–8.

latanoprost in adults with open-angle glaucoma or ocular hypertension: a three-month, multicenter, randomized, double-masked, parallel-group trial. Clin S27–37.

hypertension: a 3 month, randomised study. Br J Ophthalmol 2000;84:579–82.

Ophthalmol 1993;111:1343–50.

patients treated concomitantly with timolol. Br J Ophthalmol 1995;79:12–6.

six-month masked, multicenter trial in the United States. Ophthalmology 1996;103:138–47.

glaucoma and ocular hypertension. Ophthalmology 1996;103:126–37.

with elevated intraocular pressure: a 6-month, masked, multicenter trial. Ophthalmology 2002;109:998–1008.

patients with open-angle glaucoma or ocular hypertension. J Glaucoma 2001;10:414–22.

using the number of patients and standard error of the mean (SEM). In case neither an SD nor an SEM of the follow-up measurement was available, baseline SD was used as an estimate of the SD of the follow-up measurement.

In 2 publications, only the *P* value for the difference in IOP values between arms was reported as a measure of deviation.<sup>21,22</sup>

The *P* value and the sample sizes of the arms were used to calculate the SD of the difference in IOP between baseline and follow-up measurements.

In absence of a reported difference in IOP between baseline and follow-up measurements, change in IOP was calculated. In absence of a SD of the change in IOP, this SD was calculated by the formula:

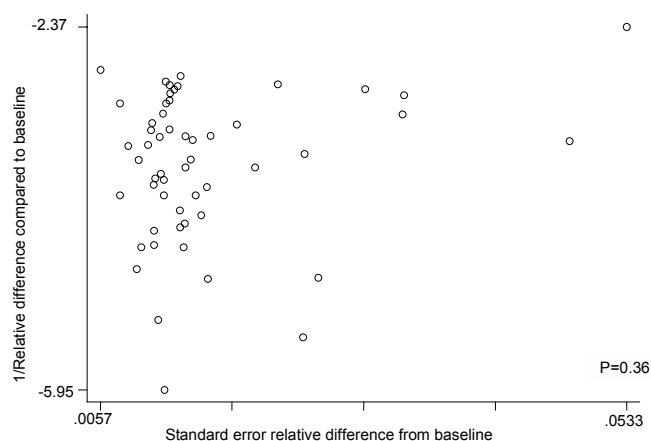


Figure 2. Funnel plot, relative change from baseline at peak moment, and P value of Egger's measure of publication bias.

$$\text{Var}(\text{IOP}_{\text{follow-up measurement}} - \text{IOP}_{\text{baseline}}) = (\text{IOP}_{\text{follow-up measurement}})^2 + \text{Var}(\text{IOP}_{\text{baseline}}) - 2\rho \text{SD}(\text{IOP}_{\text{baseline}})\text{SD}(\text{IOP}_{\text{follow-up measurement}})$$

$$\rho = \frac{\text{Var}(\text{IOP}_{\text{follow-up measurement}}) + \text{Var}(\text{IOP}_{\text{baseline}}) - \text{Var}(\text{IOP}_{\text{follow-up measurement}} - \text{IOP}_{\text{baseline}})}{2\text{SD}(\text{IOP}_{\text{baseline}})\text{SD}(\text{IOP}_{\text{follow-up measurement}})}$$

where  $\text{SD}(\text{IOP}_{\text{follow-up measurement}} - \text{IOP}_{\text{baseline}}) = \sqrt{\text{Var}(\text{IOP}_{\text{follow-up measurement}} - \text{IOP}_{\text{baseline}})}$ . The correlation coefficient  $\rho$  indicates correlation between baseline SD and SD of the follow-up measurement, as calculated out of the results of all studies reporting complete data on IOP baseline measurement and SD, follow-up measurement and SD, and difference between baseline and follow-up measurements and SD.<sup>15,23–26</sup> The value of this correlation coefficient is 0.5. In case no relative reduction was reported, this was calculated from the absolute change in IOP. The SD of relative change (%) was calculated as  $\text{SD}_{\text{relative change}} = \text{SD}_{\text{change}}/\text{IOP}_{\text{baseline}}$ . Pooled IOP values were calculated using a random effects model with STATA.<sup>27</sup>

To detect publication biases, we explored asymmetry in funnel plots. These were examined visually; furthermore, Egger's measure of publication bias was calculated.<sup>28</sup>

## Results

### Study Eligibility and Quality

The flow of the randomized clinical trials included in our analysis is shown in Figure 1. The characteristics of the eligible studies are summarized in Table 3. In general, the quality of included studies was high (Table 3). The mean total quality score for all studies is 14.2, on a scale from 0 to 20 (interquartile range, 13–16). Twenty-six articles were included, which reported on 27 trials; 56 arms were reporting peak measurements; and 52 arms were reporting trough measurements. We included 6953 subjects for peak and 6861 for trough. We could not identify heterogeneity in funnel plots; P values for absolute change from baseline Egger's measure of publication bias were 0.57 at peak and 0.36 at trough. For relative change from baseline, these P values were 0.36 at peak and 0.22 at trough. Therefore, no publication bias was found. Because no relevant differences were observed by eyeballing or by statistics, only a single funnel plot is presented (Fig 2).

### Intraocular Pressure Lowering

In Table 4, absolute and relative changes from baseline and a 95% percent confidence interval are presented. Pooled changes from baseline for a placebo were  $-1.3$  mmHg at trough and  $-1.6$  mmHg at peak. Trough change from baseline achieved by glaucoma monotherapy varied from  $-4.5$  mmHg for brimonidine to  $-7.0$  mmHg for travoprost. Change from baseline at peak varied from  $-4.4$  mmHg for brinzolamide to  $-8.4$  mmHg for bimatoprost.

Calculated in relative measures, a placebo gave a 5% change from baseline at trough and at peak. Relative change from baseline at trough ranged from  $-17\%$  for brinzolamide and dorzolamide to  $-29\%$  for travoprost. At peak, changes for baseline varied from  $-17\%$  for brinzolamide to  $-33\%$  for bimatoprost (Table 4). The results did not substantially differ when studies reporting 6-month results or 6- and 3-month results were left out of the analysis. For brinzolamide, only one eligible publication was found; therefore, the effects as reported in the publication are reported in Table 4.<sup>29</sup>

## Discussion

Our results confirm that the 8 drugs evaluated in this meta-analysis lower IOP more effectively than a placebo. The highest reduction in IOP at peak was achieved by bimatoprost (33%), followed by latanoprost, travoprost, timolol, brimonidine, betaxolol, dorzolamide, brinzolamide (17%), and a placebo (5%). At trough, the order is travoprost (31%), bimatoprost, latanoprost, timolol, betaxolol, brimonidine, brinzolamide, dorzolamide (17%), and a placebo (5%). However, the differences between prostaglandin analogs prostamide and timolol are small, especially at trough. We believe that our results are robust because the quality of the included studies was generally high, with a mean quality score of 14.2 on a scale of 0 to 20.

Several methodological aspects of our meta-analysis deserve further consideration. We selected trials in which the concentration of drug, the moment of applying, and frequency of dosing were as recommended by the American Academy of Ophthalmology.<sup>14</sup> This implies that the IOP reductions observed in this meta-analysis can be achieved in daily practice. Furthermore, the separate analysis of IOP reduction at peak and trough enables a more accurate comparison of the merits of the individual drugs.

The primary indication for the investigated drugs is a diagnosis of POAG or OH; therefore, we aimed to include a homogeneous population with these conditions. However, 8 of the 27 included trials did not specify diagnosis completely, and reported OAG and OH. These studies were included. A study conducted by the present authors showed that, in a cohort of pharmaceutically treated glaucoma patients, 93% of OAG and OH patients were diagnosed with POAG or OH (van der Valk, Schouten, Webers, unpublished data). Hence, we are confident that at least 85% of patients in each of the studies included had the condition of interest.

We scored the quality of studies included in our meta-analysis to assess the robustness of our summary estimates of effects. Out of the >60 methods that are available for validity assessment of randomized clinical trials, we chose the Delphi list,<sup>9</sup> which has been developed after consensus meetings between experts on quality assessment from dif-

Table 4. Absolute and Relative Change in Intraocular Pressure from Baseline Number of Studies

Group	Generic Product	Absolute change (mmHg)		Relative Change (%)		No. of Studies	References
		Mean Difference from Baseline	95% Confidence Limits	Mean Difference from Baseline	95% Confidence Limits		
Placebo	Trough	-1.3	-2.4 to -0.3	-5	-9 to -1	3	24,29,*
	Peak	-1.6	-2.7 to -0.5	-5	-10 to 0	3	24,29,*
β-blockers	Betaxolol, trough	-5.2	-6.3 to -4.1	-20	-23 to -17	4	16,26,†,‡
	Betaxolol, peak	-6.0	-6.6 to -5.3	-23	-25 to -22	5	16,26,†,‡,§
	Timolol, trough	-6.9	-7.4 to -6.5	-26	-28 to -25	15	16,17,19,20,22,25,26,†,‡,§,  ,¶,##,*,††,‡‡
	Timolol, peak	-6.9	-7.5 to -6.3	-27	-29 to -25	15	16-18,22,25,26,†,‡,§,  ,¶,##,*,††,‡‡
	Bimatoprost, trough	-6.5	-6.8 to -6.1	-28	-29 to -27	6	19-21,23,24,§§
Prostaglandin analogs or prostamide	Bimatoprost, peak	-8.4	-9.0 to -7.8	-33	-35 to -31	6	18,21,23,24,§§,
	Latanoprost, trough	-6.8	-7.6 to -6.1	-28	-30 to -26	11	15,17,21-24,¶,##,*,§§,¶¶
	Latanoprost, peak	-7.9	-8.3 to -7.4	-31	-33 to -29	12	15,17,21-24,¶,##,*,§§,¶¶,###
	Travoprost, trough	-7.0	-8.2 to -5.7	-29	-32 to -25	4	22,23,††,‡‡
	Travoprost, peak	-8.2	-8.7 to -7.7	-31	-32 to -29	5	22,23,††,‡‡,
α <sub>2</sub> -adrenergic agent	Brimonidine, trough	-4.5	-5.2 to -3.8	-18	-21 to -14	3	15,
	Brimonidine, peak	-6.1	-6.7 to -5.4	-25	-28 to -22	4	15,  ,##
	Brinzolamide, trough	-4.5	-5.1 to -3.9	-17	-19 to -15	1	29
Carbonic anhydrase inhibitors	Brinzolamide, peak	-4.4	-5.0 to -3.8	-17	-19 to -15	1	29
	Dorzolamide, dal	-4.5	-5.0 to -4.0	-17	-19 to -15	6	25,26,29,*;‡,¶¶
	Dorzolamide, peak	-5.9	-6.5 to -5.2	-22	-24 to -20	6	25,26,29,*;‡,¶¶

Publications cited in this table with superscript numbers can be found in "References."

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|||Noecker RJ, Earl ML, Mundorf T, et al. Bimatoprost 0.03% versus travoprost 0.004% in black Americans with glaucoma or ocular hypertension. Adv Ther 2003;20:121-8.

¶¶O'Donoghue EP, UK and Ireland Latanoprost Study Group. A comparison of latanoprost and dorzolamide in patients with glaucoma and ocular hypertension: a 3 month, randomised study. Br J Ophthalmol 2000;84:579-82.

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ferent fields, which enhances content and face validity. In addition, we added some items that are of major importance for the quality assessment of randomized clinical trials studying IOP-lowering effects of glaucoma medication (Table 2). In general, in most reports on randomized trials too little or insufficient information is provided to be able to judge properly whether randomization and masking were adequate and whether allocation of treatments truly was concealed.<sup>10-12</sup> Unfortunately, for quantifying possible baseline imbalances, insufficient data are available in most

cases.<sup>13</sup> Moreover, authors often mention the process of masking but seldom report whether masking was successful.<sup>13</sup> When studying glaucoma medication, true masking is hard because differences in side effects may reveal a patient's treatment. The latter issue and the issue of reporting success of masking addressed by Berger et al<sup>10-12</sup> resulted in an overall score of 0 for the items "Was the care provider blinded?" and "Was the outcome assessor blinded?" A weaker point of the present study is the fact that the first judgment on eligibility of articles based on the title, ab-

stract, and MeSHs was made by a single researcher; ideally, 2 independent observers should screen the abstracts.<sup>7</sup> However, the purpose of this first selection was to exclude publications that were obviously ineligible for inclusion (e.g., studies on healthy subjects, animals, excluded drugs, or IOP not as primary outcome). These issues are easy to assess, based on abstract and title or MeSH keywords. Therefore, it is not likely that eligible studies were rejected in this stage of study selection. This is confirmed by the fact that any of the publications used for the 2 meta-analyses of Zhang et al and Einarson et al<sup>3,4</sup> were present among the possible eligible articles that remained after this first selection. Moreover, if any doubt about eligibility of a study existed after reading the title, abstract, and MeSHs, the complete publication was copied and included in the further selection process.

Also, potentially eligible trials were randomly assigned to a single researcher for final judgment of the eligibility of these trials. However, eligibility criteria were extensively discussed to make the level of agreement between both reviewers as high as possible. In addition, if any doubt about the eligibility of a publication rose, this was discussed with the other 2 researchers.

Potentially eligible publications were divided randomly between 2 researchers to prevent bias. To minimize information bias,<sup>30</sup> the observers were blinded to the names of the authors and their institutions, the names of the journals, sources of funding, and acknowledgments.<sup>31</sup> We minimized language bias by including not only English language studies but also studies published in German, French, and Dutch.<sup>32,33</sup> We aimed to minimize database bias by searching in multiple databases (Medline, Embase, and the Cochrane Controlled Trials Register)<sup>34</sup> and by checking references in selected publications. We did not use references from all reviews published, to prevent citation bias.<sup>34</sup> We minimized multiple publication bias by checking the studied populations and paying extra attention when including multicenter studies. We found 4 publications reporting on the same study population. The article reporting the final results was used for this meta-analysis<sup>18</sup>; data that could not be obtained from this publication were obtained from 2 publications reporting earlier results.<sup>19,20</sup>

Two other meta-analyses were published on IOP-lowering effects of glaucoma drugs. Zhang et al reported IOP reductions at 3 months from baseline of 30% for latanoprost and 27% for timolol.<sup>3</sup> These findings are comparable to the results of the present study: we found 31% at peak and 28% at trough for latanoprost and 27% at peak and 26% at trough for timolol. Einarson et al<sup>4</sup> compared peak measurements for brimonidine with a combination of trough, peak, and diurnal measurements for latanoprost. The 26% IOP reduction for brimonidine from baseline at 3 months of this measurement was comparable to the 25% reduction at peak found in the present study. The value of 33% reduction from baseline for latanoprost at 3 months was higher than the 28% and 31% reductions at trough and peak, respectively, found in the present study and in the study of Zhang et al.<sup>3</sup> In general, one may state that our estimations for IOP reduction are comparable to or slightly lower than those reported in earlier published meta-analyses.<sup>3,4</sup>

Except for the advantage of discriminating between peak and trough moments, the present study has the advantage that the studies included did not vary in concentration of the drug, moment of applying, and frequency of dosing for the different medicines, and included more drugs. This contrasts with the trials included in the earlier mentioned meta-analyses.<sup>3,4</sup> Moreover, the present study also reports on drugs that have not been studied by meta-analysis before.

The results of this study show that prostamide or prostaglandin analogs are most effective for lowering IOP by monotherapy in POAG or OH patients. However, the  $\beta$ -blocker timolol is almost as effective and, thereby, still a good treatment option. The  $\beta$ -blocker betaxolol,  $\alpha_2$ -adrenergic agent brimonidine, carbonic anhydrase inhibitors, brinzolamide, and dorzolamide are clearly less effective. Whether these results are also applicable to patients with other forms of glaucoma remains uncertain.

Because differences between timolol, prostamide, and prostaglandin analogs in IOP reduction are small, other aspects like patient characteristics, quality of life, compliance, and costs may be taken into consideration, as suggested by the European Glaucoma Society, to decide on the starting therapy for POAG or OH. Depending on the number of randomized clinical trials of IOP-lowering effects that will be published in coming years, in the future an update of this meta-analysis may be desirable. Drug use under everyday circumstances may differ from the situation in a clinical trial due to the selection of patients and the experimental circumstances.<sup>35</sup> Therefore, apart from more controlled research as performed in clinical trials, observational research on IOP reduction reached by glaucoma medication also is desired. In summary, this meta-analysis of randomized comparisons shows that there are multiple options for effective monotherapy in POAG and OH. This enables physicians to tailor an optimal strategy for an individual patient.

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