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A pooled-data analysis of three randomized, double-masked, six-month clinical studies comparing the intraocular pressure reducing effect of latanoprost and timolol

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PURPOSE. *To compare the intraocular pressure (IOP) reduction by latanoprost and timolol, and to study factors of prognostic value for assessing this reduction.*
METHODS. *We analyzed 829 patients included in three phase III studies comparing six months' treatment with 0.005% latanoprost once daily and 0.5% timolol twice daily in patients with open-angle glaucoma or ocular hypertension. Analysis of covariance controlled for differences in baseline IOP and sex was used to assess the IOP reduction.*
RESULTS. *Latanoprost reduced diurnal IOP (average of morning, noon and afternoon assessments) by 7.7 mmHg (31%) and timolol by 6.5 mmHg (26%) after six months of treatment. Thus the diurnal IOP was reduced 1.2 mmHg (18%) more with latanoprost than with timolol ($p<0.001$). Latanoprost-treated patients showed a further decrease in morning IOP of 0.7 mmHg (9%, $p<0.001$) from the initial morning IOP reduction obtained at two weeks. No such further decrease in IOP was seen with timolol. Higher baseline diurnal IOP resulted in a larger diurnal reduction during treatment with both drugs ($p<0.001$). Diurnal IOP in women was reduced 0.7 mmHg (11%) less than males with both drugs ($p<0.001$).*
CONCLUSIONS. *Latanoprost was more effective than timolol in reducing mean diurnal IOP. The effect after two weeks was maintained for timolol while with latanoprost there was a further, significant IOP reduction from two weeks to six months. Baseline IOP was the only factor of clinical importance found to be of prognostic value for assessing the IOP reduction. (Eur J Ophthalmol 2000; 10: 95-104)*

KEY WORDS. *Open-angle glaucoma, Ocular hypertension, Intraocular pressure, Latanoprost, Prostaglandin, Timolol*

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INTRODUCTION

Latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-prostaglandin $F_{2\alpha}$-isopropyl-ester; previously PhXA41) is a phenyl-substituted prostaglandin analogue developed for the reduction of intraocular pressure (IOP) in glaucoma patients (1, 2). Several studies have shown that latanoprost given once daily reduces IOP in patients with open-angle glaucoma or ocular hypertension (3-6), without reducing aqueous humor production (7-9). Its main effect on IOP is due to increased uveoscleral outflow (9-12). Latanoprost has been compared to timolol in four phase III studies (3-6). Three had a similar design and were planned for a pooled data analysis (3-5). This report is based on the pooled data from these three studies.

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The primary objective of this pooled-data analysis was to assess the diurnal IOP reduction after six months' treatment with latanoprost or timolol in different subgroups of patients and in the total. Thus males and females, younger and older patients, with different ocular diagnoses, different duration since initial diagnosis, with and without a family history of the disease, and patients with different iris colors were compared. This had already been done in each of the three phase III studies separately. However, several of the subgroups had few patients, limiting the possibility of detecting worth-while differences in response. This pooled-data analysis increased the possibility of detecting such differences.

The secondary objective of the pooled-data analysis was to examine the pattern of IOP after the initial effect, by comparing the IOP after two weeks' treatment and after 4.5 and 6 months' treatment for each patient. This was only done by indirect comparison of the average IOP at each time point in the separate studies.

The third objective was to study the proportion of patients who reached specific IOP levels after six months' treatment (IOP ≤21, ≤19, ≤17, ≤15 mmHg and IOP reduction ≥10%, ≥20%, ≥30%, ≥40%). Late loss of treatment effect was studied by calculating the proportion of patients whose IOP was initially reduced by ≥2, ≥4, ≥6, ≥8 mmHg but who failed to reach a specified IOP reduction after six months. Late responders were the proportion of patients whose IOP had initially not been reduced by ≥2, ≥4, ≥6, ≥8 mmHg but who achieved the specified IOP reductions after six months.

PATIENTS AND METHODS

Inclusion and exclusion criteria

The Scandinavian study included 267 patients from 13 centers (3), the UK study 294 patients from 14 centers (4), and the US study 268 patients from 17 centers (5). All these patients were included in the pooled-data analysis. Patients and methods have been described in detail elsewhere (3-5), and are therefore only summarized here. Approvals were obtained from the appropriate regulatory authorities and ethics committees or internal review boards and signed informed consent was obtained from all patients before entering the study. Patients diagnosed with primary open-angle glaucoma (POAG), pseudo-exfoliation or pigmentary glaucoma or ocular hypertension (OH) were included. IOP had to be at least 22 mmHg without treatment or with a single ocular hypotensive medication at the time of screening.

There was one difference in inclusion/exclusion criteria between the centers. Patients who had been treated with topical beta-adrenergic antagonists within the last six months or for longer than three months at any time were excluded from the UK and the Scandinavian, but not the US study. In addition to this, the UK and Scandinavian centers preferred to recruit patients with no previous glaucoma treatment. It was not feasible for the US centers to focus recruitment on untreated patients since most of the investigators were specialists who primarily did not meet newly detected patients.

Patients on single-drug treatment for elevated IOP were eligible after a medication-free period before the study started of: three weeks for beta-adrenergic antagonists (only the US study), two weeks for adrenergic agonists and five days for cholinergic agonists and carbonic anhydrase inhibitors. Patients who had participated in any other clinical study within the last month were excluded. Table I summarizes the baseline characteristics.

Study design and treatment schedule

Each study was designed as a randomized, double-masked, parallel group, center stratified comparison of latanoprost and timolol. The latanoprost patients received 0.005% latanoprost once daily in the evening and placebo once daily in the morning, with the exception of about 50% of the Scandinavian latanoprost patients who received the drug in the morning and placebo in the evening (about 20% of the 460 latanoprost patients). The timolol patients received 0.5% timolol maleate twice daily. Patients were to instill the medication at 8 a.m. and 8 p.m. On visit days, the morning eye drops were instilled at the clinic after the morning examination.

The pre-study visit was followed by six visits scheduled at baseline and after 0.5, 1.5, 3, 4.5 and 6 months' treatment. Examinations were done at 9 a.m., 1 p.m. and 5 p.m. in the UK study and at 8 a.m., noon, and 4 p.m. in the US and Scandinavian studies at base-

line and after six months of treatment, and only in the morning during the other visits. Goldmann tonometry was used to determine IOP. Three measurements were recorded in each eye, and the mean of the three was used in the calculations.

Statistical methods

Diurnal IOP was analysed on an intention-to-treat basis for all 829 patients (with the last available value carried forward for the 55 patients who had missing IOP at month 6). The diurnal IOP was calculated as the average of the morning, noon and afternoon measurements at the baseline and six-month visits. All patients whose IOP were available at these time points were included in the analysis of IOP at separate time points during the day. For 652 patients (79%) in whom both eyes were eligible for the study, the average of the right and left eye was calculated for each time point and used in the analysis (13). In this population, the conclusions do not change if only the right eye or only the left eye had been selected.

The IOP reduction was analyzed by analysis of covariance (ANCOVA) with geographical area (Scandinavia, UK and USA), clinic within geographical area, drug and sex as factors, geographical area-by-drug, drug-by-sex and geographical area-by-drug-by-sex as interactions, and untreated IOP as a covariate (14). This model was also used for analysis of the IOP reduction subsequent to the initial reduction achieved after two weeks' treatment, but with IOP at two weeks treatment as the covariate.

The effect of glaucoma risk factors (age, race and family history of glaucoma/OH) and treatment risk factors (previous glaucoma medication, diagnosis, duration since ocular diagnosis and iris color) on the IOP reduction was studied separately for each factor.

The factors age, family history, duration since diagnosis and iris color were analyzed separately with the first ANCOVA model, extended with the factor and the interactions drug-by-factor, sex-by-factor, geographical area-by-drug-by-factor and geographical area-by-drug-by-sex-by-factor.

Since very few patients suffered from pigmentary or pseudo-exfoliation glaucoma the IOP reduction in patients with different diagnoses was analyzed with a simplified model: geographical area, drug and diagnosis as factors, geographical area-by-drug, drug-by-diagnosis as interactions and untreated IOP as a covariate.

The effect of previous glaucoma medication and race could only be assessed in the US study. A model corresponding to the first ANCOVA was used.

All ANCOVA of IOP reduction from baseline were controlled for differences in the untreated IOP, i.e. latanoprost treated patients with initially low untreated IOP were compared to timolol treated patients with similarly low untreated IOP, and latanoprost treated patients with high initial untreated IOP was compared to timolol treated patients with similar high untreated IOP. By using interactions of factors in the ANCOVA the IOP reduction in specific subgroups can be studied, e.g. the interaction drug-by-diagnosis provides an estimate of the mean IOP reduction in latanoprost or timolol treated patients with OH, POAG, pseudo-exfoliation or pigmentary glaucoma.

Sample means and least square means (from ANCOVA) are presented with the standard error of the mean (SEM) and/or 95% confidence interval (CI). All tests were two-tailed. SAS software was used for all data processing and statistical tests.

RESULTS

Diurnal (average of morning, noon and afternoon measurements) IOP reduction from untreated baseline after six months of treatment

Latanoprost reduced diurnal IOP by 7.7 ± 0.1 mmHg (31%) and timolol by 6.5 ± 0.1 mmHg (26%) from the overall untreated IOP of 24.8 ± 0.1. Thus the diurnal IOP was reduced 1.2 ± 0.2 mmHg (18%) more with latanoprost than with timolol ($p<0.001$, Figs. 1, 2). Higher untreated diurnal IOP resulted in a larger reduction with both drugs (regression slope = 0.5, $p<0.001$) (15). The relationship between untreated IOP and IOP reduction was the same for the two drugs with no real difference in the regression slopes (Fig. 3). Diurnal IOP was reduced less in women than men with both drugs. For timolol the difference was 1.0 ± 0.3 mmHg (16%) ($p<0.001$), for latanoprost 0.5 ± 0.3 mmHg (8%) ($p=0.0747$).

The US patients were analyzed in three groups; those who had received no previous medical glaucoma treat-

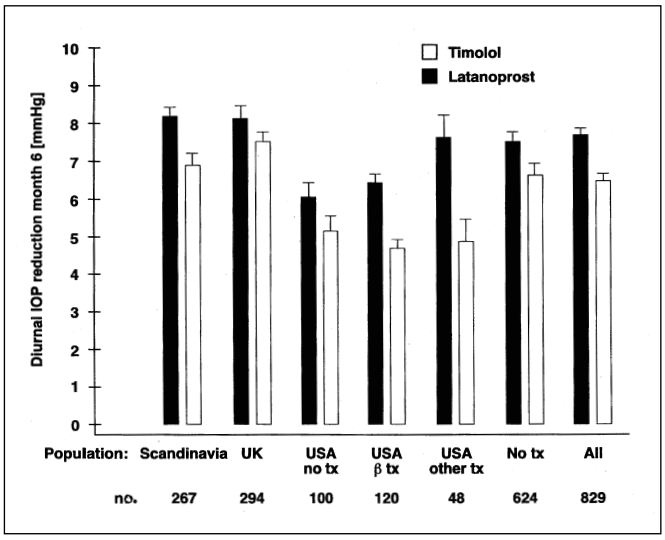

Fig. 1 - *Diurnal IOP reduction after six months' treatment with latanoprost or timolol (mean ± SEM, ANCOVA) from overall untreated baseline of 24.8 ± 0.1 mmHg per country, for all previously untreated patients (no tx) and the total. Depending on previous medical treatment, the US patients were classified as untreated (no tx), beta-blocker treated (β tx) or treatment other than beta-blocker monotherapy (other tx).*

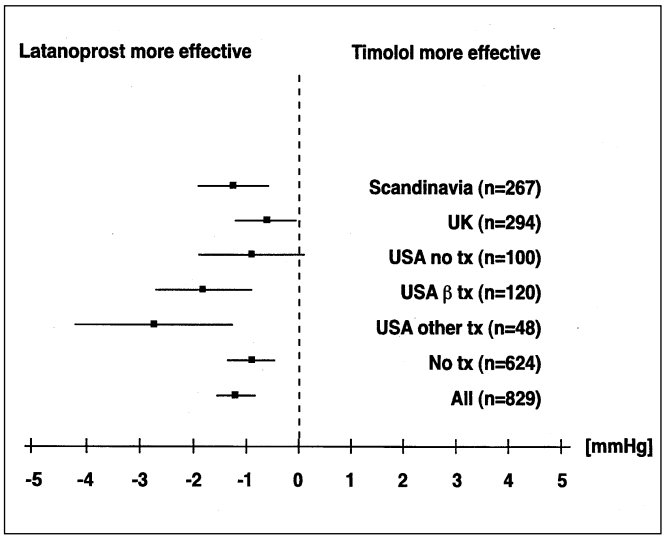

Fig. 2 - *Difference in diurnal IOP reduction after six months' treatment with latanoprost or timolol (mean ± 95% CI, ANCOVA) per country, for all previously untreated patients (no tx) and the total. Depending on previous medical treatment, the US patients were classified as untreated (no tx), beta-blocker treated (β tx) or treatment other than beta-blocker monotherapy (other tx).*

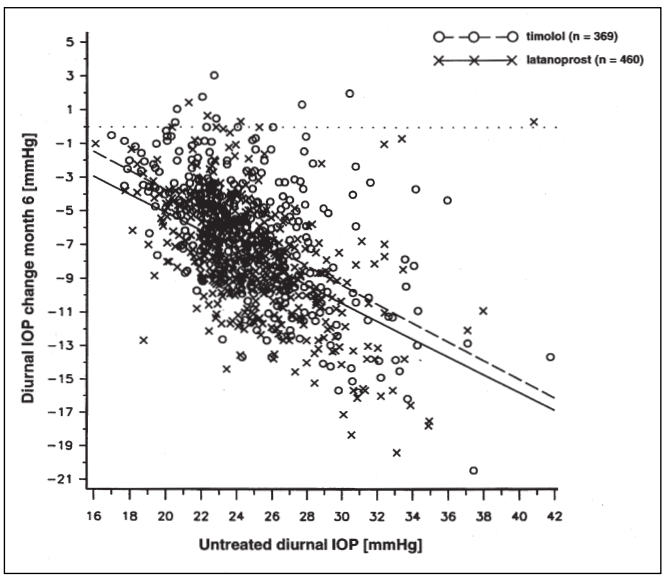

Fig. 3 - *Scatter plot of changes in diurnal IOP after six months' treatment, compared to untreated diurnal IOP, with a regression line per treatment group.*

ment (n = 100), those who had received topical beta-blockers (n=120) and those who had received other glaucoma medication than beta-blocker monotherapy (n=48, Figs. 1 and 2). With the exception of one group (latanoprost in previously treated patients who

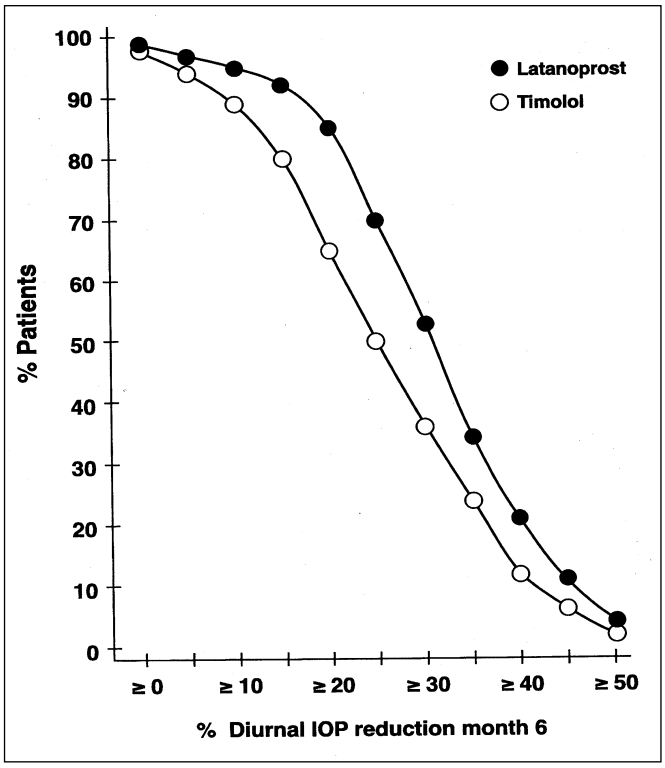

Fig. 4 - *Percentage of patients (n=829) who reached specific diurnal IOP reductions after six months' treatment with latanoprost or timolol.*

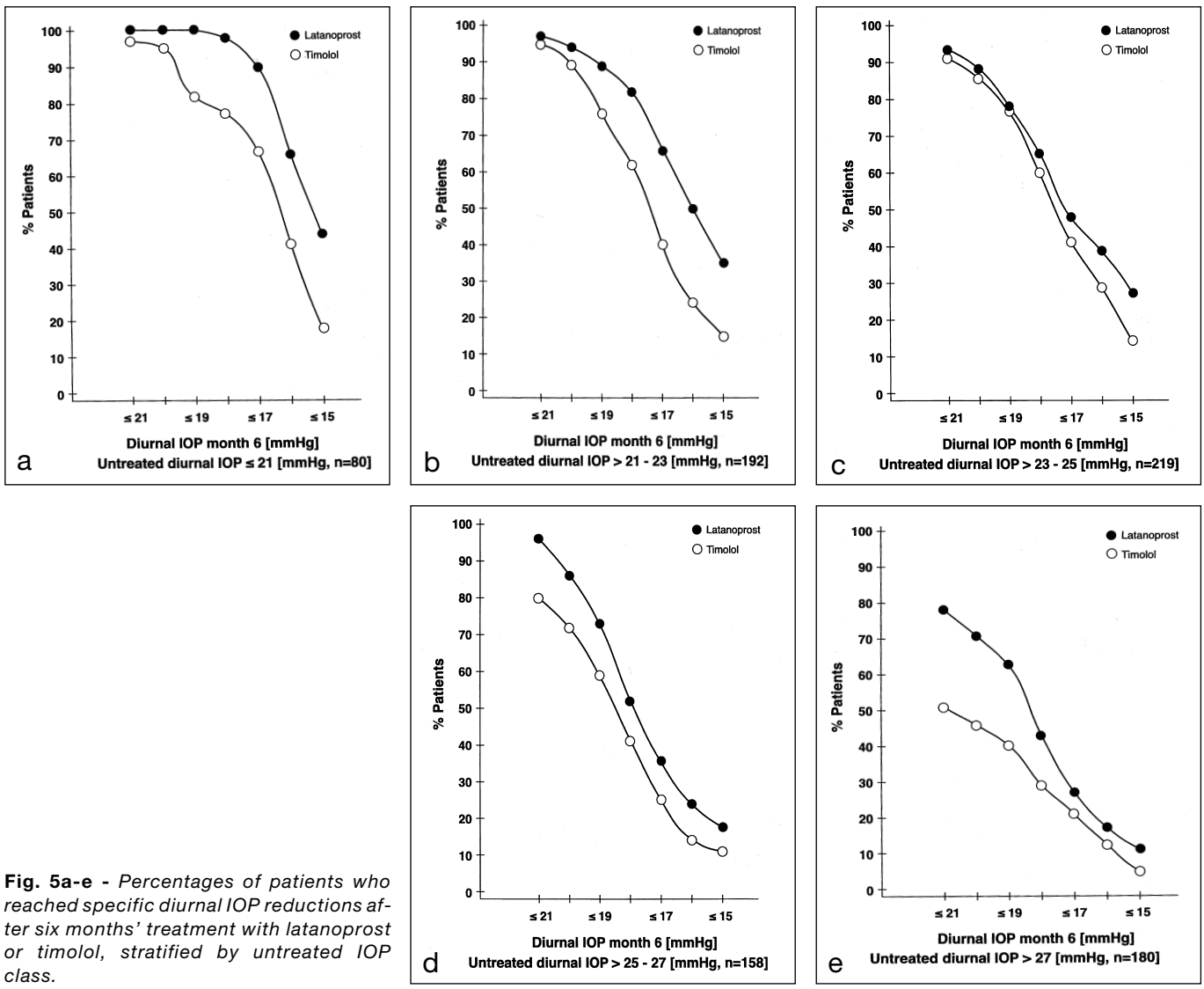

Fig. 5a-e - *Percentages of patients who reached specific diurnal IOP reductions after six months' treatment with latanoprost or timolol, stratified by untreated IOP class.*

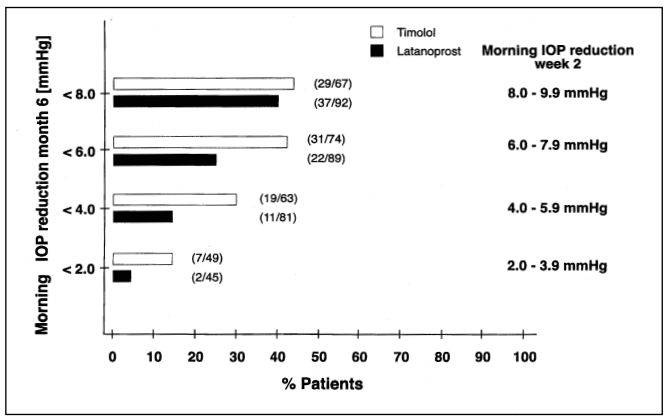

Fig. 6 - *Percentage of patients who failed to reach a specific morning IOP level after six months' treatment with latanoprost or timolol, out of the patients who initially reached that level.*

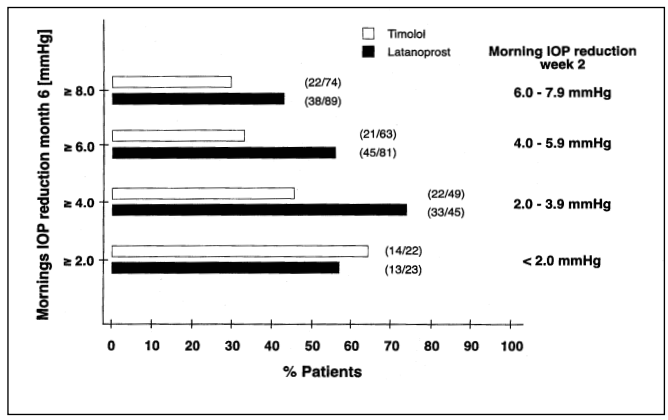

Fig. 7 - *Percentage of patients who reached a specific morning IOP level after six months' treatment with latanoprost or timolol, out of the patients who initially failed to reach that level.*

TABLE I – BASELINE CHARACTERISTICS

	Scandinavia		United Kingdom		USA		
	latanoprost (n=183)	**timolol (n=84)**	**latanoprost (n=149)**	**timolol (n=145)**	**latanoprost (n=128)**	**timolol (n=140)**	**All (n=829)**
Males	82 (45%)	34 (40%)	98 (66%)	93 (64%)	58 (45%)	56 (40%)	421 (51%)
Ethnic origin:							
African American			6 (4%)	3 (2%)	27 (21%)	38 (27%)	74 (9%)
Caucasian	182 (99%)	84 (100%)	143 (96%)	142 (98%)	94 (73%)	91 (65%)	736 (89%)
Other	1 (1%)				7(5%)	11 (8%)	19 (2%)
Age (yrs):							
<60	34 (19%)	21 (25%)	42 (28%)	45 (31%)	59 (46%)	55 (39%)	256 (31%)
60-70	77 (42%)	31 (37%)	58 (40%)	48 (33%)	29 (23%)	42 (30%)	285 (34%)
>70	72 (39%)	32 (38%)	49 (33%)	52 (36%)	40 (31%)	43 (31%)	288 (35%)
Family history of glaucoma/OH	56 (31%)	37 (44%)	39 (26%)	47 (32%)	43 (34%)	52 (37%)	274 (33%)
Both eyes designated study eyes	116 (63%)	55 (65%)	122 (82%)	132 (91%)	107 (84%)	120 (86%)	652 (79%)
Iris color:							
Blue/gray	65 (36%)	27 (32%)	15 (10%)	13 (9%)	9 (7%)	13 (9%)	142 (17%)
Brown	58 (32%)	37 (44%)	39 (26%)	41 (28%)	20 (16%)	20 (14%)	215 (26%)
Green/hazel/mixed	60 (33%)	20 (24%)	95 (64%)	90 (62%)	99 (77%)	107 (76%)	471 (57%)
Diagnosis:							
POAG	58 (32%)	33 (39%)	59 (40%)	62 (43%)	39 (30%)	45 (32%)	296 (36%)
Exfoliation glaucoma	29 (16%)	14 (17%)	3 (2%)	2 (1%)	3 (2%)	2 (1%)	53 (6%)
Pigmentary glaucoma	1 (1%)		2(1%)	1 (1%)	3 (2%)	1 (1%)	8(1%)
OH	87 (48%)	36 (43%)	80 (54%)	68 (47%)	80 (63%)	90 (64%)	441 (53%)
RE and LE different	8 (4%)	1 (1%)	5 (3%)	12 (8%)	3 (2%)	2 (1%)	31 (4%)
Diagnosis duration (yrs):							
<1	122 (67%)	61 (73%)	119 (80%)	110 (76%)	41 (32%)	48 (34%)	501 (60%)
2-<5	35 (19%)	13 (15%)	19 (13%)	20 (14%)	37 (29%)	37 (26%)	161 (19%)
≥5	26 (14%)	10 (12%)	10 (7%)	15 (10%)	50 (39%)	55 (39%)	166 (20%)
Previous therapy:							
None	173 (95%)	76 (90%)	139 (93%)	136 (94%)	51 (40%)	49 (35%)	624 (75%)
β-blocker				1 (1%)	56 (44%)	64 (46%)	121 (15%)
Other than β-blocker monotherapy	10 (5%)	8 (10%)	10 (7%)	8 (6%)	21 (16%)	27 (19%)	84 (10%)
Untreated diurnal IOP (mean +sem)	25.1±0.3	24.6±0.3	25.2±0.3	25.4±0.3	24.4±0.3	24.1±0.3	24.8±0.1

TABLE II - UNTREATED IOP AND IOP REDUCTION (mmHg) AFTER SIX MONTHS OF TREATMENT AT THE MORNING, NOON AND AFTERNOON MEASUREMENTS

Group	Time	no.	Untreated IOP mean ± SEM	IOP reduction month 6 mean ± SEM (%)
Latanoprost	morning	431	25.7 ± 0.2	8.3 ± 0.2 (32)
	noon	430	24.7 ± 0.2	7.7 ± 0.2 (31)
	afternoon	430	24.3 ± 0.2	7.5 ± 0.2 (31)
Timolol	morning	343	25.6 ± 0.2	7.0 ± 0.2 (27)
	noon	342	24.3 ± 0.2	6.4 ± 0.2 (26)
	afternoon	341	23.9 ± 0.2	6.1 ± 0.2 (26)

had not received beta-blocker monotherapy) the IOP reduction was smaller in the US patients than in the Scandinavian and UK studies. The mean reduction of diurnal IOP in all US patients who received latanoprost was 1.4 ± 0.3 mmHg (17%) less than the European latanoprost patients ($p < 0.001$). The mean reduction of diurnal IOP in all US timolol treated patients was 2.1 ± 0.3 mmHg (29%) less than the European timolol patients ($p < 0.001$). In the previously untreated patients from all three studies latanoprost reduced diurnal IOP 0.9 ± 0.2 mmHg (14%) more than timolol ($p < 0.001$, n=624, Figs. 1, 2).

The diurnal IOP reduction was not significantly different in patients with OH, POAG, pseudo-exfoliation or pigmentary glaucoma ($p = 0.15$). Age, race, duration of diagnosis, iris color or family history also had no effect on the IOP reduction.

IOP reduction at morning, noon and afternoon after six months of treatment

In the latanoprost treated patients IOP was reduced by 32% in the morning and 31% at noon and in the afternoon (Tab. II). The timolol treated patients had reductions of 27% in the morning and 26% at noon and in the afternoon.

Initial and subsequent IOP reductions

The initial IOP reduction with the two drugs was recorded in the morning after two weeks' treatment. Latanoprost reduced morning IOP by 7.9 ± 0.1 mmHg (31%) and timolol 7.4 ± 0.2 mmHg (27%) from the overall untreated morning IOP of 25.7 ± 0.1 mmHg. After 4.5 months of treatment patients treated with latanoprost showed a further decrease in morning IOP of 0.7 ± 0.1 mmHg (9%, $p<0.001$) and (0.6 ± 0.1 mmHg), (8%, $p<0.001$) at both three and six months from the initial morning IOP reduction at two weeks. This was not observed in the timolol treated patients.

Diurnal target IOP after six months' treatment

Seventy-five percent of the patients were previously untreated with prostaglandins or topical beta-blockers. There were few non-responders in the total population. Only 5% of the latanoprost-treated patients and 11% in the timolol groups had diurnal IOP reductions smaller than 10% (Fig. 4).

Figure 5 shows the percentages of patients reaching different IOP levels after six months of treatment depending on their untreated IOP. More patients on latanoprost than timolol reached a particular level, irrespective of the untreated IOP. Thus 44%, 35%, 27%, 18% and 11% of the latanoprost treated patients with untreated IOP of ≤21, 22-23, 24-25, 26-27 and ≥28 mmHg respectively, reached a diurnal IOP of 15 mmHg or lower compared to 18%, 15%, 14%, 11%, and 5% for timolol (Fig. 5a-e). Thus the chance of reaching a target IOP of 15 mmHg was better with latanoprost than with timolol for each untreated IOP level and the odds ratios ranged from 1.8 to 3.6. In previously untreated patients the results were similar. A diurnal IOP of 15 mmHg or lower was reached by 44%, 41%, 32%, 19% and 12% of the latanoprost treated patients with initial IOP of ≤21, 22-23, 24-25, 26-27 and ≥28 mmHg respectively, compared to 23%, 17%, 18%, 12%, and 8% for timolol. The odds ratios ranged from 1.6 to 3.4.

Loss of treatment effect and late response

Figure 6 shows patients with loss of the initial effect, as the percentage that failed to maintain the initial effect on IOP after six months of treatment, divided into groups of different IOP reduction after the first two weeks. More patients on timolol than on latanoprost lost effect over time. Of the latanoprost patients who initially achieved an IOP reduction of 4.0-5.9 mmHg, 14% failed to reach an IOP reduction of 4.0 mmHg after six months of treatment, compared to 30% of the timolol treated patients.

Figure 7 shows patients with a late response, as the percentage that reached various levels of IOP reduction after six months of treatment despite failure to do so after two weeks. The patients are divided into groups of different IOP reduction after the first two weeks. More patients on latanoprost than on timolol showed an increase in treatment effect with time. Patients whose IOP initially fell less than 2 mmHg were an exception. Out of the latanoprost treated patients whose initial IOP reduction amounted to 2.0-3.9 mmHg, 73% reached reduction of at least 4.0 mmHg after six months of treatment, compared to 45% of the timolol group.

DISCUSSION

There were some differences in the baseline characteristics of the patients in the three studies (Tab. I). About 20% of the Scandinavian patients were diagnosed with pseudo-exfoliation glaucoma compared to only about 2% in the UK and US studies. The possibility of treatment effects differing in the subgroups based on the differences in baseline characteristics was analyzed with analysis of covariance, so this heterogeneity was not a threat to interpretation of the results. Another difference was that a large part of the patients recruited in the US had already received anti-glaucoma medication whereas in the UK and Scandinavian studies most patients were newly diagnosed and had had no previous glaucoma treatment.

The fact that these three studies had similar designs and inclusion/exclusion criteria, were performed in parallel and were planned for pooling the data makes them suitable for pooled data analysis. None of the differences in treatment effect between subgroups in this analysis were caused by differences in the baseline IOP, since all analyses of covariance were controlled for differences in baseline IOP.

It should be pointed out that the effect on IOP was based on the diurnal pressure and not on comparing peaks and troughs, since the peak values were not recorded on timolol and the effect on IOP maintained during the day was considered clinically relevant.

The analysis showed that both latanoprost and timolol are effective IOP-reducing agents in patients with open-angle glaucoma or ocular hypertension, and that latanoprost reduced diurnal IOP 1.2 mmHg more than timolol. This result was consistent across the studies, but less pronounced in the UK study than in the US and Scandinavian studies. If we only compare patients with no previous medical glaucoma therapy the difference in diurnal IOP reduction was slightly less, 0.9 mmHg. The effect on visual field progression of a difference in IOP of only about 1 mmHg is not known but it has some practical consequences. The odds of reaching a specific target IOP were about twice as high with latanoprost as with timolol.

Both drugs were in total 22% less effective in the US patients than in the UK and Scandinavia. This could not be explained by previous treatment with glaucoma therapy, differences in untreated IOP or any other variable collected in the studies. The low response among US patients was most pronounced for timolol (Fig. 1) and did not seem to be related to previous treatment. A smaller response, compared to the Scandinavian and UK patients, was seen in all three subgroups of US patients. Thus, less response because of inadequate washout of previous treatment does not explain this unexpected difference between European patients and US. The largest difference between the drugs was seen for patients previously treated with drugs other than beta-blocker monotherapy (Fig. 2).

Baseline IOP had a significant impact on the IOP reduction by both drugs. Higher baseline IOP resulted in a larger diurnal IOP reduction during treatment with both drugs. This can be explained partly by regression towards the mean (16). This observation argues for controlling the differences in baseline IOP in any analysis of IOP after treatment. On average in females IOP was reduced slightly less than in males, for both drugs, although the difference reached statisti-

cal significance only for timolol.

A sex-related difference in response has not previously been reported for IOP-reducing drugs, maybe because the patient populations are seldom large enough to detect such small differences. One reason for sex-related differences might be different metabolic rates of drugs in males and females, but drug metabolism should not be important with topical application. Since the difference between males and females was observed for both drugs it is more likely to be due to a difference in absorption than in effect.

Glaucoma is a chronic disease and the effect of the drugs over time is of clinical interest. With prolonged treatment many drugs, including timolol, lose some of their initial effect (17, 18). In the present six months follow-up there was no significant loss of the initial effect, i.e. after two weeks of treatment. Some patients failed to maintain the reduction in IOP seen after two weeks of treatment but this is likely to be due to chance variation rather than a true loss of effect since the average effect was unchanged. However, it is worth noting that latanoprost treated patients gained on average a further 9% reduction in IOP compared to the reduction at two weeks. This was not seen in the timolol patients. It is also interesting that this additional effect was seen in patients who initially responded to latanoprost, not only in initial non-responders. This delayed effect may be due to the specific mechanism of action of prostaglandins, which increase uveoscleral flow, and recent studies show that they induce changes in the extracellular matrix of the ciliary muscle of the eye (19, 20). These changes may facilitate aqueous humor outflow through the ciliary muscle (uveoscleral route). This process might possibly not be completed in two weeks, which would explain the additional decrease in IOP after some months of treatment with latanoprost.

In summary, the present pooled-data analysis shows that latanoprost and timolol reduce IOP in patients with open angle-glaucoma or ocular hypertension, and that latanoprost reduced diurnal IOP more than timolol. Part of this difference was due to the fact that latanoprost, but not timolol, induced a further reduction in IOP after the initial effect with two weeks' treatment. Baseline IOP was the only variable of clinical importance shown to be of prognostic value for assessing the IOP-reducing effect of latanoprost and timolol, and this can be partly explained by regression towards the mean.

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REFERENCES

1. Stjernschantz J, Resul B. Phenyl substituted prostaglandin analogs for glaucoma treatment. Drugs Future 1992; 8: 691-704.
2. Resul B, Stjernschantz J, No K, et al. Phenyl-substituted prostaglandins: potent and selective antiglaucoma agents. J Med Chem 1993; 36: 243-8.
3. Alm A, Stjernschantz J, the Scandinavian Latanoprost Study Group. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Ophthalmology 1995; 102: 1743-52.
4. Watson P, Stjernschantz J, the Latanoprost Study Group. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. Ophthalmology 1996; 103: 126-37.
5. Camras CB, the United States Latanoprost Study Group. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma. A six-month, masked, multicenter trial in the United States. Ophthalmology 1996; 103: 138-47.
6. Mishima HK, Masuda K, Kitazawa Y, Azuma I, Araie M. A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. A 12-week

study. Arch Ophthalmol 1996; 114: 929-32.
7. Alm A, Villumsen J. PhXA34 a new potent ocular hypotensive drug. A study on dose-response relationship and on aqueous humor dynamics in healthy volunteers. Arch Ophthalmol 1991; 109: 1564-8.
8. Ziai N, Dolan JW, Kacere RD, Brubaker RF. The effects on aqueous dynamics of PhXA41 a new prostaglandin $F_{2\alpha}$ analogue, after topical application in normal and ocular hypertensive human eyes. Arch Ophthalmol 1993; 111: 1351-8.
9. Toris CB, Camras CB, Yablonski ME. Effects of PhXA41, a new prostaglandin $F_{2\alpha}$ analog, on aqueous humor dynamics in human eyes. Ophthalmology 1993; 100: 1297-304.
10. Crawford K, Kaufman PL. Pilocarpine antagonizes prosta- glandin $F_{2\alpha}$ induced ocular hypotension in monkeys. Evidence for enhancement of uveoscleral outflow by prostaglandin $F_{2\alpha}$. Arch Ophthalmol 1987; 105: 1112-6.
11. Gabelt BT, Kaufman PL. Prostaglandin $F_{2\alpha}$ increases uveoscleral outflow in the cynomolgus monkey. Exp Eye Res 1989; 49: 389-402.
12. Nilsson SFE, Samuelsson M, Bill A, Stjernschantz J. Increased uveoscleral outflow as a possible mechanism of ocular hypotension caused by prostaglandin $F_{2\alpha}$ 1-isopropylester in the cynomolgus monkey. Exp Eye Res 1989; 48: 707-16.
13. Ray WA, O'Day DM, Head S, Robinsson R. Statistical analysis for experimental models of ocular disease: continuous response measures. Curr Eye Res 1985; 5: 585-97.
14. Analysis of covariance. In: Snedecor GW, Cochran WG, ed. Statistical methods 7th edition. The Iowa State University Press, 1980; 365-88.
15. Regression and correlation. In: Colton T, ed. Statistics in medicine. Boston: Little Brown and Company, 1974; 189-217.
16. Blomqvist N. On the bias caused by regression toward the mean in studying the relation between change and initial value. J Clin Periodontol 1986; 13: 34-7.
17. Boger WP III, Puliafito CA, Steinert RF, Langston DP. Long-term experience with timolol ophthalmic solution in patients with open-angle glaucoma. Ophthalmology 1978; 85: 259-67.
18. Gandolfi SA. Restoring sensitivity to timolol after long-term drift in primary open-angle glaucoma. Invest Ophthalmol Vis Sci 1990; 31: 354-8.
19. Lindsey JD, Kashiwagi K, Kashiwagi F, Weinreb RN. Prostaglandin action on ciliary smooth muscle extracellular matrix metabolism: Implications for uveoscleral outflow. Surv Ophthalmol 1997; 41 (suppl): S53-9.
20. Ocklind A. Effect of latanoprost on the extracellular matrix of the ciliary muscle. A study on cultured cells and tissue sections. Exp Eye Res 1998; 67: 179-91.

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