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ORIGINAL ARTICLE

Prostaglandin Analogs and Timolol-Fixed Versus Unfixed Combinations or Monotherapy for Open-Angle Glaucoma: A Systematic Review and Meta-Analysis

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Abstract

Purpose: To estimate the intraocular pressure (IOP)-lowering effect of prostaglandin analogs (PGAs) administered in combination with β-blockers.
Methods: We searched the Medline and Embase databases for randomized trials comparing topical therapies with PGAs and timolol administered as monotherapy (Mt), or in fixed (FC) or unfixed combinations (UC) to patients with glaucoma or ocular hypertension. The efficacy endpoint was the mean difference (MeD) in the reduction in IOP from baseline; the tolerability endpoint was the incidence of hyperemia.
Results: The 18 eligible trials involved 23 comparisons of FC versus Mt, and 5 of FC versus UC. The FCs were less efficacious than UCs (MeD: 0.69, 95% CI: 0.29 to 1.08). In comparison with timolol Mt, the latanoprost/timolol FC led to a greater IOP reduction (MeD: −2.74, 95% CI: −3.24 to −2.23) than the bimatoprost/timolol FC (MeD: −1.49, 95% CI: −1.86 to −1.12) or the travoprost/timolol FC (MeD: −1.93, 95%CI: −2.98 to −0.88). The FCs led to a lower hyperemia risk than UCs [relative risk (RR): 0.70, 95% CI: 0.43 to 1.14] and PGA Mt (RR: 0.61, 95% CI: 0.53 to 0.70).
Conclusions: FCs are more efficacious than their individual components, but less efficacious than their respective UCs. FCs lead to a lower hyperemia risk than UCs and their respective PGA Mts.

Introduction

The treatment of ocular hypertension (OHT) and open-angle glaucoma (OAG) mainly involves reducing intraocular pressure (IOP) with topical medications. However, ∼40% of subjects with OHT require 2 or more topical medications to control IOP.[1,2] When target IOP is not achieved with a single agent, combined therapy using drugs with different mechanisms of action is recommended.[3] Multiple local therapies may be associated with more local and systemic side effects[4] because of increased exposure to preservatives, with a higher incidence of ocular signs and symptoms, and poor compliance.[5–7] Fixed combinations (FCs) of 2 antiglaucoma drugs have been formulated to obtain a greater reduction in IOP than that which can be achieved using single agents, allow fewer doses, and ensure less exposure to preservatives.[4]

Combinations of β-blockers and prostaglandin analogs (PGAs) are frequently used in clinical practice because of their different, but complementary mechanisms of action. PGA FCs were introduced several years ago to improve adherence to chronic topical medical therapy in patients with OHT and OAG,[8–10] and currently include 0.005% latanoprost + 0.5% timolol, 0.004% travoprost + 0.5% timolol, and 0.003% bimatoprost + timolol 0.5%. The aim of this systematic review and meta-analysis of aggregate data was to compare the efficacy and tolerability of FCs of β-blockers and PGAs with their respective unfixed combinations (UCs) and their respective monotherapies (Mts).

Material and Methods

To avoid the bias caused by *post hoc* decisions, the eligibility criteria and methods of analysis were specified in advance and documented in a protocol as detailed below.

Trials

We compared randomized trials comparing at least 2 topical pharmacological therapies administered at their authorized concentrations for at least 4 weeks.

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Patients

The eligibility criteria were patients with OAG or OHT of any age, race, or gender. OAG was defined as (1) a mean untreated IOP of >21 mmHg; (2) open drainage angles detected by gonioscopy; (3) typical optic disc damage with glaucomatous cupping and loss of the neuroretinal rim; and (4) visual field defects compatible with glaucomatous optic neuropathy. OHT was defined as (1) a mean untreated IOP of >21 mmHg; (2) open drainage angles detected by gonioscopy; (3) no typical optic disc damage with glaucomatous cupping or loss of the neuroretinal rim; and (4) no visual field defects.[3]

As it is current clinical practice to treat patients with chronic angle-closure glaucoma (CACG) and patent peripheral iridotomy in the same way as those with OAG, studies including such patients were also considered.

Interventions

Topical ocular administration of PGAs and timolol as Mt, FC, or UC.

Endpoints

Efficacy. The between-group mean difference (MeD) in the reduction in diurnal IOP from baseline to the last available assessment, expressed in mmHg.

Safety. The incidence of conjuctival hyperemia.

Search strategies

We searched the Medline and Embase databases to identify potentially eligible studies published up to February 2012, with no language limitation (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/jop). Nevertheless, in the screening phase, non-English articles for which no full-text translation was available were excluded. The reference lists of trial reports and narrative and systematic reviews were hand searched to identify additional trials.

Three reviewers (a biostatistician and 2 ophthalmologists) independently checked the titles, abstracts, and key words of the identified studies to ensure eligibility, and then read the full articles to identify those who met the inclusion criteria; any disagreements were resolved by consensus.

Data extraction

The study design, patient characteristics, interventions, and outcomes were independently recorded by 2 reviewers (a biostatistician and an ophthalmologist) using a data extraction form that had been pilot-tested using 4 randomly selected studies and was subsequently refined. Any differences in data extraction were resolved by a third reviewer, who referred back to the original article.

Risk of bias assessment

The quality of the studies was independently evaluated by 2 reviewers (a biostatistician and an ophthalmologist) using a modified version of the Delphi list[11]; a third reviewer resolved any differences. Additional items were introduced to avoid the biases most frequently highlighted in ophthalmology studies.

Statistical methods

For each eligible study, the MeD was directly retrieved (or, if not provided by the article, was computed as the between-treatment difference in the reduction in IOP from baseline), and its variance was computed as the weighed mean of the variances. If the difference from baseline was not reported for each treatment, it was calculated as the difference between the IOP values at baseline and at the time of the last follow-up examination, and its variance was computed as the weighed mean of their variances. If no mean diurnal data were available, the MeD was calculated as the average of the MeD at 8 a.m., 10 a.m., and 4 p.m. To evaluate the assumptions made when calculating variance, the rho correlation coefficient for paired data (baseline and follow-up IOP) was calculated and assessed using the approach suggested by the Cochrane Collaboration.[12]

The absolute value of MeD indicates the size of the effect difference, whereas the sign indicates the direction of this effect. A value of zero suggests no difference in efficacy between the arms. Pooled MeD estimates were calculated using the 2-step method for the random-effect model proposed by DerSimonian and Laird.[13]

Tolerability was only evaluated on the basis of the incidence of conjuctival hyperemia as an overall assessment of other adverse events (ie, eyelash growth and changes in iris colour) would have been questionable due to the heterogeneous length of treatment and follow-up across trials. The difference in the incidence of conjuctival hyperemia between treatments was expressed in terms of relative risk (RR).

Statistical heterogeneity was quantified using the I^2 statistic, which indicates the percentage of variability due to heterogeneity rather than to chance alone: 0% indicates no heterogeneity, greater values indicate increasing heterogeneity, and >50% implies substantial heterogeneity.[14] Chi-squared tests for homogeneity were also used. The assumption of homogeneity was deemed to be untenable if the P value was <0.10.

Subgroup analyses were made by the type of PGA and the time of administration of the same Mt (timolol or PGA). The studies were classified as AM, if the FC was administered in the morning, and PM, if it was administered in the evening. The chi-squared test and I^2 statistics were calculated to compare the differences between subgroups.

To detect publication bias (ie, the bias due to the fact that studies with positive results are more likely to be published than those with negative results) or small-study effect (the tendency for treatment effect estimates to be different in small and larger studies), we visually explored any asymmetry using a funnel plot in which the study size was plotted as a function of the measure of interest.[15]

All of the statistical analyses were made using SAS statistical software version 9.2 (SAS Institute, Inc., Cary, NC) and software Review Manager version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

Results

Supplementary Figure S1 shows the study selection process. The electronic searches identified 986 articles, but 953 did not meet the eligibility criteria; the remaining 33 were examined in detail, but no additional studies were identified from their references articles, and no relevant unpublished

Table 1. Characteristics of Included Studies

Author	Year	Type of design	Washout	Run in	Treatment duration (weeks)	Center	Country	Sponsor	Masking	Type analysis	Observation unit
Konstas I[16]	2009	c	Yes	No	8	Mono	1	p	p+o	uk	1 eye (random)
Higginbotham[17]	2010	p	Yes	No	12	Multi	1	p	p+o	itt	mean
Diestelhorst[18]	1998	p	No	Yes	4	Multi	1	p	p+o	pp	mean
Higginbotham[19]	2002	p	No	Yes	26	Multi	1	p	p+o	itt	mean
Pfeiffer[20]	2002	p	Uk	Yes	24	Multi	1	p	p+o	itt	1 eye (uk)
Diestelhorst[21]	2004	c	No	Yes	6	Multi	>1	no-p	p+o	itt	mean
Barnebey[22]	2005	p	Yes	No	12	Multi	1	p	p+o	itt	uk
Hughes[23]	2005	p	Yes	No	12	Multi	1	p	p+o	pp	1 eye (uk)
Konstas[24]	2005	c	Yes	No	8	Mono	1	no-p	p+o	uk	1 eye (random)
Schuman[25]	2005	p	Yes	No	12	Multi	1	p	p+o	pp	uk
Diestelhorst[26]	2006	p	Yes	No	12	Multi	>1	p	p+o	itt	mean
Konstas[27]	2006	c	Yes	No	8	Mono	1	no-p	p+o	uk	1 eye (random)
Brandt[28]	2008	p	Yes	No	12	Multi	>1	p	p+o	itt	mean
Konstas II[29]	2009	c	Yes	No	8	Mono	1	no-p	O	itt	1 eye (random)
Lewis I[30]	2010	p	Yes	Yes	48	Multi	>1	p	p+o	itt	uk
Lewis II[30]	2010	p	Yes	Yes	48	Multi	>1	p	p+o	itt	uk
Zhao[31]	2010	p	Yes	No	12	Multi	1	p	O	itt	mean
Palmberg[32]	2010	p	Yes	No	12	Multi	>1	p	p+o	itt	mean

Type of design: p, parallel; c, cross-over; sponsor: p, profit; no-p, not-for-profit; masking: p+o, patient and observer masked; o, observer masked; type of analysis: itt, intention to treat; pp, per protocol; center: mono, monocenter; multi, multicenter; observation unit: 1 eye (random), 1 eye randomly selected; mean, mean of the 2 eyes; 1 eye (uk), 1 eye unknown selection criterion; uk, unknown.

studies were found. A further 16 studies were subsequently excluded for various reasons: 4 because the PGA in the Mt was different from that in the FC; one because it was a pooled analysis of already included articles; one because it compared 2 FCs; 2 because they investigated other drugs; one because it had a different aim; 2 because they were not randomized trials; one because it was a comment letter; 3 because the treatment lasted <4 weeks; and one because it also included patients with normotensive glaucoma (Supplementary Table S2). A total of 17 articles[16–32] were therefore selected for data extraction and analysis, but as one described the results of 2 studies,[30] the total number of studies was 18.

Study characteristics

Table 1 shows the characteristics of the 18 studies. Four were carried out in a single institution, and 14 had a for-profit sponsor. Five had a crossover design, whereas the remaining 13 were parallel-arm trials. All of the studies had a

Table 2. Characteristics of Patients and Treatments (2)

Author	Year	Disease	Patients randomized	Patients analyzed/ randomized	Males	Mean age (sd) Years	Caucasian race	Treatments
Konstas I[16]	2009	OAG	34	94%	44%	63.9 (9.4)	100%	Mt: tr; FC: t+tr
Higginbotham[17]	2010	OAG+OHT	421	94%	45%	64 (11.1)	70%	Mt: t, l; FC: t+l
Diestelhorst[18]	1998	OAG	139	83%	45%	61.3 (16.7)	100%	Mt: t, l; FC: t+l
Higginbotham[19]	2002	OAG+OHT	418	100%	51%	62.3 (12.4)	72%	Mt: t, l; FC: t+l
Pfeiffer[20]	2002	OAG+OHT	436	100%	45%	63.7 (11.7)	uk	Mt: t, l; FC: t+l
Diestelhorst[21]	2004	OAG+OHT	195	97%	47%	67.5 (12.5)	100%	FC: t+l; UC: t+l
Barnebey[22]	2005	OAG+OHT	263	98%	49%	63.0 (11.2)	64%	Mt: t,tr; FC: t+tr
Hughes[23]	2005	OAG+OHT	316	93%	39%	63.7 (11.9)	65%	FC: t+tr; UC: t+tr
Konstas[24]	2005	OAG	37	95%	38%	65.8 (7.9)	100%	Mt: l; FC: t+l
Schuman[25]	2005	OAG+OHT	403	96%	41%	61.8 (11.9)	68%	Mt: t; FC: t+tr; UC: t+tr
Diestelhorst[26]	2006	OAG+OHT	517	97%	45%	65 (11.1)	98%	FC: t+l; UC: t+l
Konstas[27]	2006	OAG	34	97%	38%	62.4 (10.8)	100%	Mt: t; FC: t+l
Brandt[28]	2008	OAG+OHT+CACG	1061	100%	47%	61 (12)	81%	Mt: t, b; FC: t+b
Konstas II[29]	2009	OAG	30	97%	45%	63.7 (8.7)	100%	Mt: t; FC: t+l
Lewis I[30]	2010	OAG+OHT	520	100%	47%	59.4 (17.2)	72%	Mt: b, t; FC:b+t
Lewis II[30]	2010	OAG+OHT	541	100%	48%	62.4 (16.5)	uk	Mt: b, t; FC:b+t
Zhao[31]	2011	OAG+OHT	250	99%	53%	49.0 (14.3)	0%	FC: t+l; UC: t+l
Palmberg[32]	2010	OAG+OHT	500	100%	47%	64.8 (11.0)	71%	Mt: t, l; FC:t+l

disease: OAG, open-angle glaucoma; OHT, ocular hypertension; CACG, chronic angle closure glaucoma; therapy: Mt, monotherapy; FC, fixed combination; UC, unfixed combination; t, timolol; tr, travoprost; b, bimatoprost; l, latanoprost; uk, unknown.

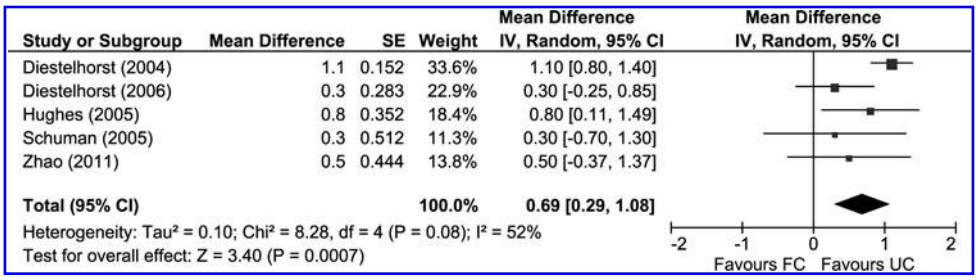

FIG. 1. Overall mean difference (MeD) in the reduction in intraocular pressure (IOP) between the fixed combination (FC) and unfixed combination (UC).

washout or run-in period, and at least one observer-masked assessment. The unit of analysis was a single eye in 6 trials (randomly selected in 4, and not specified in 2); the mean of the 2 eyes in 8; and not clearly specified in 4.

Table 2 shows the main characteristics of the patients and treatments: 5 trials considered only patients with OAG; 12 trials involved patients with OHT or OAG; and one trial considered patients with OAG, OHT, or CACG. All, but 2, of the trials had a majority of women, and age ranged from 59.4 to 67.5 years.

Risk of bias

The methodological quality of the studies (assessed using the modified Delphi list shown in Supplementary Table S3) was generally good. Selection bias could not be excluded in 14 studies[16,18,20,22–31] because of the absence of concealed allocation or unclear reporting; however, in the studies where this information was not reported, the double-masked design may have assured concealed allocation. Attrition bias could not be excluded in 6 studies[16,18,23–25,27] in which the analysis was not specified or was not based on the intention-to-treat approach.

There was no detectable asymmetry in the funnel plot, thus suggesting a low risk of publication bias.

Effects of interventions

The 18 studies involved a total of 28 comparisons and 6,141 patients: 13[16–20,22,24,27–30,32] involved 22 comparisons of Mt and FC and a total of 4,372 patients; 4 involved 4 comparisons of an FC and UC[21,23,26,31] and 1,233 patients; and one study[25] of 381 patients compared an Mt and a FC, as well as a FC and an UC.

FCs versus UCs

In all 5 studies involving comparisons of FCs and UCs,[21,23,25,26,31] the FCs were less effective in reducing IOP than the UCs. The pooled estimate of the MeD was 0.69 (95% CI: 0.29 to 1.08; test for overall effect: Z 3.40, $P = 0.0007$), although the studies were characterized by quantitative heterogeneity (ie, different sizes of the effect difference): I^2 52%; test for heterogeneity: χ^2: 8.28, df 4, $P = 0.08$. (Fig. 1).

FCs versus Mt

As there was considerable heterogeneity among the studies comparing FCs and Mts (I^2: 78%, test for heterogeneity: χ^2: 101.03, df 22, $P < 0.0001$), we made a subgroup analysis by type of Mt.

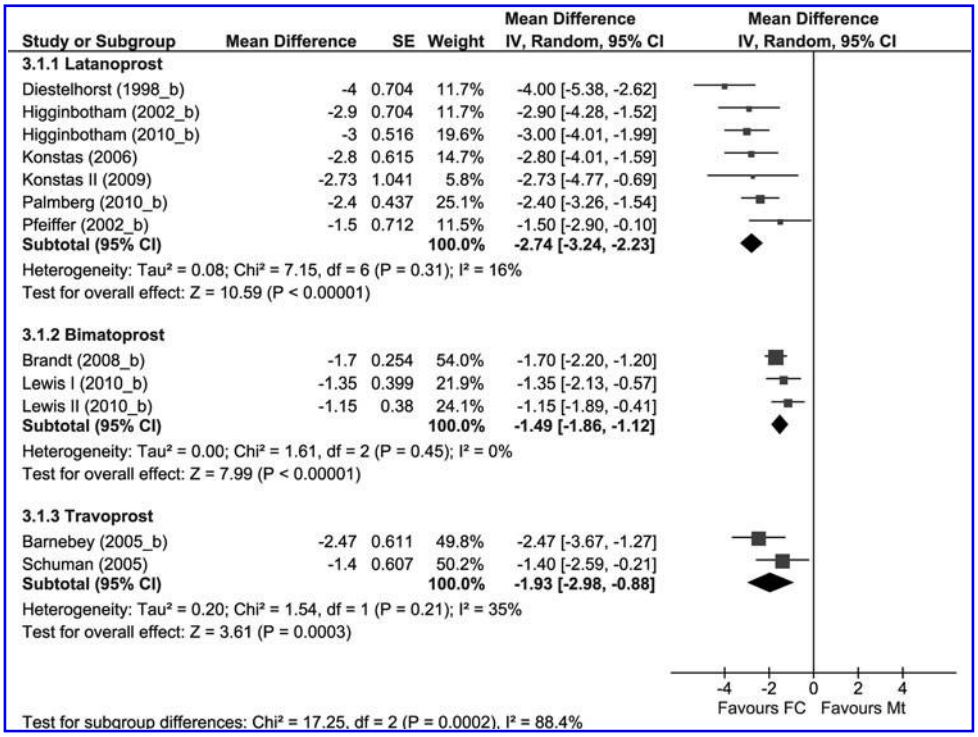

FIG. 2. Overall MeD in the reduction in IOP between the FC and monotherapy (Mt) with timolol. Subgroup analysis by type of FC: latanoprost, bimatoprost, or travoprost.

Of the 23 comparisons of FCs versus Mt, the Mt was timolol in 12,[17–20,22,25,27–30,32] latanoprost in 6,[17–20,24,32] travoprost in 2,[16,22] and bimatoprost in 3.[28,30] The MeD was significantly greater (test for subgroup differences: χ^2: 46.6 df 1, $P<0.0001$) when the FCs were compared with timolol Mt (MeD: −2.16, 95% CI: −2.63 to −1.70; test for overall effect: Z 9.11, $P<0.0001$), than when they were compared with PGA Mt (MeD: −0.90, 95%CI: −1.40 to −0.41; test for overall effect: Z 3.57, $P=0.0004$) (Supplementary Fig. S2).

The subgroup analysis by the type of FC (Fig. 2) showed that, in comparison with timolol Mt, the latanoprost/timolol FC led to a greater reduction in IOP (MeD: −2.74, 95%CI: −3.24 to −2.23) than the bimatoprost/timolol FC (MeD: −1.49, 95%CI: −1.86 to −1.12) or the travoprost/timolol FC (MeD: −1.93, 95%CI: −2.98 to −0.88).

The differences in these reductions were statistically significant (test for subgroup differences: χ^2: 17.3 df 2, $P=0.0002$). No heterogeneity was detected in the trials comparing latanoprost and bimatoprost with their respective FCs, whereas the 2 studies comparing travoprost with its FC were heterogeneous (I^2 35%).

The analysis by type of PGA Mt (Fig. 3) showed that the difference in efficacy was significantly greater (test for subgroup differences: χ^2: 21.6 df 2, $P<0.0001$) in the comparison between the FC and travoprost Mt (MeD: −2.14, 95%CI: −3.05 to −1.24) than in that of latanoprost Mt (MeD: −1.09, 95% CI: −1.57 to −0.60) or bimatoprost Mt (MeD: −0.13, 95%CI: −0.49 to 0.43). No heterogeneity was detected within the subgroups.

The FCs were more efficacious when administered in the evening. The difference in efficacy was significantly greater (test for subgroup differences: χ^2: 15.5 df 1, $P<0.0001$) in the comparison of PM FCs versus timolol Mt (MeD: −2.87, 95%CI: −3.38 to −2.36) than in the comparison of AM FCs versus timolol Mt (MeD: −1.68, 95%CI: −2.12 to −1.25) (Supplementary Fig. S3). Regarding the comparison of AM versus PM FCs with their respective PGA Mt, the MeD was significantly greater (test for subgroup differences: χ^2: 12.2 df 1, $P=0.0005$) for the PM FCs (MeD: −1.51, 95%CI: −2.22 to −0.79) than the AM FCs (MeD: −0.41, 95%CI: −0.86 to 0.05) (Supplementary Fig. S4).

Sensitivity analysis

Five studies[16,22–24,27] allowed a calculation of the rho correlation coefficient, and the result of 0.04 suggested that the assumption of no correlation due to paired data was tenable.

Tolerability analysis

The FC bore a higher risk of conjuctival hyperemia than timolol Mt (RR: 3.04, 95%CI: 2.12 to 4.36), whereas the comparisons of the FC with the PGA Mt and the UC showed that the FC bore lower risk (RR: 0.61, 95%CI: 0.53 to 0.70; RR: 0.70, 95%CI: 0.43 to 1.14 respectively) (Fig. 4). In the subgroup analysis by the type of PGA (Supplementary Fig. S5), there were no statistically significant differences between the different PGAs. In comparison with timolol Mt, the FC with latanoprost seemed to lead to a lower increase in risk than the other FCs.

When FC was compared with PGA Mt, the RR of conjuctival hyperemia was lower in the comparison of bimatoprost (RR: 0.59, 95% CI: 0.51 to 0.68) than in that of travoprost (RR:0.94, 95% CI: 0.50 to 1.77), but superimposable to latanoprost (RR: 0.65, 95% CI: 0.42 to 0.99).

Discussion

This systematic review offers an overview of the randomized trials comparing topical medical therapies in which timolol, bimatoprost, latanoprost, and travoprost were administered alone, in FCs or in UCs for at least 4 weeks.

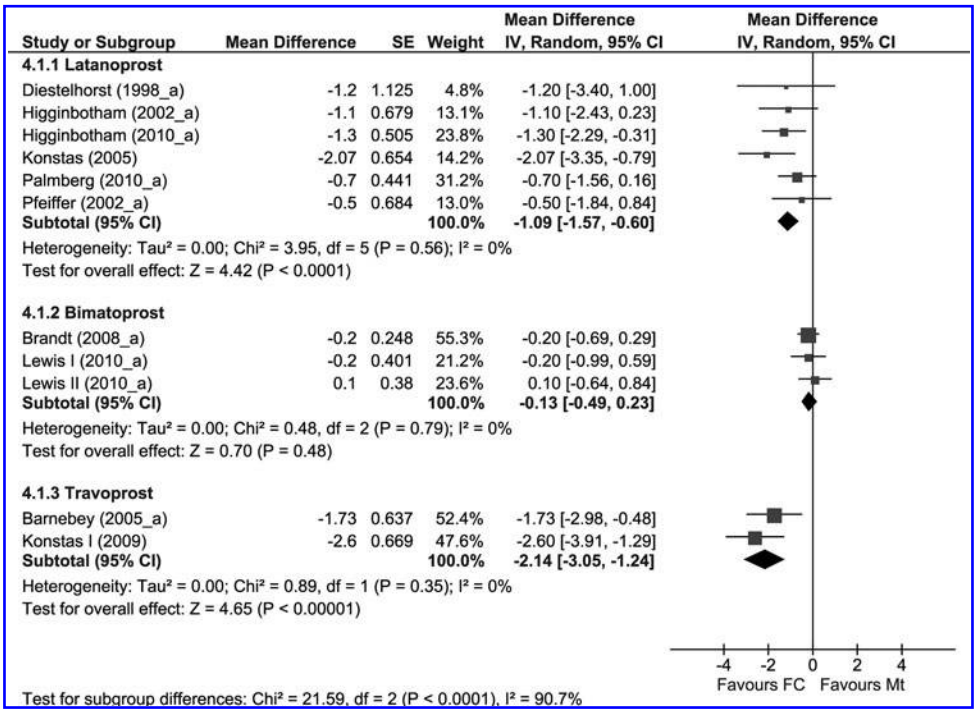

FIG. 3. Overall MeD in the reduction in IOP between the FC and Mt. Subgroup analysis by type of Mt: latanoprost, bimatoprost, or travoprost.

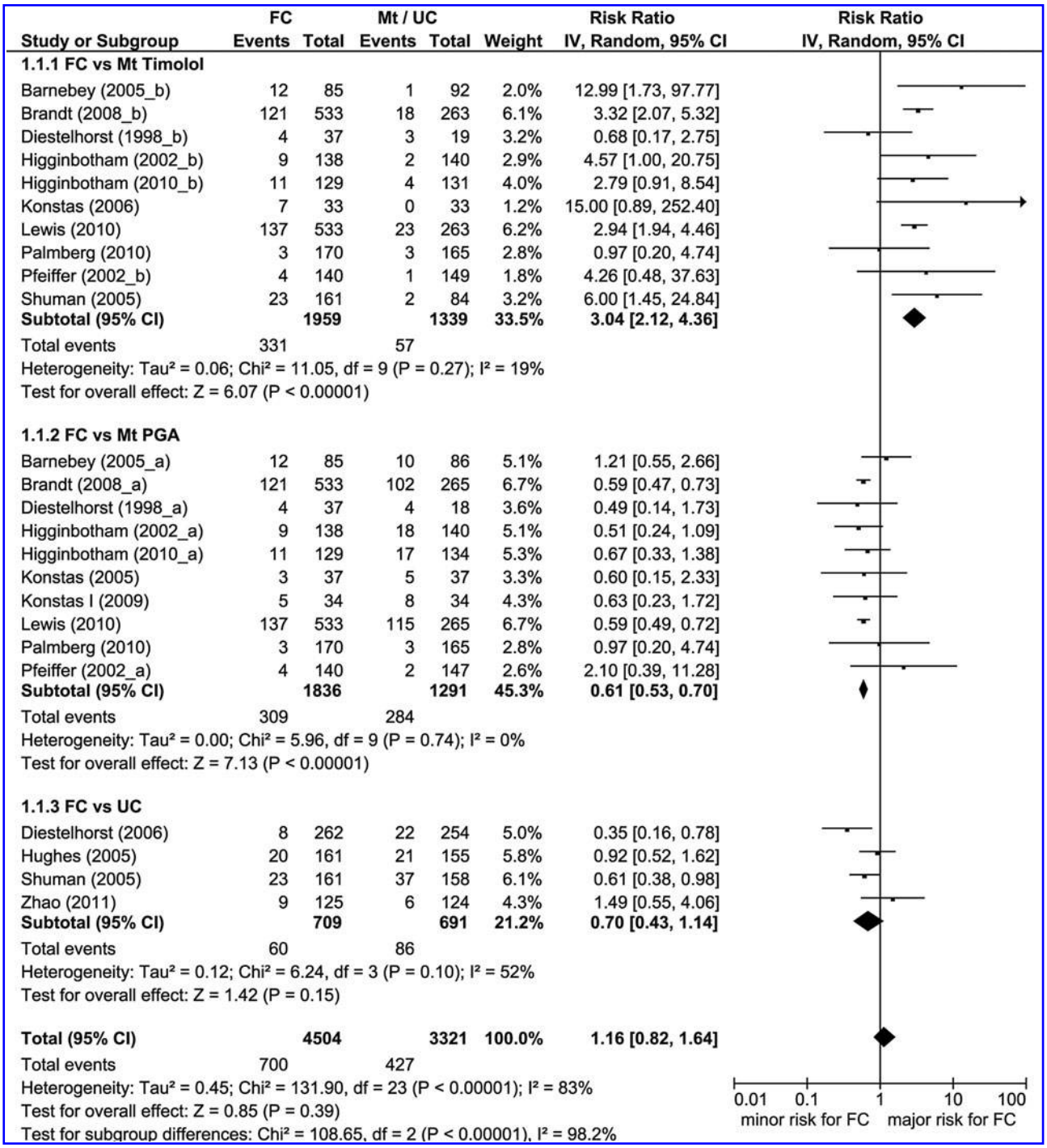

FIG. 4. Relative Risk (RR) of hyperemia of FC versus Mt or versus UC. Subgroup analysis: FC versus Mt with timolol, FC versus Mt with prostaglandin analogs (PGAs), and FC versus UC.

Multidrug therapy is frequently required in the management of glaucoma, and β-blockers are frequently added to PGAs. A previous meta-analysis found that the addition of a β-blocker to a PGA is more efficacious than adding an α-adrenergic or topical carbonic anhydrase inhibitor.[33]

As expected, all of the FCs were more efficacious than timolol Mt, although the difference in efficacy was significantly greater for the latanoprost/timolol FC (MeD: −2.74, 95%CI: −3.24 to −2.23) than the travoprost/timolol FC (MeD: −1.93, 95%CI: −2.98 to −0.88) or the bimatoprost/timolol FC (MeD: −1.49, 95%CI: −1.86 to −1.12). However, it needs to be underlined that, although our results suggest the superiority of the latanoprost FC over the travoprost and bimatoprost FCs, the small number of studies (2 of the travoprost FC and 3 of the bimatoprost FC) and the absence of a direct comparison of FCs do not allow any definite conclusion to be drawn.

Moreover, FCs have a greater IOP-lowering effect than their respective PGA Mt, with a difference of about 1 mmHg for latanoprost (MeD −1.09; 95% CI: −1.57 to −0.60) and

2 mmHg for travoprost (MeD −2.14; 95% CI: −3.05 to −1.24). These results are consistent with the findings of Aptel et al.[34] The significance of such small additional differences in IOP is not known, but are likely clinically relevant, especially in patients requiring a greater IOP reduction or at a greater risk of glaucoma progression.

On the other hand, the FC of bimatoprost does not perform similar to the other 2 FCs: the lack of a statistically significant difference between FC of bimatoprost and the respective PGA Mt in IOP reduction is unclear. It is likely a result of different dosing time between the 2 treatments (FC administered AM and bimatoprost PM), or the challenges in showing additivity to an effective PGA.

Our data suggest that FCs are more efficacious when administered in the evening, although it should be noted that the inclusion of studies with mainly or exclusively day-time IOP measurements may overestimate the efficacy of an FC administered in the evening, because most if the measurements were made at about the time of peak PGA efficacy (ie, 12 h after administration).

Our results indicate that UCs are more potent than their respective FCs. One possible explanation might be that patients treated with UCs are actually receiving 2 doses of a β-blocker, whereas those treated with FCs receive only one. Another explanation may be that, in 4 of the 5 analyzed studies, the FC was administered in the morning.[21,23,25,31] As mentioned above, the inclusion of studies with day-time measurements may overestimate the efficacy of PGAs and their respective FCs administered in the evening, and underestimate the efficacy of PGAs, and their respective FCs administered in the morning, because their peak efficacy remains largely unrecorded unless IOP is measured at night.

All 3 FCs were better tolerated than their respective PGA Mt, and less tolerated than timolol. This has been previously reported by Brandt et al., who compared the effects of the bimatoprost/timolol FC with those of each of its individual components and found a significantly lower incidence of conjuctival hyperemia in the FC group.[28]

The mechanism underlying the reduction in conjuctival hyperemia when a PGA is used in a FC with a β-blocker is not completely clear. It has been postulated that it may be due to the α_1-adrenergic agonist effect of endogenous catecholamines, which is unopposed by β_2-adrenergic agonists after timolol-induced β-blockade.[35]

The FCs also showed a lower risk of conjunctival hyperemia than the UCs, although these differences were not statistically significant.

In conclusion and as expected, all of the FCs are more efficacious than timolol Mt, and their evening administration leads to a greater IOP-lowering effect than morning administration. The FC of latanoprost seems to induce a greater reduction in IOP, although no direct comparisons between the different PGAs are yet available. Adding timolol to latanoprost and travoprost seems to lead to a greater reduction in IOP than the respective PGAs in Mt. UCs seem to be more efficacious than their respective FCs, but are probably less well tolerated; however, our search identified only few studies comparing FCs and UCs, and prevented any further analyses of the efficacy of the different PGAs.

Author Disclosure Statement

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Conflict of interest: None of the authors has any financial conflict of interest.

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