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Short-term efficacy of latanoprostene bunod for the treatment of open-angle glaucoma and ocular hypertension: a systematic literature review and a network meta-analysis

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ABSTRACT

Background/aims To assess the comparative efficacy of latanoprostene bunod (LBN), a novel prostaglandin analogue (PGA), to other medications for open-angle glaucoma and ocular hypertension on lowering intraocular pressure (IOP).

Methods A systematic literature review adapted from the Li *et al* (Ophthalmology, 2016) study was conducted. Medline, Embase and PubMed were searched for randomised controlled trials published between 1 January 2014 and 19 March 2020. Studies had to report IOP reduction after 3 months for at least two different treatments among placebo, PGAs (bimatoprost 0.01%, bimatoprost 0.03%, latanoprost, LBN, tafluprost, unoprostone) or apraclonidine, betaxolol, brimonidine, brinzolamide, carteolol, dorzolamide, levobunolol, timolol, travoprost. A Bayesian network meta-analysis was performed to provide the relative effect in terms of mean difference (95% credible interval) of IOP reduction and ranking probabilities. Surface under the cumulative ranking curve (SUCRA) was generated.

Results A total of 106 trials were included with data for 18 523 participants. LBN was significantly more effective than unoprostone (−3.45 (−4.77 to −2.12)). Although relative effect was not significative, compared with other PGAs, LBN numerically outperformed latanoprost (−0.70 (−1.83 to 0.43)) and tafluoprost (−0.41 (−1.87 to 1.07)), was similar to bimatoprost 0.01% (-0.02(−1.59 to 1.55)) and was slightly disadvantaged by bimatoprost 0.03% (−0.17 (−1.42 to 1.07)). LBN was significantly more efficient than the beta-blockers apraclonidine, betaxolol, brimonidine, brinzolamide, carteolol, dorzolamide and timolol. According to SUCRA, LBN was ranked second after bimatoprost 0.03%, followed by bimatoprost 0.01%.

Conclusion LBN was significantly more effective than the PGA unoprostone and most of the beta-blockers. Compared with the most widely used PGAs, LBN numerically outperformed latanoprost and travoprost and was similar to bimatoprost 0.01%.

INTRODUCTION

Glaucoma is a group of progressive optic neuropathies characterised by degeneration of retinal ganglion cells which may lead to vision loss and blindness.[1] It is the number one cause of irreversible vision loss and the second leading cause of blindness worldwide.[2 3] Primary open-angle glaucoma (POAG) is the most common form of the disease in North America with a prevalence of 3.3% (2.7 million people) in adults aged between 40 and 80 years in 2013.[4]

The goal of treatment is to reduce intraocular pressure (IOP), which is the only modifiable risk factor at this time.[3 5] Initial treatment consists of topical therapies with several classes available, including prostaglandin analogues (PGAs), α-adrenergic agonist, beta-blockers and carbonic anhydrase inhibitors and parasympathomimetic agents.[3 6 7] Among these, PGAs are the most effective medication because of their unmatched safety profile, IOP-lowering capabilities and their once-daily administration, with latanoprost, bimatoprost and travoprost being the most frequently used.[8] Of note, in 2012, Lumigan (bimatoprost 0.03%) was discontinued and replaced by Lumigan RC (bimatoprost 0.01%) due to its favourable tolerability profile.[9]

In order to compare the different treatments a comprehensive assessment of their relative efficacy is crucial for clinicians and healthcare decision-makers,[8 10] however, no head-to-head trials comparing all relevant competing therapies have been published. In the absence of direct evidence, the use of a network meta-analysis (NMA) may provide useful evidence.[10] In 2016, Li *et al* published the results of a systematic review and an NMA which aimed to compare the effectiveness of first-line medications for patients with POAG or ocular hypertension (OH) and to provide relative ranking of these treatments. The authors conducted a systematic review in March 2014 in order to identify all randomised controlled trials (RCTs) comparing single active topical medication with no treatment/placebo or with another single topical treatment. Following a systematic review of 114 eligible trials, results of the NMA indicated that, compared with beta-blockers, α-adrenergic agonists and carbonic anhydrase inhibitors, PGAs were more efficacious in reducing IOP at 3 months. Authors also concluded that drugs within the PGA class, namely bimatoprost, latanoprost and travoprost were among the most efficacious, with intraclass difference found to be small and not clinically meaningful.[11]

Vyzulta (latanoprostene bunod (LBN) ophthalmic solution, 0.024% w/v), a novel nitric oxidedonating prostaglandin F2α analogue has received approbation for commercialisation in six different countries.[12] The safety and efficacy of LBN has been well established through clinical studies (APOLLO and LUNAR studies),[13 14] where LBN demonstrated enhanced efficacy compared with latanoprost and timolol.[13–15] However, the effectiveness of LBN in comparison to other topical therapies other than latanoprost and timolol has not yet been evaluated. The objective of this study was to assess, through a systematic review and an NMA, the relative efficacy, as well as provide a relative ranking, of LBN compared with other topical medications, with a focus on PGAs, for the treatment of POAG and OH.

MATERIAL AND METHODS

The pool of studies included in Li *et al*[11] previously described was considered and an exhaustive literature review was performed for studies published after 2013. An NMA was conducted according to a predefined protocol and was conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[16] extension for NMA. The review question was established using the population, intervention, comparators, outcomes (PICO) framework. This systematic review was adapted from the work by Li *et al* previously described.[11]

Search strategy

MEDLINE, EMBASE and PubMed databases were searched on 19 March 2020 to identify RCTs published in English or French between 1 January 2014 and 19 March 2020. A manual search of reference lists was also performed to identify potentially relevant papers and systematic reviews. The same search strategy elaborated by Li *et al* was used but 'latanoprostene bunod' was added as a keyword.[11] Detailed search strategies are presented in online supplemental appendix A.

Eligibility

Studies were selected if they reported relative efficacy between at least two different treatments (placebo, bimatoprost 0.01%, bimatoprost 0.03%, latanoprost, LBN, tafluprost, unoprostone, apraclonidine, betaxolol, brimonidine, brinzolamide, carteolol, dorzolamide, levobunolol, timolol or travoprost) in terms of IOP reduction after 3 months of usage. All eligibility criteria were defined a priori and were rigorously considered assuming the similarity assumption. Inclusion criteria included the following: RCTs with a parallel-group design (cross-over trials excluded); at least 60% of patients with a diagnostic of POAG and/or OH; trials that assess a monotherapy regimen (combination of medical treatments excluded); studies published in English and French between 1 January 2014 and 19 March 2020.Trials were excluded if they enrolled fewer than 10 participants in each group or if they evaluated a combination of medical treatments. Although no maximum or minimum duration of treatment was required, participants had to be followed for at least 28 days after randomisation.

Study selection and data extraction

Two reviewers independently screened the titles and abstracts of publications for potential eligibility. Using a predefined eligibility form (online supplemental appendix B), both reviewers screened the full text of all potentially eligible trials. Any disagreements were resolved by consensus or with the help of a third reviewer.

Data extraction was performed by two independent reviewers. Data extracted included: first author's name, year of publication, trial design, location of trial, sample size, patients' baseline characteristics, intervention characteristics and quantitative results with regard to treatment effect. For studies presenting multiple treatment durations, the duration closest to 3 months was used. If many IOP measures were available, the selection was made in this order: mean diurnal IOP, 24-hour mean IOP, peak IOP reduction and morning IOP. Any discrepancies were resolved by consensus or with the help of a third reviewer.

Quality assessment

As part of their systematic review, Li *et al* assessed the quality of included trials using the Cochrane Risk of Bias Tool, where the following seven methodological domains were graded as 'low', 'high' or 'unclear' risk of bias: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, funding of the trial and financial relationship reported by the authors.[11 17] Based on their work, new trials identified by the current systematic review were assessed using the same method.

Outcome definition

The primary outcome was defined as the mean reduction (MR) of IOP in continuous mmHg units after 3 months of treatment. The mean difference (MD) of the MR of IOP between two treatments with a 95% CI or credible interval (CrI) was calculated. An MD under 0 indicated that the treatment of reference performed a higher IOP reduction relative to its comparator and was therefore more effective.

Data synthesis and analysis

Using the 'meta' package in R, a pairwise meta-analysis (ie, direct comparisons) with a random-effect model was conducted for every treatment comparison with at least two trials. Statistical heterogeneity between studies was assessed using the I^2 statistic, which describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (chance).[18] Cochrane Handbook developed a rough guide for interpretation of I^2: less than 40% might not be important, 30%–60% may represent moderate heterogeneity; 50%–90% may represent substantial heterogeneity and 75%–100% represented considerable heterogeneity.[18] Pairwise comparisons with an I^2 value greater than 65% were investigated to identify studies possibly causing heterogeneity.

An NMA, which combined direct and indirect comparisons, was conducted using a Bayesian random-effect model with Markov Chain Monte Carlo simulations executed with the 'gemtc' package in R.[19] Using four parallel chains, 50 000 samples after 20 000-sample burn-in were obtained in each chain. Convergence of the model was assessed using the Brooks-Gelman-Rubin diagnostic in the 'coda' package in R. Consistency of the NMA, defined as a statistical discrepancy between direct and indirect comparison results, was evaluated using a node-splitting approach with the 'gemtc' package in R.[19]

The model ranked each treatment by their relative effect (probabilities of being more effective). Cumulative probability of being the most effective treatment was calculated. With that, the surface under the cumulative ranking curve (SUCRA) of each treatment is obtained.[20] Specifically, SUCRA is a numeric presentation of the overall ranking and presents a single number, ranging from 0% to 100%, associated with each treatment, where 0% represents the least effective treatment and 100% represents the most effective treatment.[21]

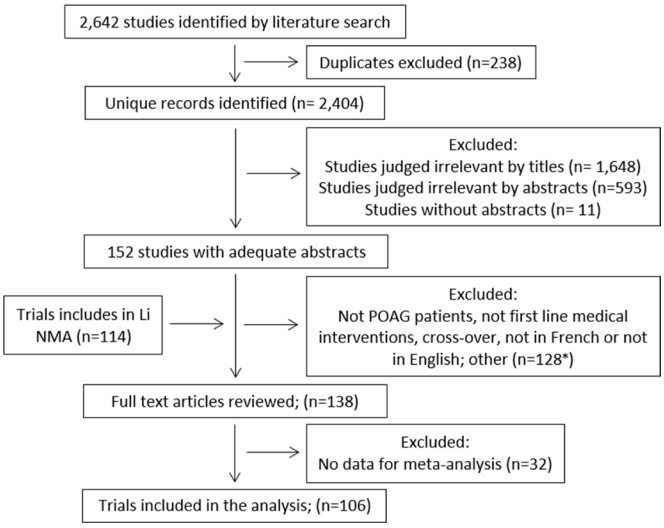

Figure 1 Organisational chart of the literature review. *Among the 128 excluded studies, seven were included in the Li *et al* publication. NMA, network meta-analysis; POAG, primary open-angle glaucoma.

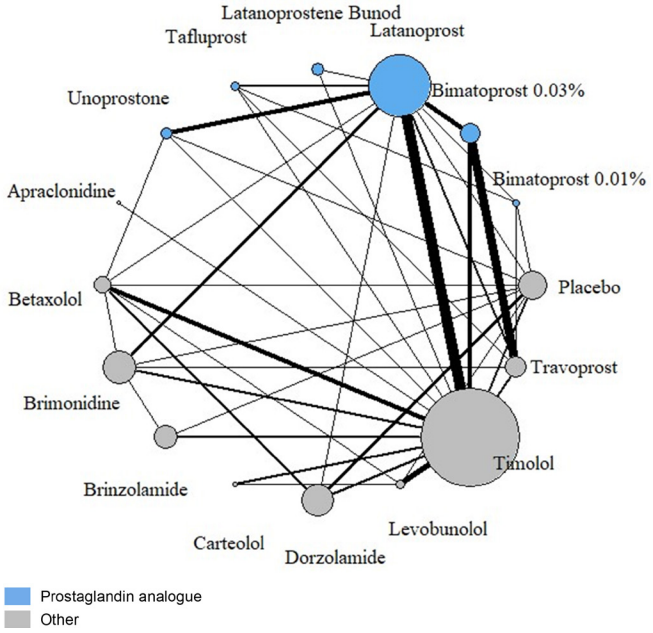

Figure 2 Network Graph. The nodes are weighted according to the number of participants randomised to that drug. The edges are weighted according to the number of direct comparison studies between drugs.

Sensitivity analyses were conducted to assess the impact of heterogeneity between studies and inconsistency results by removing studies identified as possibly causing heterogeneity and including inconsistent combinations, respectively.

Supplementary analyses were conducted to evaluate the heterogeneity between baseline characteristics among trials included.

All concentrations of the same medication were combined in the same group except for bimatoprost 0.01% and bimatoprost 0.03%.

RESULTS

Of the 2642 publications identified by the systematic review and the 114 studies used by Li *et al*, 106 RCTs met the a priori eligibility criteria and were included (figure 1; references of these RCTs are listed in online supplemental appendix C). Of these, 11 (10%) were published between 2014 and 2020. The total number of participants contributing to this network is 18 523 (complete characteristics of included studies are listed in online supplemental appendix D.

Of the 106 trials, risk of selection bias (online supplemental appendix E) was rated as low for 54 (51%) and 33 (31%) studies when assessing sequence generation or allocation concealment, respectively, whereas the remaining trials were rated as having an 'unclear risk' except for one study with a 'high risk' in allocation concealment. Risk of performance bias, associated with blinding of participants, was rated as low (ie, reported blinding), high (ie, reported not blinding) or unclear (ie, not reported or unclear), for 42%, 37% and 21% of studies, respectively. Risk of detection bias, associated with blinding of the outcome assessor, was rated as low (ie, reported blinding), high (ie, reported not blinding) or unclear risk (ie, not reported) for 24%, 63% and 13% of studies, respectively. Of the 69 articles who reported funding for their research, 64 (93%) were funded by the industry. Of the 55 articles that reported financial relationship, 15 (27%) declared having no financial conflict of interest.

The 106 studies included compared 16 interventions (figure 2). A total of 138 direct comparisons were performed based on 93 two-arm trials, 11 three-arm trials and 2 four-arm trials. Results of the pairwise meta-analysis are presented in table 1. LBN was compared with timolol in two studies and latanoprost in one study. In both cases, LBN significantly lowers IOP more than the other treatments after 3 months (LBN vs timolol: MD (95% CI)=−1.42 (−1.84 to −1.01) and LBN vs latanoprost: −1.23 (−1.76 to −0.70)).

Results of the NMA indicate that, when compared with placebo, all active drugs demonstrate an improved reduction of IOP at 3 months (table 2 and online supplemental appendix F). More specifically, the MDs in IOP reduction at 3 months for active drug in comparison to placebo range from −1.97 mm Hg for unoprostone to −5.59 mm Hg for bimatoprost 0.03% and are all statistically significative. Importantly, LBN shows the second greatest reduction in IOP vs placebo with an MD (95% CrI) of −5.42 mm Hg (−6.68 to –4.16). Furthermore, these results highlight the statistically significant superiority in efficacy of LBN compared with the PGA unoprostone (−3.45 (−4.77 to −2.12)) and the beta-blockers apraclonidine (−2.55 (−4.52 to −0.55)), betaxolol (−2.89 (−4.17 to −1.60)), brimonidine (−1.75 (−3.02 to −0.49)), brinzolamide (−2.88 (−-4.29 to −1.47)), carteolol (−2.17 (−3.65 to −0.69)), dorzolamide (−2.87 (−4.17 to −1.55)) and timolol (−1.69 (−2.80 to −0.58)). Although the relative effect was not significative, compared with other PGAs, LBN numerically outperformed latanoprost (−0.70 (−1.83 to 0.43)) and tafluoprost (−0.41 (−1.87 to 1.07)), was similar to bimatoprost 0.01% (−0.02 (−1.59 to 1.55)) and bimatoprost 0.03% demonstrated a slightly advantage over LBN (−0.17 (−1.42 to 1.07)) (table 2 and online supplemental appendix F). The model ranked each treatment by their relative effect (probabilities of being more effective) (table 3). According to these results, treatment with the higher probability of being ranked first is bimatoprost 0.03% with a probability of 37%, followed by LBN with a probability of 29%. LBN has a probability of 51% to be under the two best treatments and 70% to be under the three best treatments. Cumulative probability of being the most effective

Table 1 Summary estimates for intraocular pressure at 3 months derived from the pairwise meta-analysis

Control	Experimental	Total no of studies	Mean difference*	95%CI		τ^2†	I^2‡
				Low	Up		
Placebo	Bimatoprost 0.01%	1	**−4.60**	**−5.60**	**−3.60**	**NA**	**NA**
	Latanoprost	1	**−3.10**	**−3.98**	**−2.22**	**NA**	**NA**
	Unoprostone	1	−0.30	−1.50	0.90	NA	NA
	Betaxolol	2	**−3.16**	**−4.17**	**−2.15**	**0.3**	**52%**
	Brimonidine	1	**−2.30**	**−3.99**	**−0.61**	**NA**	**NA**
	Brinzolamide	1	**−2.22**	**−3.48**	**−0.96**	**NA**	**NA**
	Dorzolamide	4	**−2.48**	**−3.84**	**−1.12**	**1.3**	**76%**
	Levobunolol	2	**−7.90**	**−8.94**	**−6.85**	**0.0**	**0%**
	Timolol	4	**−3.75**	**−4.75**	**−2.76**	**0.6**	**58%**
Bimatoprost 0.01%	Latanoprost	2	**1.02**	**0.68**	**1.37**	**0.0**	**0%**
	Tafluprost	1	2.30	−0.91	5.51	NA	NA
	Travoprost	2	1.50	−1.98	4.97	5.2	80%
Bimatoprost 0.03%	Latanoprost	7	**0.99**	**0.46**	**1.53**	**0.3**	**61%**
	Travoprost	8	0.44	−0.52	1.40	1.4	86%
Latanoprost	Latanoprostene bunod	1	**−1.23**	**−1.76**	**−0.70**	**NA**	**NA**
	Tafluprost	3	**−0.99**	**−1.92**	**−0.07**	**0.0**	**0%**
	Unoprostone	6	**2.90**	**2.16**	**3.63**	**0.3**	**37%**
	Travoprost	7	−0.15	−1.30	1.00	1.9	87%
Apraclonidine	Timolol	2	−0.44	−3.91	3.03	5.6	89%
Betaxolol	Latanoprost	2	**−1.84**	**−3.22**	**−0.47**	**0.0**	**0%**
	Unoprostone	1	**0.60**	**0.09**	**1.11**	**NA**	**NA**
	Dorzolamide	2	−0.21	−0.82	0.40	0.0	0%
	Levobunolol	2	−4.65	−10.13	0.84	13.3	84%
	Timolol	6	**−1.30**	**−2.46**	**−0.13**	**1.2**	**67%**
Brimonidine	Latanoprost	5	**−1.22**	**−2.13**	**−0.31**	**0.8**	**78%**
	Betaxolol	1	**2.00**	**0.90**	**3.10**	**NA**	**NA**
	Brinzolamide	2	**0.90**	**0.39**	**1.42**	**0.0**	**0%**
	Timolol	4	**0.42**	**0.04**	**0.81**	**0.0**	**0%**
	Travoprost	1	−1.20	−3.77	1.37	NA	NA
Brinzolamide	Dorzolamide	2	−0.34	−0.84	0.16	0.0	0%
Carteolol	Levobunolol	1	**−2.90**	**−4.59**	**−1.21**	**NA**	**NA**
	Timolol	4	−0.27	−1.11	0.57	0.4	60%
Dorzolamide	Latanoprost	1	−2.90	−3.70	−2.10	0.0	NA
Levobunolol	Timolol	9	0.11	−0.40	0.62	0.1	15%
Timolol	Bimatoprost 0.03%	6	**−2.06**	**−2.36**	**−1.75**	**0.0**	**0%**
	Latanoprost	15	**−1.18**	**−1.65**	**−0.70**	**0.6**	**76%**
	Latanoprostene bunod	2	**−1.42**	**−1.84**	**−1.01**	**0.0**	**0%**
	Tafluprost	2	−0.50	−1.12	0.12	0.1	38%
	Unoprostone	2	0.94	−0.43	2.31	0.9	87%
	Brinzolamide	3	**1.10**	**0.52**	**1.69**	**0.0**	**0%**
	Dorzolamide	4	**0.99**	**0.34**	**1.64**	**0.1**	**26%**
	Travoprost	4	**−0.89**	**−1.26**	**−0.52**	**0.0**	**0%**
Travoprost	Tafluprost	1	−1.30	−2.93	0.33	NA	NA
Total	16 drugs	**138**§					

, PGA

*Difference between the reduction in IOP during the study of the experimental drug and the control drug (mean difference under 0 favours the experimental drug). Results presented in bold are significant.

†τ^2 describes the underlying between-study variability.

‡I^2 is the percentage of variability in the treatment estimates which is attributable to heterogeneity.

§106 trials considered: 93 two-arm trials, 11 three-arm trials and 2 four-arm trials.

IOP, intraocular pressure; NA, not available; PGA, prostaglandin analogue.

treatment was calculated and the cumulative ranking curve of each treatment (presented in online supplemental appendix G) was obtained to calculate the SUCRA. According to SUCRA results, LBN (SUCRA=88%) emerges as the second best treatment after bimatoprost 0.03% (94%) and followed in order by bimatoprost 0.01% (87%), tafluprost (78%), travoprost (73%), levobunolol (72%), latanoprost (68%), timolol (48%), brimonidine (47%), carteolol (38%), apraclonidine (30%), dorzolamide (23%), brinzolamide (22%), betaxolol (22%), unoprostone (11%) and placebo (0%).

Table 2 Mean difference in intraocular pressure at 3 months (95% credible interval) derived from the NMA

	−5.39	−5.59	−4.72	−5.42	−5.00	−1.97	−2.86	−2.53	−3.66	−2.53	−3.24	−2.55	−4.79	−3.73	−4.84
Placebo	**(−6.60 to −4.21)**	**(−6.43 to−4.75)**	**(−5.39 to−4.04)**	**(−6.68 to−4.16)**	**(−6.15 to−3.88)**	**(−2.88 to−1.06)**	**(−4.65 to−1.12)**	**(−3.32 to−1.75)**	**(−4.48 to−2.85)**	**(−3.52 to−1.56)**	**(−4.40 to−2.09)**	**(−3.33 to−1.78)**	**(−5.64 to−3.95)**	**(−4.36 to−3.10)**	**(−5.69 to−3.98)**
5.39	**Bimatoprost 0.01%**	−0.20	0.67	−0.02	0.39	**3.42**	**2.53**	**2.86**	**1.73**	**2.85**	**2.15**	**2.84**	0.60	**1.66**	0.55
(4.21 to 6.60)		(−1.41 to1.03)	(−0.44 to1.80)	(−1.59 to1.55)	(−1.06 to1.82)	**(2.11 to 4.75)**	**(0.51 to 4.51)**	**(1.59 to 4.15)**	**(0.47 to 2.99)**	**(1.45 to 4.27)**	**(0.65 to 3.65)**	**(1.55 to 4.13)**	(−0.70 to1.92)	**(0.52 to 2.81)**	(−0.60 to1.72)
5.59	0.20	**Bimatoprost 0.03%**	**0.88**	0.17	0.59	**3.62**	**2.73**	**3.06**	**1.93**	**3.06**	**2.35**	**3.04**	0.80	**1.86**	**0.75**
(4.75 to 6.43)	(−1.03 to1.41)		**(0.26 to 1.48)**	(−1.07 to1.42)	(−0.54 to1.69)	**(2.69 to 4.55)**	**(0.94 to 4.47)**	**(2.18 to 3.95)**	**(1.09 to 2.76)**	**(2.01 to 4.10)**	**(1.18 to 3.50)**	**(2.12 to 3.94)**	(−0.12 to1.71)	**(1.24 to 2.48)**	**(0.08 to 1.43)**
4.72	−0.67	**−0.88**	**Latanoprost**	−0.70	−0.29	**2.75**	**1.85**	**2.18**	**1.05**	**2.18**	**1.47**	**2.17**	−0.08	**0.99**	−0.12
(4.04 to 5.39)	(−1.80 to0.44)	**(−1.48 to−0.26)**		(−1.83 to0.43)	(−1.28 to0.69)	**(2.01 to 3.49)**	**(0.13 to 3.53)**	**(1.46 to 2.92)**	**(0.41 to 1.69)**	**(1.27 to 3.09)**	**(0.41 to 2.53)**	**(1.41 to 2.92)**	(−0.85 to0.70)	**(0.58 to 1.39)**	(−0.75 to0.52)
5.42	0.02	−0.17	0.70	**Latanoprostene Bunod**	0.41	**3.45**	**2.55**	**2.89**	**1.75**	**2.88**	**2.17**	**2.87**	0.62	**1.69**	0.58
(4.16 to 6.68)	(−1.55 to1.59)	(−1.42 to1.07)	(−0.43 to1.83)		(−1.07 to1.87)	**(2.12 to 4.77)**	**(0.55 to 4.52)**	**(1.60 to 4.17)**	**(0.49 to 3.02)**	**(1.47 to 4.29)**	**(0.69 to 3.65)**	**(1.55 to 4.17)**	(−0.68 to1.92)	**(0.58 to 2.80)**	(−0.69 to1.85)
5.00	−0.39	−0.59	0.29	−0.41	**Tafluprost**	**3.04**	**2.14**	**2.47**	**1.34**	**2.47**	**1.76**	**2.46**	0.21	**1.28**	0.17
(3.88 to 6.15)	(−1.82 to1.06)	(−1.69 to0.54)	(−0.69 to1.28)	(−1.87 to1.07)		**(1.83 to 4.25)**	**(0.20 to 4.05)**	**(1.31 to 3.66)**	**(0.21 to 2.49)**	**(1.18 to 3.77)**	**(0.38 to 3.15)**	**(1.27 to 3.65)**	(−0.97 to1.41)	**(0.30 to 2.27)**	(−0.92 to1.28)
1.97	**−3.42**	**−3.62**	**−2.75**	**−3.45**	**−3.04**	**Unoprostone**	−0.90	−0.56	**−1.70**	−0.57	**−1.28**	−0.58	**−2.82**	**−1.76**	**−2.87**
(1.06 to 2.88)	**(−4.75 to−2.11)**	**(−4.55 to−2.69)**	**(−3.49 to−2.01)**	**(−4.77 to−2.12)**	**(−4.25 to−1.83)**		(−2.73 to0.90)	(−1.50 to0.38)	**(−2.63 to−0.75)**	(−1.69 to0.56)	**(−2.52 to−0.03)**	(−1.57 to0.41)	**(−3.83 to−1.81)**	**(−2.53 to−0.99)**	**(−3.82 to−1.92)**
2.86	**−2.53**	**−2.73**	**−1.85**	**−2.55**	**−2.14**	0.90	**Apraclonidine**	0.33	−0.80	0.33	−0.38	0.31	**−1.93**	−0.86	**−1.98**
(1.12 to 4.65)	**(−4.51 to−0.51)**	**(−4.47 to−0.94)**	**(−3.53 to−0.13)**	**(−4.52 to−0.55)**	**(−4.05 to−0.20)**	(−0.90 to2.73)		(−1.43 to2.14)	(−2.54 to0.99)	(−1.51 to2.21)	(−2.28 to1.54)	(−1.46 to2.13)	**(−3.70 to−0.13)**	(−2.49 to0.81)	**(−3.73 to−0.18)**
2.53	**−2.86**	**−3.06**	**−2.18**	**−2.89**	**−2.47**	0.56	−0.33	**Betaxolol**	**−1.13**	0.00	−0.71	−0.02	**−2.26**	**−1.20**	**−2.31**
(1.75 to 3.32)	**(−4.15 to−1.59)**	**(−3.95 to−2.18)**	**(−2.92 to−1.46)**	**(−4.17 to−1.60)**	**(−3.66 to−1.31)**	(−0.38 to1.50)	(−2.14 to1.43)		**(−1.99 to−0.29)**	(−1.06 to1.03)	(−1.90 to0.46)	(−0.87 to0.81)	**(−3.17 to−1.37)**	**(−1.88 to−0.52)**	**(−3.21 to−1.40)**
3.66	**−1.73**	**−1.93**	**−1.05**	**−1.75**	**−1.34**	**1.70**	0.80	**1.13**	**Brimonidine**	**1.13**	0.42	**1.11**	**−1.13**	−0.06	**−1.17**
(2.85 to 4.48)	**(−2.99 to−0.47)**	**(−2.76 to−1.09)**	**(−1.69 to−0.41)**	**(−3.02 to−0.49)**	**(−2.49 to−0.21)**	**(0.75 to 2.63)**	(−0.99 to2.54)	**(0.29 to 1.99)**		**(0.21 to 2.04)**	(−0.75 to1.59)	**(0.23 to 1.99)**	**(−2.05 to−0.21)**	(−0.70 to0.57)	**(−2.02 to−0.32)**
2.53	**−2.85**	**−3.06**	**−2.18**	**−2.88**	**−2.47**	0.57	−0.33	0.00	**−1.13**	**Brinzolamide**	−0.71	−0.01	**−2.26**	−1.19	**−2.30**
(1.56 to 3.52)	**(−4.27 to−1.45)**	**(−4.10 to−2.01)**	**(−3.09 to−1.27)**	**(−4.29 to−1.47)**	**(−3.77 to−1.18)**	(−0.56 to1.69)	(−2.21 to1.51)	(−1.03 to1.06)	**(−2.04 to−0.21)**		(−2.01 to0.60)	(−0.99 to0.95)	**(−3.34 to−1.17)**	(−2.06 to−0.32)	**(−3.36 to−1.24)**
3.24	**−2.15**	**−2.35**	**−1.47**	**−2.17**	**−1.76**	**1.28**	0.38	0.71	−0.42	0.71	**Carteolol**	0.69	**−1.55**	−0.48	**−1.59**
(2.09 to 4.40)	**(−3.65 to−0.65)**	**(−3.50 to−1.18)**	**(−2.53 to−0.41)**	**(−3.65 to−0.69)**	**(−3.15 to−0.38)**	**(0.03 to 2.52)**	(−1.54 to2.28)	(−0.46 to1.90)	(−1.59 to0.75)	(−0.60 to2.01)		(−0.51 to1.89)	**(−2.68 to−0.42)**	(−1.46 to0.50)	**(−2.76 to−0.42)**
2.55	**−2.84**	**−3.04**	**−2.17**	**−2.87**	**−2.46**	0.58	−0.31	0.02	**−1.11**	0.01	−0.69	**Dorzolamide**	**−2.24**	**−1.18**	**−2.29**
(1.78 to 3.33)	**(−4.13 to−1.55)**	**(−3.94 to−2.12)**	**(−2.92 to−1.41)**	**(−4.17 to−1.55)**	**(−3.65 to−1.27)**	(−0.41 to1.57)	(−2.13 to1.46)	(−0.81 to0.87)	**(−1.99 to−0.23)**	(−0.95 to0.99)	(−1.89 to0.51)		**(−3.18 to−1.29)**	**(−1.88 to−0.47)**	**(−3.21 to−1.35)**
4.79	−0.60	−0.80	0.08	−0.62	−0.21	**2.82**	**1.93**	**2.26**	**1.13**	**2.26**	**1.55**	**2.24**	**Levobunolol**	**1.06**	−0.05
(3.95 to 5.64)	(−1.92 to0.70)	(−1.71 to0.12)	(−0.70 to0.85)	(−1.92 to0.68)	(−1.41 to0.97)	**(1.81 to 3.83)**	**(0.13 to 3.70)**	**(1.37 to 3.17)**	**(0.21 to 2.05)**	**(1.17 to 3.34)**	**(0.42 to 2.68)**	**(1.29 to 3.18)**		**(0.38 to 1.75)**	(−0.98 to0.89)
3.73	**−1.66**	**−1.86**	**−0.99**	**−1.69**	**−1.28**	**1.76**	0.86	**1.20**	0.06	**1.19**	0.48	**1.18**	**−1.06**	**Timolol**	**−1.11**
(3.10 to 4.36)	**(−2.81 to−0.52)**	**(−2.48 to−1.24)**	**(−1.39 to−0.58)**	**(−2.80 to−0.58)**	**(−2.27 to−0.30)**	**(0.99 to 2.53)**	(−0.81 to2.49)	**(0.52 to 1.88)**	(−0.57 to0.70)	**(0.32 to 2.06)**	(−0.50 to1.46)	**(0.47 to 1.88)**	**(−1.75 to−0.38)**		**(−1.76 to−0.46)**
4.84	−0.55	**−0.75**	0.12	−0.58	−0.17	**2.87**	**1.98**	**2.31**	**1.17**	**2.30**	**1.59**	**2.29**	0.05	**1.11**	**Travoprost**
(3.98 to 5.69)	(−1.72 to0.60)	**(−1.43 to−0.08)**	(−0.52 to0.75)	(−1.85 to0.69)	(−1.28 to0.92)	**(1.92 to 3.82)**	**(0.18 to 3.73)**	**(1.40 to 3.21)**	**(0.32 to 2.02)**	**(1.24 to 3.36)**	**(0.42 to 2.76)**	**(1.35 to 3.21)**	(−0.89 to0.98)	**(0.46 to1.76)**	

, PGA

, others

Results presented in bold are significant.
Mean difference under 0 favours the drug in the column.
NAM, network meta-analysis; PGA, prostaglandin analogue.

Table 3 Ranking probabilities and SUCRA

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Ranks	Placebo	Bimatoprost 0.01%	Bimatoprost 0.03%	Latanoprost	Latanoprostene bunod	Tafluprost	Unoprostone	Apraclonidine	Betaxolol	Brimonidine	Brinzolamide	Carteolol	Dorzolamide	Levobunolol	Timolol	Travoprost
1	0.000	0.266	0.367	0.000	0.288	0.067	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.009	0.000	0.002
2	0.000	0.221	0.374	0.002	0.220	0.117	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.039	0.000	0.025
3	0.000	0.204	0.190	0.023	0.193	0.180	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.104	0.000	0.104
4	0.000	0.126	0.055	0.103	0.118	0.198	0.000	0.004	0.000	0.000	0.000	0.000	0.000	0.176	0.000	0.220
5	0.000	0.072	0.011	0.251	0.071	0.144	0.000	0.005	0.000	0.000	0.000	0.001	0.000	0.195	0.000	0.250
6	0.000	0.052	0.002	0.358	0.050	0.120	0.000	0.007	0.000	0.002	0.000	0.003	0.000	0.193	0.000	0.214
7	0.000	0.052	0.000	0.256	0.052	0.153	0.000	0.016	0.000	0.020	0.000	0.010	0.000	0.263	0.005	0.174
8	0.000	0.006	0.000	0.008	0.006	0.016	0.000	0.089	0.000	0.328	0.001	0.107	0.000	0.018	0.409	0.011
9	0.000	0.001	0.000	0.000	0.001	0.004	0.000	0.063	0.001	0.353	0.005	0.120	0.002	0.001	0.446	0.001
10	0.000	0.001	0.000	0.000	0.001	0.001	0.003	0.150	0.036	0.230	0.058	0.352	0.041	0.000	0.128	0.000
11	0.000	0.000	0.000	0.000	0.000	0.000	0.015	0.201	0.152	0.062	0.170	0.232	0.157	0.000	0.011	0.000
12	0.000	0.000	0.000	0.000	0.000	0.000	0.041	0.107	0.259	0.004	0.231	0.088	0.271	0.000	0.000	0.000
13	0.000	0.000	0.000	0.000	0.000	0.000	0.087	0.094	0.271	0.001	0.220	0.049	0.278	0.000	0.000	0.000
14	0.000	0.000	0.000	0.000	0.000	0.000	0.220	0.123	0.223	0.000	0.214	0.029	0.192	0.000	0.000	0.000
15	0.001	0.000	0.000	0.000	0.000	0.000	0.635	0.136	0.059	0.000	0.102	0.009	0.058	0.000	0.000	0.000
16	0.999	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SUCRA*	**0.0%**	**87.2%**	**93.5%**	**68.4%**	**87.6%**	**77.9%**	**10.6%**	**30.1%**	**22.2%**	**46.7%**	**22.3%**	**37.8%**	**22.7%**	**71.8%**	**48.5%**	**72.7%**
Ranking according SUCRA*	**16**	**3**	**1**	**7**	**2**	**4**	**15**	**11**	**14**	**9**	**13**	**10**	**12**	**6**	**8**	**5**

, PGA

*Higher is the SUCRA, better is the rank of this treatment.
SUCRA, surface under the cumulative ranking curve.

Sensitivity analyses

A total of 10 direct comparisons were identified as possibly causing heterogeneity (online supplemental appendix H). When excluding these studies, the sensitivity analysis revealed no significant change in the NMA results (online supplemental appendix I). LBN was still significantly better than unoprostone and non-PGAs treatments, except for levobunolol and travoprost that was numerically superior. Although the relative effect was not significative, compared with other PGAs, LBN numerically outperformed latanoprost (−0.72 (−1.60 to 0.16)), tafluoprost (−0.60 (−1.80 to 0.61)) and bimatoprost 0.01% (-0.40 (−1.70 to 0.83)) and bimatoprost 0.03% demonstrated a slight advantage over LBN (0.13 (−0.88 to 1.10)).

The node-splitting approach allowed for the identification of two inconsistent nodes (levobunolol vs placebo and timolol vs levobunolol) (online supplemental appendix J). When excluding these nodes, the sensitivity analysis revealed no significant change in the NMA results. Compared with unoprostone (PGA) and other non-PGAs, results indicated that LBN was significantly better, excluding travoprost but including levobunolol (online supplemental appendix I). Compared with other PGAs, although the relative effect was not significative, LBN was still numerically superior to latanoprost (−0.66 (−1.60 to 0.31)), similar to bimatoprost 0.01% (0.09 (−1.30 to 1.50)) and disadvantaged by bimatoprost 0.03% (0.20 (−0.87 to 1.30)).

Four supplementary analyses were also conducted to evaluate the heterogeneity between baseline characteristics among trials by considering: (1) only studies published from 2000 onward, (2) studies with a washout period before randomisation, (3) studies that excluded prior glaucoma and cataract surgery, and (4) studies that excluded prior glaucoma laser. These analyses revealed that heterogeneity between baseline characteristics had no significant impact on the NMA results (online supplemental appendix K).

Also, the Brooks-Gelman-Rubin plot (online supplemental appendix L) illustrates that the NMA model converges.

DISCUSSION

The objective of this study was to assess the relative efficacy of a new IOP-lowering medication, LBN, compared with other topical medications for the treatment of POAG and OH and to provide a relative ranking of these treatments. Findings from this NMA confirm that all drugs are more effective when compared with the placebo. Importantly, results also indicate that LBN is significantly more effective than unoprostone (PGA) and other non-PGAs drugs except levobunolol and travoprost for which LBN is numerically better although not significant. This demonstrates that LBN is more effective than timolol, which aligns with the conclusion drawn from the individual studies (APOLLO and LUNAR).[13 14] Moreover, compared with other PGAs, LBN was numerically more effective than tafluoprost, similar to bimatoprost 0.01% and slightly disadvantaged by bimatoprost 0.03%.

This systematic review was adapted from the one conducted by Li *et al* that was previously published in a peer-reviewed journal.[11] A clear research question was formed using the PICO framework and the analysis was conducted based on the predefined protocol. It should be noted that of the 114 trials eligible in the NMA published by Li *et al*, 19 were not included in this NMA. This is explained by the fact that our systematic review was limited to English or French publications, whereas Li *et al* did not impose any language restriction. Moreover, some full-text articles were not accessible via the databases exploited for this study. Nonetheless, results presented herein are consistent with the findings of Li *et al*. Indeed, when comparing PGAs in terms of IOP reduction at 3 months, the intraclass differences are relatively small and not significantly meaningful. In addition, this systematic review and NMA, which include the most recent PGA, namely LBN, provides new findings relevant to clinicians and decision-makers as it allows for the comparison of drugs that had not yet been evaluated in head-to-head trials.

It should be noted that there are some limitations associated with this NMA. First, although an NMA represents a powerful tool and may provide crucial information, an inherent limitation associated with NMA resides in the variability and the risk of biases of studies included. Due to possible variability between studies and between the comparisons made, a critical step when performing an NMA consists of validating the homogeneity and consistency assumptions. The sensitivity analyses conducted did not significantly alter the results, suggesting that the assumptions and conclusions made based on the statistical analysis are reliable and robust.

Second, this NMA focused on IOP reduction and did not include visual field outcomes. We acknowledge that the ultimate goal in the management of glaucoma consists of slowing or stopping structural damages leading to vision loss and that, consequently, visual field outcomes would be more clinically meaningful than IOP when comparing treatment response. However, due to the lag time between onset of optic neuropathy and clinically detectable visual field defects, the use of visual field outcomes to assess relative effectiveness of different interventions requires an extended time frame which poses challenges to the conduct of RCTs. Thus, although IOP does not measure structural of functional glaucomatous optic neuropathy, it remains the most commonly used surrogate endpoint of RCTs.[10 20 22] Li *et al* reported that only 11% of trials included in their NMA reported any analysable visual field data. Moreover, the authors mentioned that since visual field data were reported in many different ways, the conduct of a pairwise meta-analysis or NMA would have been impossible.[11] Finally, although our study provided a relative ranking of topical treatments for glaucoma based on IOP reduction at 3 months, the choice of treatment remains a multifactorial decision to take into consideration different factors, such as patient's medical history and preference, risk factors and likelihood of compliance.

CONCLUSION

Results from the NMA showed that, LBN was significantly more effective than the PGA unoprostone and most of the beta-blockers. Although there was no significant relative effect, compared with the most widely used PGAs, LBN was numerically more efficient than latanoprost and tafluoprost, was similar to bimatoprost 0.01% and was slightly disadvantaged by bimatoprost 0.03%. LBN could potentially become a promising option for glaucoma patients.

Contributors PH analysed the data and drafted and revised the manuscript for important intellectual content. CR designed the study, acquired and analysed the data, drafted the initial manuscript and reviewed the manuscript. AXC, MB, KJ-G, KM, JL and CB designed the study and reviewed the manuscript.

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Competing interests PH has received consultant honoraria from Bausch Health, Canada. CR is an employee of PeriPharm Inc. AXC, MB and KJ-G are employees of Bausch Health, Canada. KM is an employee of PeriPharm and Université de Montréal. JL and CB have received research funds from Bausch Health, Canada to conduct this study.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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Appendix A. Search Strategies

MEDLINE (OVID)

1. exp clinical trial/ [publication type]
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8.or/1-7
9. exp animals/
10. exphumans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma open angle'
14. exp ocular hypertension'
15. (open adj2 angle ajd2 glaucoma$).tw.
16. (POAG or OHT).tw.
17. (increes$ pr elevat$ or high$).tw.
18. (ocular or intra-ocular;).tw.
19. pressure.tw.
20. 17 and 18 and 19
21. 13 or 14 or 15 or 16 or 20
22. exp adrenergic beta antagonist/
23. exp timolol/
24. timolol$.tw.
25. exp metipranolol/
26. metipranolol$.tw.
27. exp carteolol/
28. carteolol$.tw.
29. exp levobunolol/
30. levobunolol$.tw.
31. exp betaxolol/
32. betaxolol$.tw.
33. exp carbonic anhydrase inhibitors/
34. (carbonic adj2 anhydrase adj2 inhibitor$).tw.
35. exp Acetazolamide/
36. acetazolamide$.tw.
37. brinzolamide$.tw.
38. dorzolamide%.tw.
39. exp Prostaglandins, Synthetic/
40. latanoprost$.tw.
41. travoprost$.tw.
42. bimatoprost$.tw.
43. unoprostone$.tw.
44. brimonidine$.tw.
45. exp antihypertensive agents1
46. exp pilocarpine/

47. pilocarpine$.tw.
48. exp epinephrine/
49. epinephrine$.tw.
50. dipivefrin$.tw.
51. exp Adrenergic alpha-2 Receptor Agonists/
52. ((adrenergic adj2 alpha$ ajd2 receptor$) or (adrenergic adj2 alpha$ ajd2 agonist$)).tw.
53. aoraclonidin$.tw.
54. tafluprost.tw.
55. monoprost$.tw.
56. latanoprostene bunod.tw.
57. ((drugs$ or medic$ or pharmacologic$) adj3 (treat$ or therap$ or intervent$)).tw.
58. 22 or 23 or 24 or 25 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59. 21 and 58
60. 12 and 59
61. limit 60 to yr “2014- Current

Embase

1 exp randomization/
2 randomized controlled trial/
3 double blind procedure/
4 single blind procedure/
5 random*.ti,ab.
6 1 or 2 or 3 or 4 or 5
7 (animal or animal experiment).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8 human/
9 7 and 8
10 (#7 not #9).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
11 (#6 not #10).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
12 exp clinical trial/
13 (clin* adj3 trial*).ab,ti.
14 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ab,ti.
15 exp placebo/
16 placebo*.ab,ti.
17 random*.ti,ab.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/

21 exp latin square design/
22 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 (#22 not #10).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
24 (#23 not #11).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control* or prospectiv* or volunteer*).ab,ti.
29 25 or 26 or 27 or 28
30 (#29 not #10).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
31 (#30 not (#11 or #23)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
32 11 or 24 or 31
33 exp open angle glaucoma/
34 exp intraocular hypertension/
35 ((open adj2 angle) and (angle adj2 glaucoma*)).ab,ti.
36 (poag or oht).ab,ti.
37 (((increas* or elevat* or high*) adj3 (ocular or 'intra ocular')) and pressure).ab,ti.
38 33 or 34 or 35 or 36 or 37
39 exp beta adrenergic receptor blocking agent/
40 exp timolol/
41 timolol*.ab,ti.
42 exp metipranolol/
43 metipranolol*.ab,ti.
44 exp carteolol/
45 carteolol*.ab,ti.
46 exp levobunolol/
47 levobunolol*.ab,ti.
48 exp betaxolol/
49 betaxolol*.ab,ti.
50 exp carbonate dehydratase inhibitor/
51 ((carbonic adj2 anhydrase) and (anhydrase adj2 inhibitor*)).ab,ti.
52 exp acetazolamide/
53 acetazolamide*.ab,ti.
54 brinzolamide*.ab,ti.
55 dorzolamide*.ab,ti.

56 exp latanoprost/
57 latanoprost*.ab,ti.
58 exp travoprost/
59 travoprost*.ab,ti.
60 exp bimatoprost/
61 bimatoprost*.ab,ti.
62 exp unoprostone isopropyl ester/
63 unoprostone*.ab,ti.
64 exp tafluprost/
65 tafluprost*.ab,ti.
66 exp monoprost/
67 monoprost*.ab,ti.
68 exp latanoprostene bunod/
69 exp brimonidine/
70 brimonidine*.ab,ti.
71 exp antihypertensive agent/
72 exp pilocarpine/
73 pilocarpin*.ab,ti.
74 exp adrenalin/
75 epinephrin*.ab,ti.
76 dipivefrin*.ab,ti.
77 exp alpha 2 adrenergic receptor stimulating agent/
78 ((adrenergic adj2 alpha*) and (alpha* adj2 agonist*)).ab,ti.
79 apraclonidin*.ab,ti.
80 ((drug* or medic* or pharmacologic*) adj3 (treat* or therap* or intervent*)).ab,ti.
81 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80
82 38 and 81
83 32 and 82

Appendix B. Eligibility Form

Reviewer Name:	Date:
First author, journal, year of publication:	
Study included	Study excluded

For each identified study, answer the following questions:

1. What was the diagnosis of the patients included in the clinical study?
   - Primary open angle glaucoma (POAG) -> 60% of patients
   - Ocular hypertension (OH) -> 60% of patients
   - POAG and / or OH -> 60% of patients
   - Other (exclude)
2. What is the treatment of interest assessed in this clinical trial?
   - Prostaglandin analogue
   - Beta blocker
   - Carbonic anhydrase inhibitor
   - Agonist adrenergic alpha-2 receptors
   - Other (exclude)
3. Does the treatment of interest is administered alone?
   - Yes
   - No, in combination (exclude)
4. What is the comparator in this clinical trial?
   - Active treatment alone
   - Placebo / no treatment
   - Combination (exclude)
5. Other (exclude)What was the study design?
   - Randomized parallel group
   - Crossover allowed (exclude)
   - Other (exclude)
6. Does the study was able to aim for the reduction of intraocular pressure?
   - Yes
   - No (exclude)
7. What was the follow-up time?
   - At least 28 days after randomization
   - Least than 28 days after randomization (exclude)
8. How many patients were included in the clinical study?
   - Over 10
   - Less than 10 (exclude)

Appendix C. References of Included Studies

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Appendix D. Baseline Characteristics

Table 1. Characteristics of the Selected Studies

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
1	1983	Placebo & Betaxolol	Inc.	Inc.	NA	Exc.	NA	≥26 in both eyes	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	1	40	NR
2	1984	Betaxolol & Timolol	Inc.	NA	NA	NA	Inc.	elevated IOPs	NR	Exc.	NA	Exc.	Yes	Yes	Multi (2)	USA	6	46	Other
3	1985	Placebo & Levobunolol	Inc.	Inc.	NA	NA	NA	NR	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	3	17	NR
4	1985	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	≥23 in each eye?	≥18	Exc.	NA	Exc.	Yes	Yes	Can't tell	NR	15	92	NR
5	1985	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	≥23	NR	Exc.	NA	Exc.	Yes	Yes	Can't tell	NR	15	85	NR
6	1985	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	≥23 in each eye	NR	NA	NA	NA	Yes	Yes	Multi (NR)	NR	12	67	NR
7	1986	Betaxolol & Timolol	Inc.	NA	NA	NA	NA	≥26 in at least one eye	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	6	29	NR
8	1988	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	NR	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	12	72	NR
9	1988	Betaxolol & Timolol	Inc.	Inc.	NA	NA	NA	average measurement >25.5 and no measurement <22	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (3)	USA	6	28	Responders
10	1988	Betaxolol & Levobunolol	Inc.	Inc.	NA	NA	Inc.	≥22 in at least one eye?	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	3	73	NR
11	1988	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	≥21	NR	NA	NA	NA	Yes	Yes	Multi (2)	Canada	3	25	NR
12	1989	Placebo & Timolol	NA	Inc.	NA	NA	NA	≥22 and ≤28 in at least one eye	NR	Exc.	NA	Exc.	No	No	Single	USA	60	107	Intention-to-treat; Other
13		Placebo & Timolol										Exc.	Can't tell	No	Multi (2)	USA	61	124	NR
14	1991	Placebo & Timolol	NA	Inc.	NA	NA	NA	≥22	≥45 and ≤70	Exc.	NA	Exc.	Can't tell	No	Can't tell	NR	73	137	Intention-to-treat; Other
15	1991	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	exclude patients whose increased IOP was not controlled by a single drug therapy	NR	NA	NA	NA	Yes	Yes	Multi (NR)	NR	3	70	Other
16	1992	Levobunolol & Timolol	Can't tell	Inc.	NA	NA	Exc.	NR	NR	Exc.	Exc.	NA	Yes	Yes	Multi (7)	NR	2	128	NR
17	1992	Carteolol & Timolol	Inc.	NA	NA	NA	NA	>21	≥18 and ≤80	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	NR	12	144	Compilers or Adheres
18	1993	Timolol & Unoprostone	Inc.	Inc.	Exc.	Exc.	Exc.	≥22 and ≤35	NR	Exc.	NA	Exc.	Yes	Yes	Multi (18)	Japan	3	147	NR
19	1993	Apraclonidine & Timolol	Inc.	Inc.	NA	NA	NA	NR	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	NR	3	56	NR
20	1993	Placebo & Dorzolamide	Inc.	Inc.	NA	NA	NA	NR	NR	Exc.	NA	Exc.	Yes	Yes	Multi (3)	USA	1	42	Per protocol
21	1994	Carteolol & Levobunolol	Inc.	Inc.	NA	NA	Inc.	≥22	NR	NA	NA	NA	Yes	Yes	Multi (NR)	NR	3	52	NR
22	1994	Placebo & Levobunolol	NA	Inc.	NA	NA	NA	≥22 and ≤30	NR	NA	NA	NA	Can't tell	No	Can't tell	NR	24	46	NR
23	1995	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥22	≥40	Exc.	Exc.	Exc.	Yes	Yes	Multi (13)	Sweden & Denmark &	6	243	NR

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
																Finland & Norway			
24	1995	Placebo & Timolol	NA	Inc.	NA	NA	NA	≥21 and <35	NR	Exc.	Exc.	Exc.	Can't tell	No	Single	USA	24	74	NR
25	1995	Betaxolol & Timolol & Dorzolamide	Inc.	Inc.	NA	NA	NA	≥23	≥21 and ≤85	Exc.	NA	Exc.	Yes	Yes	Multi (34)	Costa Rica & Colombia & United States & Mexico & United Kingdom	12	516	Intention-to-treat; Per protocol
26	1996	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥22	>40	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	Sweden	6	20	NR
27	1996	Timolol & Latanoprost	Inc.	Inc.	NA	NA	NA	NR	NR	Exc.	Exc.	Exc.	No	Yes	Multi (35)	Japan	3	154	NR
28	1996	Brimonidine & Timolol	Inc.	Inc.	NA	NA	NA	post washout IOP ≥23 mmHg and <35 mmHg in each eye; Exc. IOP asymmetry of more than 5 mmHg	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	NR	12	647	Safety population or safety analysis
29	1996	Brimonidine & Betaxolol	Inc.	Inc.	NA	NA	NA	≥22 and ≤34, and difference between two eyes ≤5	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (13)	USA	3	177	Per protocol; Safety population or safety analysis
30	1996	Apraclonidine & Timolol	Inc.	Inc.	NA	NA	NA	≥22 and ≤35, and difference between two eyes ≤4	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (16)	USA	3	230	NR
31	1996	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥22	≥40	Exc.	Exc.	Exc.	Yes	Yes	Multi (14)	United Kingdom	6	255	NR
32	1996	Carteolol & Timolol	Inc.	Inc.	NA	NA	NA	NR	≥40 and ≤70	Exc.	NA	Exc.	Yes	No	Multi (3)	Japan	4	33	NR
33	1997	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	≤20 in both eyes and difference between two eyes ≤4, and IOP fluctuation between both eyes ≤2 at baseline and 6 weeks prior to the study	≥20 and ≤75	Exc.	Exc.	Exc.	Yes	No	Multi (24)	Japan	3	58	Intention-to-treat
34	1997	Carteolol & Timolol	Inc.	Inc.	NA	NA	Exc.	≥22 and ≤34, and difference between two eyes <5	≥18 and ≤85	Exc.	Exc.	NA	Yes	Yes	Multi (13)	USA	3	176	Intention-to-treat
35	1998	Timolol & Dorzolamide	Inc.	Inc.	NA	Exc.	NA	NR	≥21 and ≤85	Exc.	Exc.	Exc.	No	Yes	Multi (27)	USA	3	220	Per protocol; Other
36	1999	Timolol & Dorzolamide	Inc.	Inc.	NA	Exc.	NA	≥22 at 9AM and 11AM	≥21	Exc.	Exc.	Exc.	Yes	No	Multi (22)	USA	3	149	Per protocol; Safety population or safety

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
																			analysis; Other
37	1998	Timolol & Latanoprost	Inc.	NA	NA	Exc.	Inc.	≥25 with IOP reducing therapy or ≥30 without IOP reducing therapy	≥18	Exc.	Exc.	Exc.	Yes	No	Multi (13)	Germany	1	37	NR
38	1998	Brimonidine & Timolol	Inc.	Inc.	NA	NA	Exc.	≥23 and ≤35, and difference between two eyes ≤5	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	NR	12	418	Per protocol; Safety population or safety analysis
39	1998	Betaxolol & Dorzolamide	Inc.	Inc.	NA	Exc.	NA	≥23 in at least one eye?	≥21	Exc.	NA	Exc.	Yes	Yes	Multi (24)	USA	3	310	Per protocol; At least receiving one treatment
40	1998	Timolol & Brinzolamide & Dorzolamide	Inc.	Inc.	Exc.	Exc.	Inc.	NR	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (42)	USA & Germany & France & Belgium & Portugal & the Netherlands & Iceland	3	491	Intention-to-treat; Per protocol; Responders; At least receiving one treatment; Safety population or safety analysis
41	1999	Carteolol & Timolol	Inc.	Inc.	NA	NA	Exc.	NR	NR	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	USA	3	107	Intention-to-treat
42	1999	Placebo & Brimonidine	NA	Inc.	NA	NA	NA	≥20 and ≤40	NR	Exc.	Exc.	Exc.	Yes	No	Single	USA	1	56	NR
43	2000	Timolol & Latanoprost	Inc.	Inc.	NA	NA	Inc.	NR	>40	NA	NA	NA	Can't tell	No	Multi (13)	Sweden	6	243	NR
44	2000	Dorzolamide & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	NR	NR	Exc.	Exc.	Exc.	Yes	Yes	Multi (12)	NR	3	213	NR
45	2000	Placebo & Brinzolamide & Dorzolamide	Inc.	Inc.	Exc.	Exc.	Inc.	≥24 and ≤36 at 8AM and ≥ 21 and ≤ 36 mmHg at 10AM and 6PM	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (24)	USA	3	395	Intention-to-treat; Per protocol; Safety population or safety analysis
46	2001	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥21	NR	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	France	1	33	NR
47	2001	Brimonidine & Latanoprost	Inc.	Inc.	NA	NA	NA	≥22 and ≤34	≥18	Exc.	Exc.	Can't tell	Yes	Yes	Multi (5)	USA	3	125	Per protocol
48	2001	Latanoprost & Unoprostone	NA	Inc.	NA	NA	NA	≥21 and ≤29 in each eye	≥20 and ≤79	Exc.	Exc.	Exc.	No	No	Can't tell	NR	2	36	Safety population or safety analysis; Other
49	2001	Latanoprost & Unoprostone	Inc.	Inc.	NA	Exc.	NA	≥21	≥18	Exc.	Exc.	Exc.	Yes	Yes	Single	Brazil	2	105	Intention-to-treat; Per protocol

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
50	2002	Latanoprost & Unoprostone	Inc.	Inc.	NA	Exc.	Exc.	>21	≥21	Exc.	Exc.	Exc.	No	No	Multi (2)	Singapore	2	30	NR
51	2002	Placebo & Dorzolamide	Inc.	NA	NA	Inc.	NA	Exc. mean IOP of two eyes >30 or any IOP >35 in one eye	NR	Exc.	Exc.	Exc.	No	No	Single	Sweden	1	44	Intention-to-treat
52	2002	Timolol & Travoprost	Inc.	Inc.	NA	NA	Inc.	≥24 and ≤36	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (44)	USA	6	605	Intention-to-treat; Per protocol; Safety population or safety analysis
53	2002	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥25 with IOP reducing therapy or ≥30 without IOP reducing therapy	≥18	Exc.	Exc.	Exc.	Yes	No	Multi (38)	USA	12	280	Intention-to-treat; Safety population or safety analysis
54	2002	Latanoprost & Unoprostone	Inc.	Inc.	NA	Exc.	NA	≥21	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (24)	USA	2	164	Intention-to-treat; Safety population or safety analysis
55	2002	Brimonidine & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	NR	NR	Exc.	Exc.	Exc.	Yes	Yes	Multi (30)	Germany & United Kingdom & Spain & Finland	6	375	Intention-to-treat
56	2002	Betaxolol & Timolol & Unoprostone	Inc.	Inc.	NA	NA	Inc.	NR	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (27)	Europe & Israel	24	552	Intention-to-treat
57	2002	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥25 with IOP reducing therapy or ≥30 without IOP reducing therapy	≥18	Exc.	Exc.	Exc.	Yes	No	Multi (37)	NR	6	296	Intention-to-treat; At least receiving one treatment
58	2002	Brimonidine & Latanoprost	Inc.	Inc.	NA	NA	NA	≥18 and ≤34, and difference between two eyes ≤5	≥21	NA	NA	NA	Yes	No	Multi (14)	USA	3	74	NR
59	2002	Latanoprost & Unoprostone	Inc.	Inc.	NA	Exc.	NA	≥21 and ≤27, and difference between two eyes <2	≥18	Exc.	NA	Exc.	Yes	Yes	Single	USA	1	50	NR
60	2002	Latanoprost & Unoprostone	NA	NA	NA	NA	NA	≥21 and <30	NR	Exc.	NA	Exc.	Yes	Yes	Multi (10)	Japan	2	44	NR
61	2003	Timolol & Latanoprost	Inc.	Inc.	Can't tell	Can't tell	Can't tell	NR	NR	Can't tell	Can't tell	Can't tell	Yes	Yes	Multi (17)	USA	6	248	Intention-to-treat; Responders
62	2003	Latanoprost & Travoprost	Inc.	NA	Exc.	Exc.	Exc.	>20	≥40 and ≤60	NA	NA	NA	No	No	Single	Italy	6	18	NR
63	2003	Brimonidine & Latanoprost	Inc.	Inc.	NA	NA	NA	NR	NR	Exc.	Exc.	Exc.	Yes	Yes	Can't tell	NR	3	38	NR
64	2003	Placebo & Betaxolol	NA	Inc.	NA	NA	NA	≥22 and ≤35	>35	NA	NA	NA	Can't tell	No	Single	United Kingdom	37	356	Intention-to-treat
65	2003	Bimatoprost 0.03% &	Inc.	Inc.	NA	Exc.	Inc.	≥21	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (45)	USA	3	410	Intention-to-treat; Per

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
		Latanoprost & Travoprost																	protocol; Safety population or safety analysis
66	2004	Betaxolol & Latanoprost	Inc.	NA	NA	NA	NA	NR	NR	Exc.	NA	Exc.	No	No	Can't tell	NR	3	31	NR
67	2004	Placebo & Unoprostone	Inc.	NA	NA	NA	NA	NR	NR	NA	NA	NA	Yes	No	Single	NR	2	50	NR
68	2004	Timolol & Bimatoprost 0.03%	Inc.	Inc.	Exc.	Exc.	Exc.	<16 on timolol for 12 months	≥40 and ≤60	NA	NA	NA	Can't tell	No	Single	Italy	6	38	NR
69	2004	Timolol & Bimatoprost 0.03% & Latanoprost	Inc.	Inc.	NA	NA	NA	≥22 and ≤34, and difference between two eyes ≤5	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (7)	USA	1	112	Intention-to-treat; Modified intention[to[treat; Safety population or safety analysis
70	2004	Timolol & Brinzolamide	Inc.	NA	NA	Exc.	NA	≥20 and ≤30	NR	NA	NA	NA	Yes	Yes	Single	Taiwan	1	48	NR
71	2005	Timolol & Travoprost	Inc.	Inc.	Exc.	Exc.	Exc.	NR	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (33)	USA	3	176	Intention-to-treat
72	2005	Brimonidine & Latanoprost	Inc.	Inc.	NA	Exc.	NA	≥22	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (23)	USA	6	301	Intention-to-treat; Per protocol; Safety population or safety analysis
73	2005	Placebo & Dorzolamide	NA	Inc.	NA	NA	NA	≥22 and ≤29 in at least one eye?	≥30 and ≤80	Exc.	NA	Exc.	Yes	Yes	Multi (18)	Belgium & Germany & Italy & Portugal	61	976	Intention-to-treat; Safety population or safety analysis
74	2006	Betaxolol & Latanoprost	Inc.	NA	NA	NA	NA	NR	NR	Exc.	Exc.	Exc.	No	No	Can't tell	NR	3	40	NR
75	2007	Bimatoprost 0.03% & Latanoprost & Travoprost	Inc.	Inc.	NA	NA	NA	≥22 and ≤36	≥18	Exc.	Exc.	Exc.	No	No	Can't tell	NR	6	60	Other
76	2007	Timolol & Bimatoprost 0.03%	Inc.	Inc.	NA	NA	Inc.	≥24 and ≤34	>18	Exc.	Exc.	Exc.	Yes	Yes	Can't tell	Spain	6	60	NR
77	2008	Bimatoprost 0.03% & Travoprost	Inc.	NA	NA	NA	Inc.	≤36	≥18	Exc.	Exc.	Exc.	No	No	Single	Turkey	6	82	NR
78	2008	Timolol & Bimatoprost	Inc.	Inc.	NA	Inc.	NA	≥18 with IOP reducing medication or ≥24 for treatment naïve patients in at least one eye	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (59)	USA & Canada	3	528	Intention-to-treat
79	2008	Timolol & Brinzolamide	Inc.	Inc.	NA	Exc.	Inc.	≥18 at 8AM or ≥21 at 10AM and ≤36 in at least one eye	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (35)	USA	6	346	Intention-to-treat; Per protocol

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
80	2008	Brimonidine & Timolol & Travoprost	Inc.	NA	NA	NA	Exc.	>21	NR	NA	NA	NA	Yes	No	Single	Brazil	1	50	NR
81	2008	Timolol & Bimatoprost	Can't tell	Inc.	Can't tell	Can't tell	Can't tell	≥22 and ≤34	NR	NA	NA	NA	Yes	Yes	Multi (15)	USA	49	113	Intention-to-treat; Per protocol; At least receiving one treatment; Safety population or safety analysis
82	2008	Bimatoprost 0.03% & Latanoprost & Travoprost	Inc.	NA	NA	Exc.	NA	>22	≥18	Exc.	NA	Exc.	No	No	Can't tell	NR	2	48	NR
83	2009	Bimatoprost 0.03% & Latanoprost	Can't tell	Inc.	Can't tell	Can't tell	Can't tell	≥17 and ≤22 in each eye	≥18	Exc.	NA	Exc.	Yes	No	Multi (8)	Australia	6	208	Intention-to-treat; Safety population or safety analysis
84	2009	Betaxolol & Levobunolol & Timolol	Inc.	NA	Inc.	NA	NA	NR	≥40 and ≤80	Exc.	NA	Exc.	Yes	No	Single	India	3	62	NR
85	2010	Bimatoprost 0.03% & Latanoprost & Travoprost	Inc.	Inc.	NA	NA	Inc.	>23 and <36	NR	Exc.	Exc.	Exc.	Yes	Yes	Multi (9)	Canada	6	83	Per protocol
86	2010	Placebo & Bimatoprost 0.01%	NA	Inc.	NA	NA	NA	difference between two eyes ≤5	≥18	Exc.	Exc.	NA	Yes	No	Multi (15)	USA	1	218	Modified intention-to-treat
87	2010	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥26 and ≤36	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (58)	USA	3	265	Intention-to-treat; At least receiving one treatment; Eligible population; Safety population or safety analysis
88	2010	Bimatoprost 0.03% & Travoprost	Can't tell	Inc.	can't tell	can't tell	can't tell	inadequate IOP control after at least 30 days on latanoprost monotherapy, judged by the investigator	adults	Exc.	NA	Exc.	Yes	No	Multi (17)	NR	3	260	intention-to-treat
89	2010	Bimatoprost 0.03% & Travoprost	Inc.	Inc.	Exc.	Exc.	can't tell	≥21 and ≤35 in each eye	≥18	Exc.	NA	Exc.	Yes	Yes	Multi (NR)	Egypt	6	72	NR
90	2010	Latanoprost & Tafluprost	Inc.	Inc.	NA	NA	Inc.	≥22 and ≤34 in at least one eye	≥18	Exc.	NA	Exc.	Yes	Yes	Multi (3)	Italy & Finland	1	36	Intention-to-treat; At least receiving one

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
																			treatment; Safety population or safety analysis
91	2012	Timolol & Tafluprost	Inc.	Inc.	NA	NA	Inc.	≥23 and ≤36, and difference between two eyes < 5	≥18	Exc.	NA	Exc.	Yes	Yes	Multi (50)	USA & Spain & Switzerland	3	610	Per protocol; At least receiving one treatment
92	2013	Bimatoprost 0.01% & Travoprost	Inc.	Inc.	NA	NA	NA	NR	≥18	Exc.	NA	Exc.	Yes	Yes	Multi (15)	Canada & United States	3	109	Intention-to-treat; Per protocol; Safety population or safety analysis
93	2013	Timolol & Latanoprost	Inc.	Inc.	Exc.	Exc.	Exc.	≤18	≥18 and ≤90	NA	NA	NA	Yes	No	Multi (45)	France	3	143	Per protocol; other
94	2013	Brimonidine & Brinzolamide	NA	Inc.	Exc.	Exc.	Exc.	≥24 and ≤36at 8AM, or≥21 AND ≤36 in both eyes at all time points	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (66)	USA	3	405	Intention-to-treat; Safety population or safety analysis
95	2013	Brimonidine & Brinzolamide	Inc.	Inc.	NA	Exc.	NA	≥24 and ≤36at 8AM, or≥21 AND ≤36 in both eyes at all time points	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (65)	USA	6	419	Intention-to-treat safety population or safety analysis
96	2014	Timolol & Bimatoprost 0.03% & Latanoprost & Levobetaxolol	Inc.	NA	Exc.	Exc.	Exc.	IOP≥ 21 mm Hg for 1 or 2 eyes	≥ 18	Exc.	Exc.	Exc.	No	No	Single	NR	3	140	comparaison
97	2015	Latanoprost & Tafluprost	Inc.	Inc.	Inc.	Exc.	Exc.	NR	≥ 18	Exc.	Exc.	Exc.	No	No	NR	Italie	12	67	Post-hoc
98	2015	Placebo & Latanoprost	Inc.	NA	Exc.	Exc.	Exc.	IOP ≥ 30 mmHg Exc.	≥ 20	Exc.	Exc.	Exc.	Yes	No	Multi (10)	UK	24	461	comparaison
99	2015	Latanoprost & Latanoprostene bunod	Inc.	Inc.	Exc.	Exc.	Exc.	IOP of 22-32 mmHg, IOP of ≥24 mmHg for at least 2 of the 3-time points during the visit 3	≥ 18	NA	NA	NA	No	yes	Multi (23)	USA & European Union	1	165	comparaison
100	2016	Timolol & Tafluprost	Inc.	Inc.	Exc.	Exc.	Exc.	IOP ≥24 and ≤36 mm Hg at least one eye at 8 h, and be < 5 mmHg difference in mean (or median) IOP between the eyes at all the hour time points.	18-80	Exc.	Exc.	Exc.	Yes	Yes	Multi	India	2,5	167	Non-inferiority

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
101	2016	Timolol & Latanoprostene bunod	Inc.	Inc.	Exc.	Exc.	Exc.	IOP≥ 26 mm Hg at a minimum of 3 h (8 AM, 12 PM, and 4 PM), ≥ 24 mm Hg at a minimum of 1-time point, and ≥ 22 mm Hg at 1 time point, IOP ≤36 mm Hg at all times point in both eyes	≥ 18	Exc.	Exc.	Exc.	No	yes	Multi (46)	USA & European Union	3	387	Non-inferiority
102	2016	Timolol & Latanoprost	Inc.	NA	Exc.	Exc.	Exc.	IOP≥ 21 mm Hg in each eye	≥ 40	Exc.	Exc.	Exc.	No	yes	Single	India	3	110	Superiority
103	2016	Timolol & Latanoprostene bunod	Inc.	Inc.	Exc.	Exc.	Exc.	IOP ≥ 26 mmHg at a minimum of 1-time point, ≥ 24 mmHg at least 1 time point, ≥ 22 mmHg at 1 point in the same eye, IOP ≤ 36 mmHg in both eyes baseline	≥ 18	Exc.	Exc.	Exc.	No	yes	Multi	USA & Europe	3	413	Non-inferiority
104	2018	Bimatoprost 0.01% & Latanoprost & Travoprost & Levobetaxolol	Inc.	NA	Exc.	Exc.	Exc.	IOP ≥ 20 mmHg after 1 month of treatment: Exc.	≥ 18	Exc.	Exc.	Exc.	No	No	Single	Lebanon	6	32	comparison
105	2019	Bimatoprost 0.01% & Latanoprost	Inc.	Exc.	Exc.	Exc.	Exc.	IOP > 20 mmHg at 8 am	≥ 18	Exc.	NA	Exc.	No	No	Single	Pakistan	1	240	Comparison
106	2019	Brimonidine & Timolol	Inc.	Exc.	Exc.	Exc.	Exc.	Treated with IOP <21 mmHg in both eyes	≥ 20	Exc.	Exc.	Exc.	Yes	No	Single	Japan	24	56	Comparison

* Information taken directly from Li *et al.* (2016) publication for years before 2014 (all reference numbers except 105-106)
Ref.: Reference
Exc.: Excluded
Inc.: Included
NA: Not applicable
NR: Not reported
IOP: Intraocular pressure

Appendix D. Baseline Characteristics

Table 2. Characteristics of Included Studies per Treatment Arm

Characteristics (mean* (range))	Placebo	Bimatoprost 0.01%	Bimatoprost 0.03%	Latanoprost	Latanoprostene Bunod	Tafluprost	Unoprostone
Age (years)	63.7 (53.6, 74.0) [3]	52.1 (30.4, 65.1) [5]	61.1 (48.3, 69.0) [4]	62.0 (32.0, 69.0) [4]	64.3 (60.8, 65.0) [5]	62.3 (56.7, 68.5) [4]	62.7 (54.0, 64.2) [4]
% Female	48.5 (34.0, 75.0) [3]	60.1 (50.0, 64.3) [5]	54.9 (35.0, 65.8) [4]	52.7 (14.3, 84.2) [4]	59.7 (58.3, 68.7) [5]	51.7 (0.4, 0.7) [5]	51.3 (48.1, 63.2) [4]
Baseline IOP	23.3 (18.0, 28.7) [5]	21.0 (16.8, 26.1) [5]	23.2 (17.0, 27.2) [5]	23.8 (15.8, 28.3) [5]	26.6 (26.0, 26.7) [5]	24.5 (18.5, 26.7) [5]	23.9 (19.1, 25.7) [5]

Characteristics (mean (range))	Apraclonidine	Betaxolol	Brimonidine	Brinzolamide	Carteolol	Dorzolamide	Levobunolol
Age (years)	59.9 (59.8, 60.5) [5]	63.0 (49.6, 66.5) [4]	63.3 (53.6, 67.4) [5]	63.1 (42.4, 65.0) [3]	60.2 (54.2, 70.3) [5]	63.5 (61.3, 72.0) [3]	60.8 (55.9, 65.8) [4]
% Female	56.8 (54.5, 57.2) [5]	48.9 (39.0, 65.0) [4]	55.0 (46.2, 75.0) [5]	56.1 (40.0, 57.6) [5]	63.5 (33.3, 100.0) [5]	53.7 (42.0, 56.9) [3]	53.8 (40.0, 62.9) [4]
Baseline IOP	25.5 (25.5, 25.7) [5]	25.7 (23.1, 31.2) [5]	24.4 (12.7, 25.8) [5]	25.9 (24.7, 27.1) [5]	24.2 (20.8, 25.2) [5]	25.3 (22.5, 28.1) [5]	25.7 (18.3, 33.5) [5]

Characteristics (mean (range))	Timolol	Travoprost
Age (years)	62.0 (41.9, 70.5) [4]	62.3 (46.1, 65.9) [5]
% Female	53.3 (23.4, 100.0) [4]	51.3 (44.4, 78.9) [5]
Baseline IOP	25.1 (12.9, 33.8) [5]	24.9 (16.4, 29.6) [5]

* Weighted average of the mean by number of patients.

[1] Characteristics reported in < 25% of n (arm specific)
[2] Characteristics reported in 25%-50% of n related to this treatment arm
[3] Characteristics reported in 50%-75% of n related to this treatment arm
[4] Characteristics reported in 75%-100% of n related to this treatment arm
[5] Characteristics reported in 100 % of n related to this treatment arm

Appendix E. Risk of Bias Table

Information were taken directly from *Li et al.* (2016) publication, except references number 105-106

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
1	NR	NR	NR/CT	NR/CT	Yes	Yes	No
2	Randomly numbered with a unique code by a third party	Each patient, in sequence, was assigned a study number corresponding to a test drug... The code was broken at the end of the study.	Yes	Yes	No	NR	No
3	NR	NR	NR/CT	NR/CT	Yes	Yes	Yes
4	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
5	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
6	NR	NR	NR/CT	NR/CT	Yes	NR	No
7	NR	NR	Yes	NR/CT	Yes	Yes	Yes
8	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
9	NR	Patients were then randomly assigned in a double-masked fashion to one of two	NR/CT	NR/CT	Yes	Yes	No
10	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
11	NR	NR	Yes	Yes	No	NR	No
12	The treatment assignment was done in stratified groups based on the patient's baseline IOP and the number of eyes which were entered in the study.	The randomization list was kept by the research secretary, and the examining physician did not know to which group a newly recruited patient would be assigned	No	Yes	No	Yes	No
13	NR	NR	NR/CT	NR/CT	Yes	Yes	No
14	NR	NR	No	NR/CT	No	Yes	No
15	NR	NR	Yes	NR/CT	Yes	NR	No
16	NR	NR	Yes	NR/CT	No	NR	Yes
17	Participating patients were distributed randomly, i.e. each new patient entering the study received the next-numbered, masked bottle.		NR/CT	NR/CT	Yes	Yes	No
18	The containers were confirmed as indistinguishable, and allotted in a randomized manner by the controller. The key code table was retained by the controller.		Yes	NR/CT	Yes	NR	No
19	NR	NR	Yes	NR/CT	Yes	Yes	Yes
20	NR	NR	NR/CT	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
21	NR	NR	NR/CT	NR/CT	Yes	Yes	Yes
22	NR	NR	NR/CT	NR/CT	No	NR	No
23	The patients were allocated to treatment	NR	Yes	NR/CT	Yes	Yes	Yes

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	groups according to a computer generated scheme prepared by Pharmacia.						
24	Subjects were then places on either placebo or timolol drops in both eyes twice a day in a double masked manner using randomized number tables.	NR	Yes	Yes	No	Yes	Yes
25	NR	NR	Yes	NR/CT	Yes	Yes	Yes
26	NR	NR	NR/CT	NR/CT	Yes	Yes	No
27	NR	NR	Yes	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
28	NR	NR	Yes	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
29	NR	NR	NR/CT	NR/CT	Yes	NR	No
30	NR	NR	Yes	NR/CT	Yes	Yes	Reported none of the authors has any financial relationship
31	The patients were allocated to different treatment groups according to a pregenerated randomization list.	NR	NR/CT	NR/CT	Yes	Yes	Yes
32	Envelope method		NR/CT	NR/CT	No	NR	Reported none of the authors has any financial relationship
33	NR	NR	NR/CT	NR/CT	Yes	NR	No
34	NR	NR	NR/CT	NR/CT	Yes	Yes	No
35	Patients with an IOP of greater than or equal to 24 mm Hg in at least one eye (the same eye) at hours 0 and 2 were then randomly assigned, according to a computer-generated allocation schedule.	NR	Yes	NR/CT	Yes	NR	Yes

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
36	Patients randomly (according to a computer-generated allocation schedule) received one of the following masked treatment regimens for 3 months	All study medication was packaged in identical bottles by allocation number	Yes	NR/CT	Yes	Yes	Yes
37	The patients were allocated to the treatment groups according to a computer-generated list prepared by Pharmacia & Upjohn (Uppsala, Sweden)	NR	NR/CT	NR/CT	Yes	Yes	Yes
38	Randomization schedules were generated for each site using SAS (Version 6.08; SAS Institute, Cary, NC) procedure, PROC PLAN.	Patients were assigned sequentially to masked treatment according to a randomization schedule generated by the study sponsor (Allergan Inc). Each bottle of test medication was coded with a shipment number and labeled with a study number. Each time a bottle was dispensed to a patient, the tearoff portion of the label was attached to the patient's case-report form.	Yes	Yes	No	Yes	Reported none of the authors has any financial relationship
39	NR	NR	Yes	NR/CT	Yes	Yes	Yes
40	Computer-generated randomization code	All clinical supplies were labeled based on a computer-generated randomization code and dispensed in numerical sequence to patients at each investigational site.	Yes	NR/CT	Yes	Yes	Yes
41	NR	NR	NR/CT	NR/CT	Yes	Yes	No
42	NR	NR	NR/CT	NR/CT	Yes	NR	No
43	NR	NR	No	No	Yes	Yes	No
44	NR	NR	No	No	No	Yes	No
45	NR	NR	Yes	NR/CT	Yes	Yes	No
46	The randomization was stratified for centre and performed in blocks of six consecutive patients within each centre.	NR	NR/CT	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
47	NR	NR	Yes	NR/CT	Yes	Yes	Reported none of the authors has

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
							any financial relationship
48	Patients were randomized using computer-generated numbers (0= receive latanoprost in the right eye and unoproste in the left eye, 1= receive unoprostone in the right eye and latanoprost in the left eye).	NR	No	Yes	No	NR	No
49	Patients were dispensed study medication that was packaged in identical bottles according to a computer-generated randomization list provided by Pharmacia & Upjohn, Sweden.	Patients were dispensed study medication that was packaged in identical bottles according to a computer-generated randomization list provided by Pharmacia & Upjohn, Sweden. Disclosure envelopes were kept in a locked cabinet at the study site. In the event of an emergency requiring identification of the masked treatment, the envelope could be opened. No enveloped were opened during the trial.	Yes	NR/CT	Yes	Yes	No
50	On the baseline day, the patients were randomized (by block randomisation) to two parallel study groups.	NR	No	Yes	No	No	Yes
51	The method used for preparing the allocation schedule was based on blocked randomization in blocks of eight allocation numbers.	The method used for preparing the allocation schedule was based on blocked randomization, in blocks of eight allocation numbers. During the study the assignment codes were kept in sealed envelopes in a locked space at the study location, and were delivered with unbroken seals on completion of trial.	Yes	Yes	No	Yes	No
52	Patients who met all study eligibility criteria were assigned a patient number	Medication description was concealed from the patient, investigator, and	Yes	Yes	No	Yes	Reported none of the authors has

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	and sequentially randomly assigned to one in an equal (1:1:1) ratio by means of a computer generated randomization schedule prepared by the Alcon Biostatistics Department. Randomization was stratified by site to ensure balanced treatment within each site.	clinical study staff. Masked medication was packaged in identical Drop-Tainers and provided to the investigators along with sealed envelopes containing the medication description for each patient.					any financial relationship
53	Patients were allocated to 1 of 3 treatment groups according to a computer-generated randomization code list. A single block randomization list was generated for the entire study.	Drug was issued according to patient numbers that were given in consecutive order at baseline. Medications were provided in identical coded bottles. Study medication was shipped to the individual study sites in sets such that each set was a multiple of the block size used in generating the randomization.	NR/CT	NR/CT	Yes	Yes	No
54	Randomization codes were generated and medical supplies were prepared by Pharmacia clinical Supply Logistics (Kalamazoo, Michigan, USA).	Each center received prepackaged clinical supplies with patients numbers, which were allocated sequentially.	No	NR/CT	No	Yes	Yes
55	NR	NR	NR/CT	NR/CT	Yes	Yes	No
56	Computer-generated randomization schedule	Medication identity was concealed in individually sealed envelopes stored at the study sites.	Yes	NR/CT	Yes	Yes	No
57	NR	NR	Yes	NR/CT	Yes	Yes	Reported none of the authors has any financial relationship
58	The randomization code was maintained at the central coordination center.	NR	Yes	NR/CT	Yes	Yes	No
59	NR	NR	No	NR/CT	Yes	Yes	Yes
60	The central Registration System controller randomly allocated patients into these two groups by assigning patients into blocks in sequence of registration to the center, which was determined by the investigators. Each block consisted of six patients for a set of treatments		NR/CT	NR/CT	NR/CT	NR	No

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	(three latanoprost, three unoprostone) where the order of treatments within the block had been randomized.						
61	NR	NR	NR/CT	NR/CT	Yes	Yes	Yes
62	NR	NR	Yes	Yes	Yes	Yes	No
63	NR	NR	No	No	No	NR	Reported none of the authors has any financial relationship
64	The chief pharmacist at Moorfields Eye Hospital, who had no other direct involvement with the trial, randomised one of the patients in each pair to treatment with either betaxolol drops or placebo drops. The fellow member of the pair was then allocated to the alternative treatment arm. Randomisation was carried out by means of randomisation tables.	Each patient was assigned drops coded either A, B, C or D that corresponded to their trial number.	Yes	Yes	No	Yes	Reported none of the authors has any financial relationship
65	NR	NR	No	Yes	No	Yes	No
66	NR	NR	No	Yes	Yes	NR	No
67	NR	NR	NR/CT	NR/CT	No	NR	No
68	At the baseline visit (day 0), eligible patients were randomly assigned, using a computer-generated randomization code list, to 1 of 2 treatment groups.	NR	No	No	No	NR	No
69	The randomization schedule was generated using a SAS (version 6.12) program and stored in a locked cabinet until the study was completed.		No	No	Yes	Yes	Yes
70	A computer-generated list of random assignments decided which treatment patients would receive.	The list was sealed and could be opened only after the completion of the study protocol or after any serious adverse event occurred.	NR/CT	NR/CT	Yes	NR	No
71	Computer-generated	Assign patient numbers sequetially; opaque syndiotactic polypropylene oval bottles.	Yes	NR/CT	Yes	Yes	No
72	Randomization was performed by centralized allocation by Voice Processing plus, inc., via an interactive phone registration system.		NR/CT	Yes	No	Yes	Yes
73	Randomization was obtained at the	Bottles of drug and placebo were given to	Yes	Yes	No	Yes	No

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	Coordinating Center. Each clinical center had its own randomization list that was stratified for pseudoexfoliation, pigmentary dispersion syndrome, and diabetes mellitus.	each center according to the randomization list. Patients were given a bottle marked with a code label. The allocation code was secured at the Coordinating Center at the office of the Project Coordinator.					
74	NR	NR	NR/CT	NR/CT	Yes	NR	No
75	NR	NR	NR/CT	Yes	Yes	NR	No
76	NR	NR	NR/CT	Yes	No	No	Reported none of the authors has any financial relationship
77	Randomization was achieved by asking the participants to choose any numbers between 1 to 10; even and odd numbers were assigned to bimatoprost (n=41) and travoprost (n=49) groups respectively.	NR	NR/CT	Yes	No	NR	No
78	Patients were randomized in a ratio of 2:1:1 to the FC (q.d., mornings), BIM 0.03% (q.d., evenings), or TIM 0.5% (b.i.d.) using a computer-generated randomization llist (PROC PLAN, SAS Version 8.2, Cary, NC).	NR	NR/CT	NR/CT	Yes	Yes	Yes
79	NR	White plastic dropper bottles, each labeled with a unique patient number.	Yes	NR/CT	Yes	Yes	Yes
80	NR	NR	Yes	NR/CT	Yes	Yes	Yes
81	A list of random numbers	Standard containers were used and they were concealed with a study specific cover and all kept in a standard opaque black medicine vial	Yes	NR/CT	Yes	NR	No
82	Randomization lists were used to preallocate treatment kits to each patient number by personnel not involved with the management of the study.		No	No	No	Yes	No
83	Allocation was based on computer-generated random numbers and was concealed by using sequentially numbered opaque sealed envelopes.		NR/CT	NR/CT	No	NR	Reported none of the authors has

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
							any financial relationship
84	Fifty opaque envelopes containing random numbers (drugs in code forms), generated with the help of table of randomization, were prepared in advance by an investigator who was not related to the study. Whenever, a study participant was found to be eligible, an envelope was opened by another person in the department and the patient was put on the allocation plan as found inside the envelope in coded form.		Yes	No	No	NR	No
85	A randomization schedule, balanced for ethnicity and drug assignment, was produced for each participating site by the biostatistician.	NR	No	Yes	No	No	No
86	The randomization sequence was computer-generated.	The randomization code was retained by the study sponsor and made available to the investigators only after the study had ended.	Yes	No	Yes	Yes	Yes
87	Randomization codes were generated by Pfizer according to standard operating procedures and were kept at Global Pharmacy Operations (New York, New York).	NR	NR/CT	Yes	No	Yes	Yes
88	The randomisation code was computed-generated	NR	No	NR/CT	Yes	Yes	Yes
89	NR	NR	NR/CT	NR/CT	No	No	Reported none of the authors has any financial relationship
90	Patients were randomized using Proc Plan, SAS for Windows (version 8.; SAS Institute Inc., Cary, NC)	NR	Yes	NR/CT	Yes	Yes	Yes
91	Patients were assigned to treatment using a computer generated randomized allocation schedule prepared by a statistician at Merck	Personnel at each study site used an interactive voice response system to determine which masked treatment containers should be given to which patient.	Yes	Yes	No	Yes	Yes
92	NR	NR	No	NR/CT	Yes	Yes	Yes
93	NR	NR	No	No	No	NR	Yes
94	A list of sequential patient numbers was generated	A list of sequential patient numbers was generated	Yes	NR/CT	No	Yes	Yes

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	by a member of the sponsor programming group (SAS Institute) not involved in the conduct of the study.	by a member of the sponsor programming group (SAS Institute) not involved in the conduct of the study. Study medications were provided in identical bottles. Staff members who provided the study medications to patients did not discuss those medications with other site personnel.					
95	NR	NR	Yes	NR/CT	Yes	Yes	Yes
96	Computer-generated random table numbers with an equal allocation of 35 patients into each study group	NR	Yes	Yes	Yes	NR	No
97	List of random numbers	NR	NR	Yes	No	Yes	Yes
98	Randomly allocated participants (1:1) in permuted blocks of varying sizes (block sizes range from 4 to 10), stratified by participating center, to either latanoprost 0·005% or latanoprost vehicle eye drops (placebo) alone once a day in both eyes.	The randomisation schedule, drawn up by the research and development statisticians at Moorfields Eye Hospital on a randomisation website, was sent to the Pharmaceutical Manufacturing Unit, which labelled the bottles with the participant study identification number only.	Yes	Yes	Yes	Yes	Yes
99	NR	Because the active control bottle (Xalatan) was visibly different than the investigational bottles, a designee at each study site, other than the investigator, was responsible for the dispensing study treat-ment at Visit 3, instructing patients on proper installation of study medication, and retrieval of materials at the end of the study. Attempts were made to mask the subjects by removing commercial labelling, replacing with	No	No	Yes	Yes	Yes

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
		identical investigational labels and packaging in identical kit boxes.					
100	Computer-generated	Subjects received masked kits for 2 weeks of study medication via an interactive voice response system using a computer-generated random allocation schedule.	Yes	NR/CT	Yes	Yes	No
101	Computer-generated	A statistician created a randomization schedule prior to any study enrolment not otherwise involved in the study using SAS (SAS Institute, Cary, North Carolina, USA; Version 9.2). Allocation of study drug was completed through the use of IRT (Interactive Response Technology), which determined which kit to assign to each subject. Adults with OAG or OHT from 46 clinical sites (United States and European Union) were randomized 2:1 to LBN instilled once daily (QD) in the evening and vehicle in the morning or timolol instilled twice a day (BID) for 3 months.	Yes	Yes	Yes	Yes	Yes
102	Enrolled patients were randomly divided into two groups by block randomization	NR	No	No	No	NR	No
103	Study drug was dispensed via an Interactive Response Technology system. Randomization schedules were created by a designated unmasked statistician using SAS Version 9.2 (SAS Institute, Inc., Cary, NC).	For masking purposes, each treatment was labeled with identical investigational labels and packaged in identical kit boxes. Eligible subjects were randomized 2:1 to receive LBN 0.024% qPM and vehicle every morning or timolol 0.5% BID for 3 months.	Yes	NR/CT	Yes	Yes	No
104	Included patients were randomly assigned to	NR	No	No	No	NR	No

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	receive one of the four PGAs: bimatoprost 0.01% (with BAK 0.02%), latanoprost 0.005% (with BAK 0.02%), travoprost 0.004% (with 0.001% polyquad), and tafluprost 0.0015% (preservative-free).						
105	Randomized in permuted blocks of size 2 by the study drug coordinator at a ratio of 1:1. Managed and retained independently until study completion.	No	No	No	No	Yes	No
106	Lottery method	NR	No	No	No	No	No

Appendix F. Mean difference (MD) in Intraocular Pressure at 3 months (95% Credible Interval [95% CrI]).

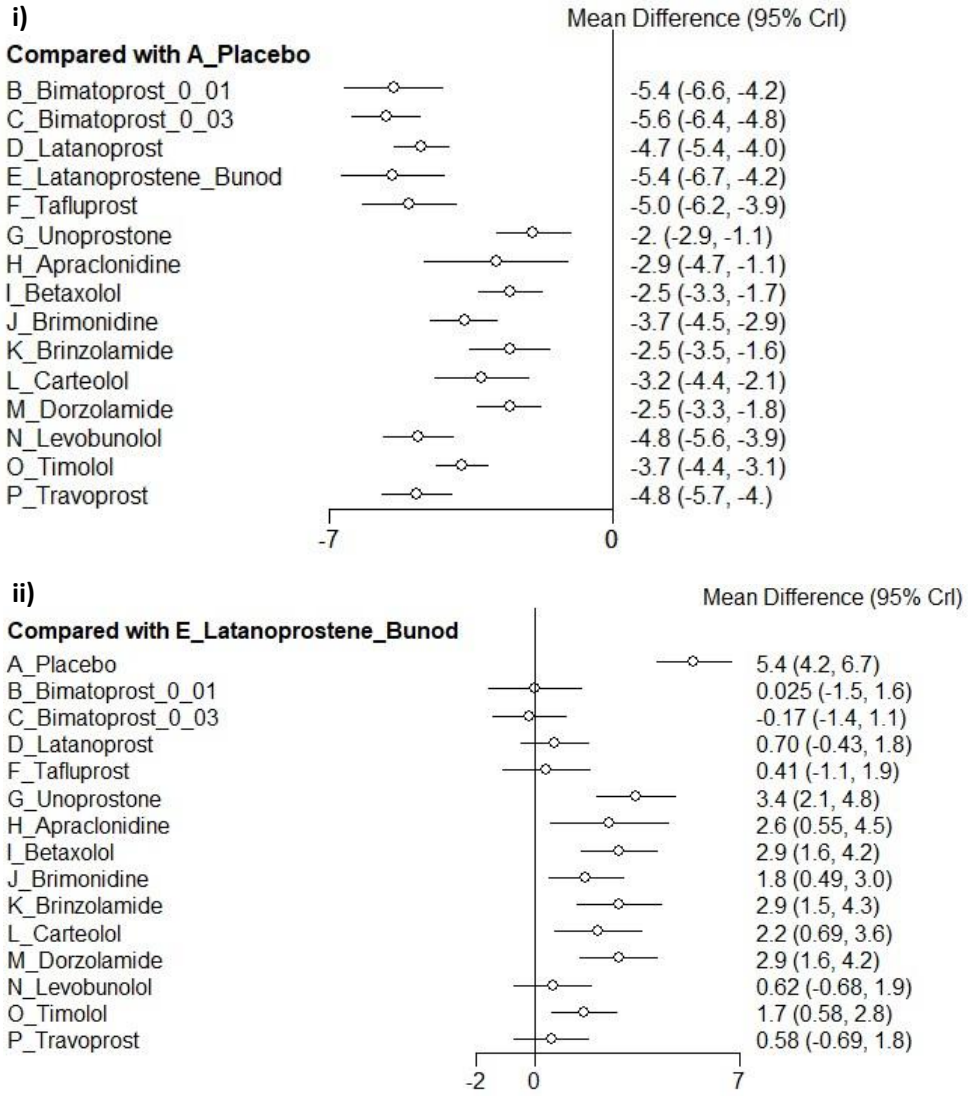
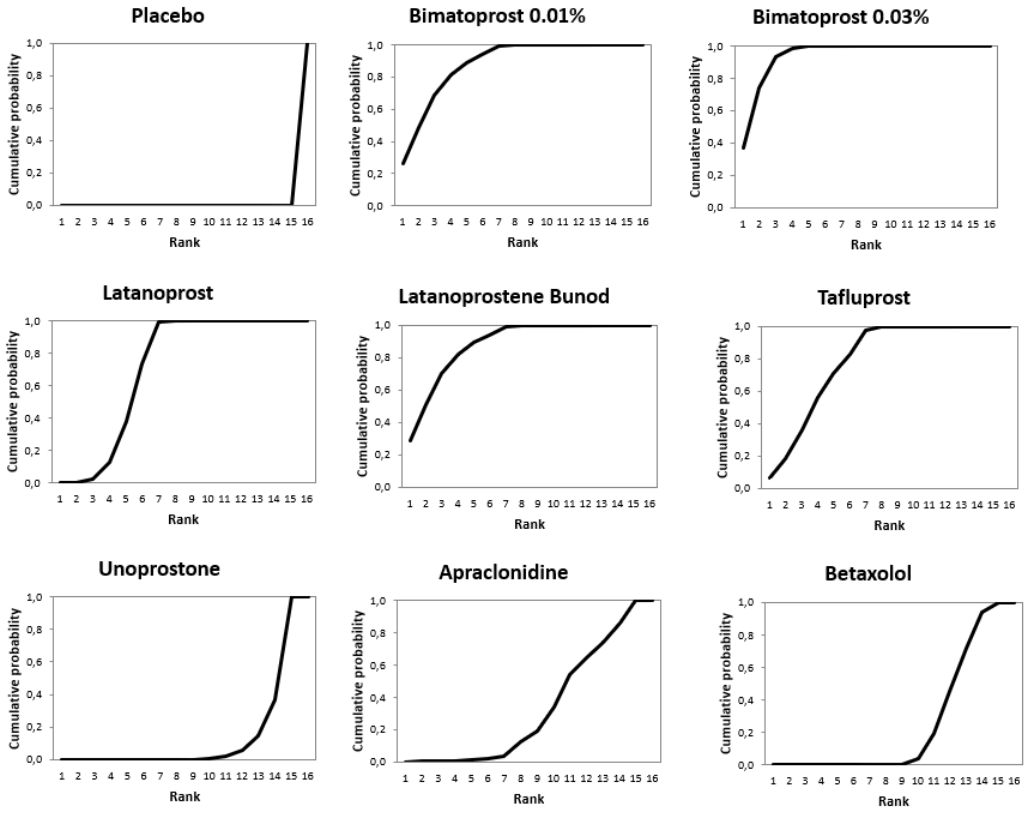


Figure 1. MD with a 95% CrI including 0 (crossing 0 in the forest plot) are not significant. PGAs = B, C, D, E, F and G
i) All treatments compared to placebo, MD > 0 favors placebo. ii) All treatments compared to LBN, MD > 0 favors placebo.

Appendix G. Cumulative Ranking Probabilities Plot

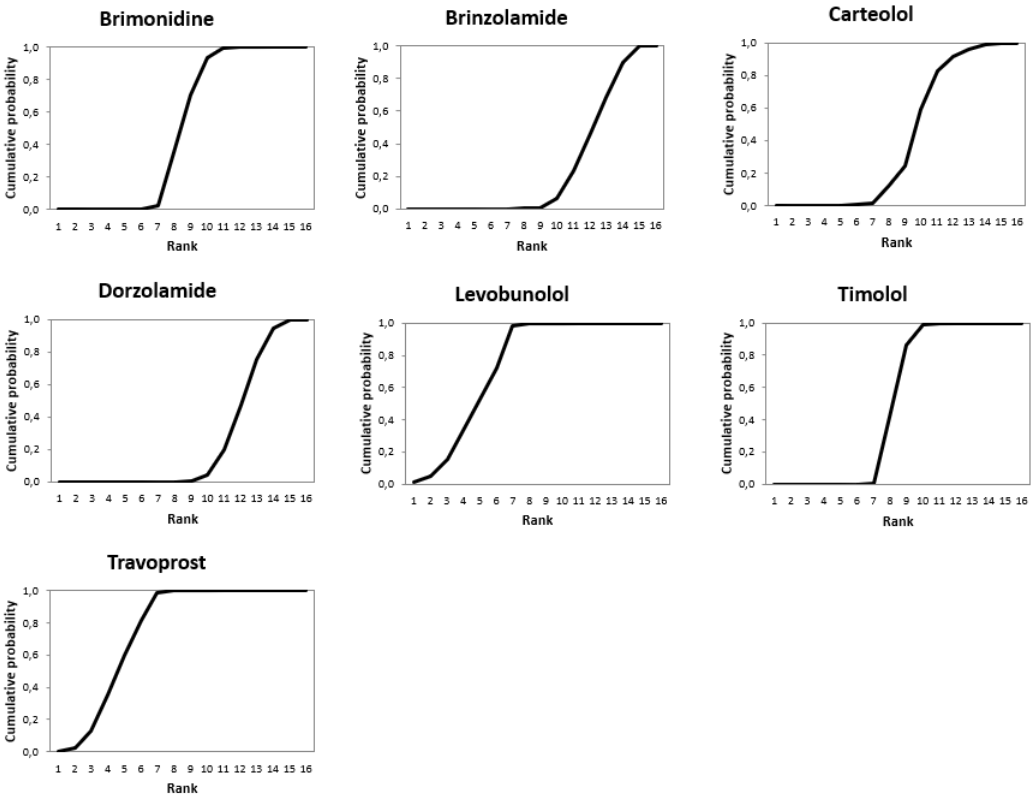
The surface under the cumulative ranking (SUCRA) probabilities for each treatment represents the average proportion of treatments worse than this treatment. Higher is the SUCRA (bigger surface under the cumulative ranking curve), better is the rank of this treatment.



SUCRA:

Placebo	0.0%
Bimatoprost 0.01%	87.2%
Bimatoprost 0.03%	93.5%
Latanoprost	68.4%
Latanoprostene Bunod	87.6%
Tafluprost	77.9%
Unoprostone	10.6%
Apraclonidine	30.1%
Betaxolol	22.2%

PGA



SUCRA:

Brimonidine	46.7%
Brinzolamide	22.3%
Carteolol	37.8%
Dorzolamide	22.7%
Levobunolol	71.8%
Timolol	48.5%
Travoprost	72.7%

PGA

Appendix H. Studies Identified as Possibly Causing Heterogeneity

As mentioned in the Cochrane Handbook[1], although a random effect model was used for the NMA, which assumes heterogeneity between studies, this does not mean that the problem of heterogeneity is eliminated. To quantify inconsistency across studies, the parameter "I^2" has been developed. I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Cochrane Handbook developed a rough guide for interpretation of I^2: less than 40% might not be important, 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity and 75% to 100% represented considerable heterogeneity.

All comparisons with I^2 higher than 65% were investigated. Based on Cochrane Handbook for a systematic review of intervention, "*If results of smaller studies are systematically different from results of larger ones, which can happen as a result of publication bias or within-study bias in smaller studies, then a random-effect meta-analysis will exacerbate the effects of the bias. In this situation, it may be wise to perform a sensitivity analysis in which small studies are excluded*." Therefore, if the investigation did not find any reason for the heterogeneity and smaller trials differed from larger ones, I^2 was tested without trials with the smallest cohort.

Comparison with I^2 higher than 65%	Reference* number of studies identified as possibly causing heterogeneity and explications	I^2 with all studies	I^2 without studies identified
Placebo vs. dorzolamide	Study 73: Baseline criteria for the IOP were stricter compared to other studies	76%	0%
Bimatoprost 0.01% vs travoprost	Study 104 (small cohorts compared to the other)	80%	NA
Bimatoprost 0.03% vs travoprost	Study 82: small cohort compared to others and MR completely different from the others	86%	29%
Latanoprost vs. travoprost	Study 82: small cohort compared to others and MR completely different from the others	87%	0%
Apraclonidine vs. timolol	Study 19: small cohort compared to the other	89%	NA
Betaxolol vs. levobunolol	Study 84: small cohort compared to the other + MR and SD very big comparatively to other trials	84%	NA
Betaxolol vs. timolol	Study 84: small cohort compared to the other + MR and SD very big comparatively to other trials	67%	0%
Brimonidine vs. latanoprost	Studies 47; 58; 63: small cohort compared to others	78%	16%
Timolol vs. latanoprost	Studies 26; 37; 46; 69; 96; 102: small cohort compared to others	76%	45%
Timolol vs. unoprostone	Study 18: small cohort compared to the other	87%	NA

MR: Mean reduction of IOP after 3 months
SD: Standard deviation of the MR
* See Reference in **Appendix B**.

[1] The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. http://handbook-5-1.cochrane.org/. Published 2011. Accessed August 5, 2018.

Appendix I. Sensitivity Analyses

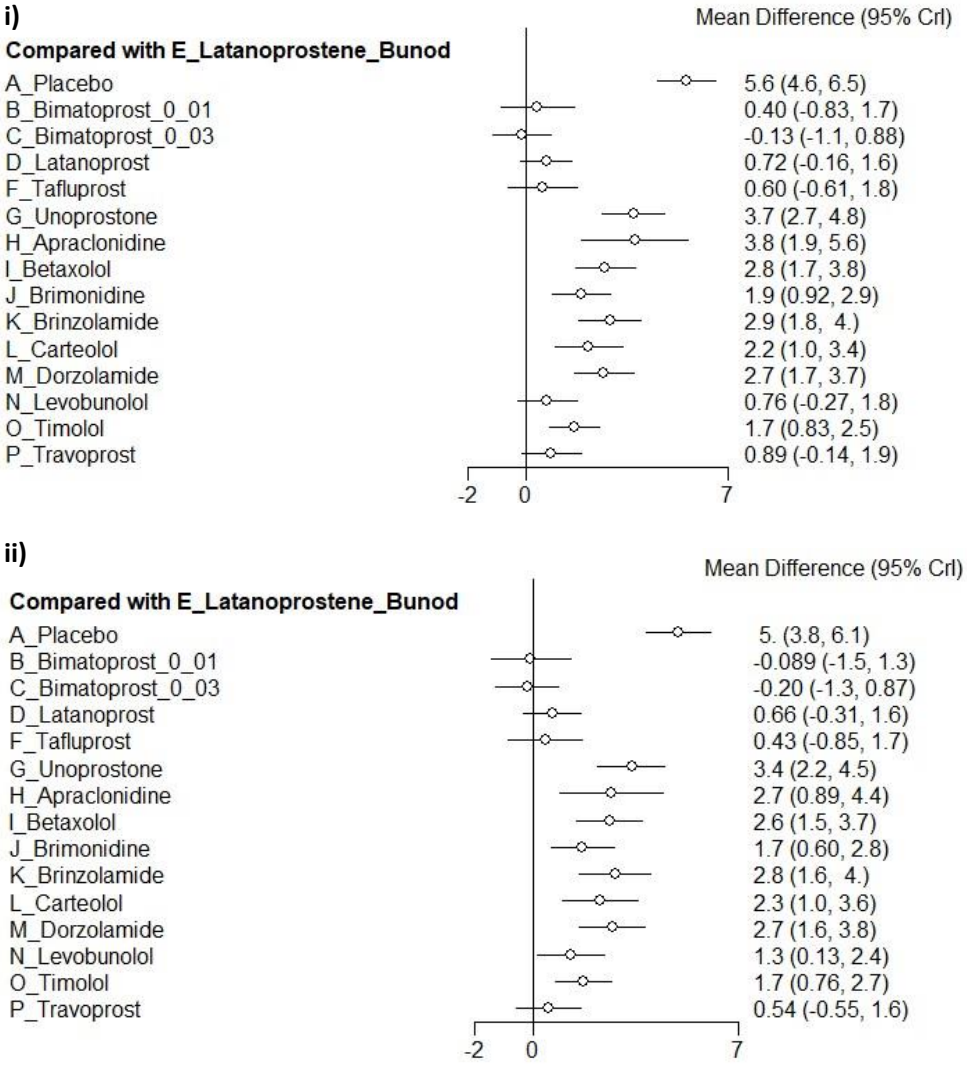
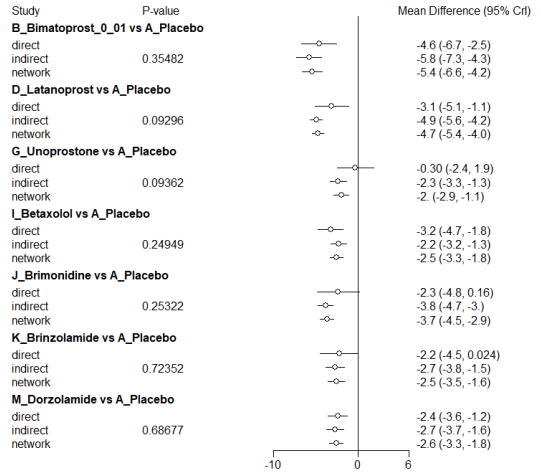
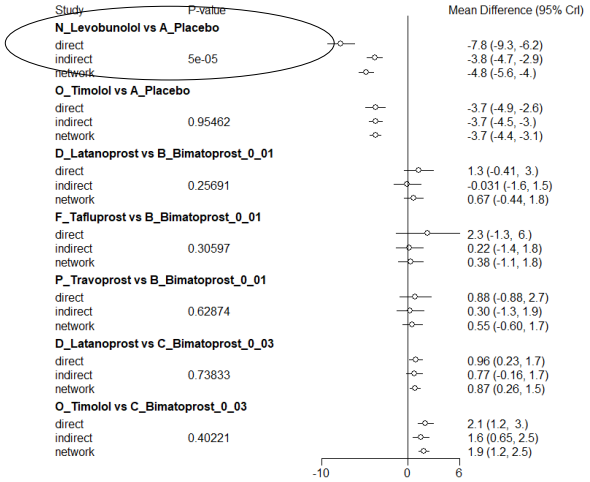


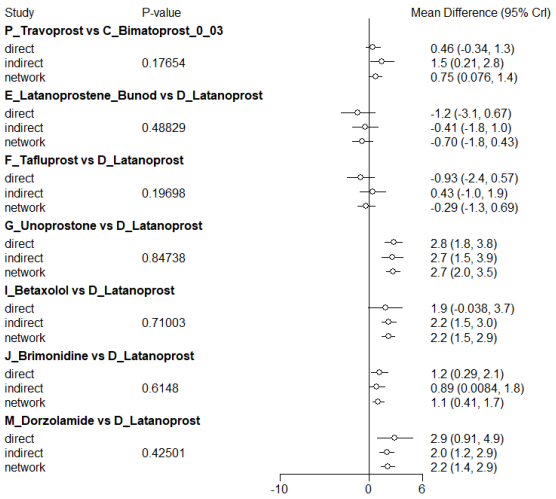
Figure 2. MD > 0 favors LBN. MD with a 95% CrI including 0 (crossing 0 in the forest plot) are not significant. PGAs = B, C, D, E, F and G
i) All Treatments Compared with Latanoprostene Bunod (without trials identified as possibly causing heterogeneity). ii) All Treatments Compared with Latanoprostene Bunod (without studies identified as causing inconsistency)

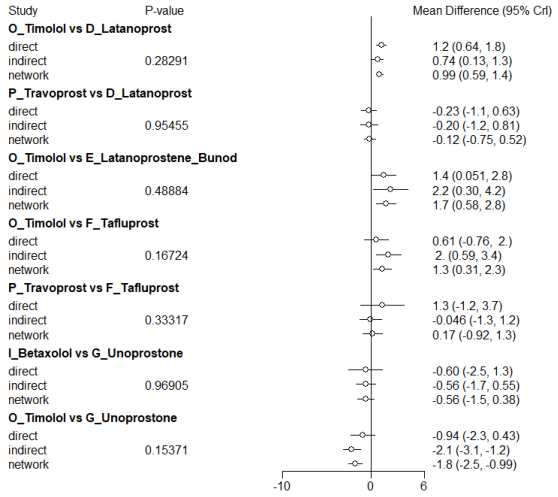
Appendix J. Inconsistency (Node-Splitting Approach Results)

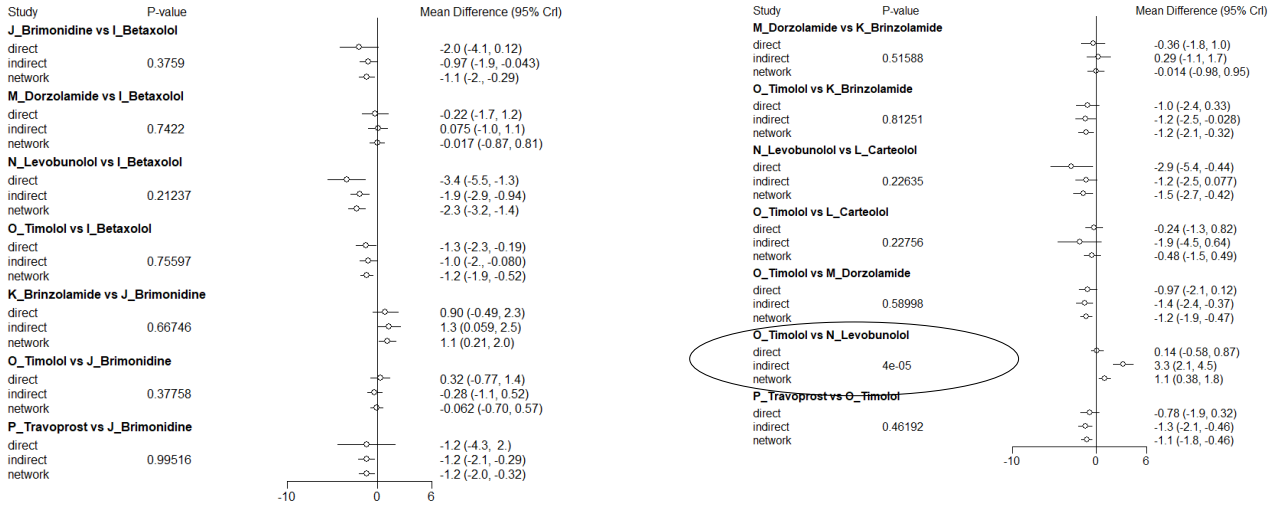
Inconsistent nodes are circled (p-value < 0.05)










Study
P-value
Mean Difference (95% CrI)
J_Brimonidine vs I_Betaxolol
direct
indirect 0.3759
network
-2.0 (-4.1, 0.12)
-0.97 (-1.9, -0.043)
-1.1 (-2., -0.29)
M_Dorzolamide vs I_Betaxolol
direct
indirect 0.7422
network
-0.22 (-1.7, 1.2)
0.075 (-1.0, 1.1)
-0.017 (-0.87, 0.81)
N_Levobunolol vs I_Betaxolol
direct
indirect 0.21237
network
-3.4 (-5.5, -1.3)
-1.9 (-2.9, -0.94)
-2.3 (-3.2, -1.4)
O_Timolol vs I_Betaxolol
direct
indirect 0.75597
network
-1.3 (-2.3, -0.19)
-1.0 (-2., -0.080)
-1.2 (-1.9, -0.52)
K_Brinzolamide vs J_Brimonidine
direct
indirect 0.66746
network
0.90 (-0.49, 2.3)
1.3 (0.059, 2.5)
1.1 (0.21, 2.0)
O_Timolol vs J_Brimonidine
direct
indirect 0.37758
network
0.32 (-0.77, 1.4)
-0.28 (-1.1, 0.52)
-0.062 (-0.70, 0.57)
P_Travoprost vs J_Brimonidine
direct
indirect 0.99516
network
-1.2 (-4.3, 2.)
-1.2 (-2.1, -0.29)
-1.2 (-2.0, -0.32)
-10
0
6
Study
P-value
Mean Difference (95% CrI)
M_Dorzolamide vs K_Brinzolamide
direct
indirect 0.51588
network
-0.36 (-1.8, 1.0)
0.29 (-1.1, 1.7)
-0.014 (-0.98, 0.95)
O_Timolol vs K_Brinzolamide
direct
indirect 0.81251
network
-1.0 (-2.4, 0.33)
-1.2 (-2.5, -0.028)
-1.2 (-2.1, -0.32)
N_Levobunolol vs L_Carteolol
direct
indirect 0.22635
network
-2.9 (-5.4, -0.44)
-1.2 (-2.5, 0.077)
-1.5 (-2.7, -0.42)
O_Timolol vs L_Carteolol
direct
indirect 0.22756
network
-0.24 (-1.3, 0.82)
-1.9 (-4.5, 0.64)
-0.48 (-1.5, 0.49)
O_Timolol vs M_Dorzolamide
direct
indirect 0.58998
network
-0.97 (-2.1, 0.12)
-1.4 (-2.4, -0.37)
-1.2 (-1.9, -0.47)
O_Timolol vs N_Levobunolol
direct
indirect 4e-05
network
0.14 (-0.58, 0.87)
3.3 (2.1, 4.5)
1.1 (0.38, 1.8)
P_Travoprost vs O_Timolol
direct
indirect 0.46192
network
-0.78 (-1.9, 0.32)
-1.3 (-2.1, -0.46)
-1.1 (-1.8, -0.46)
-10
0
6

Appendix K. Supplementary Analyses

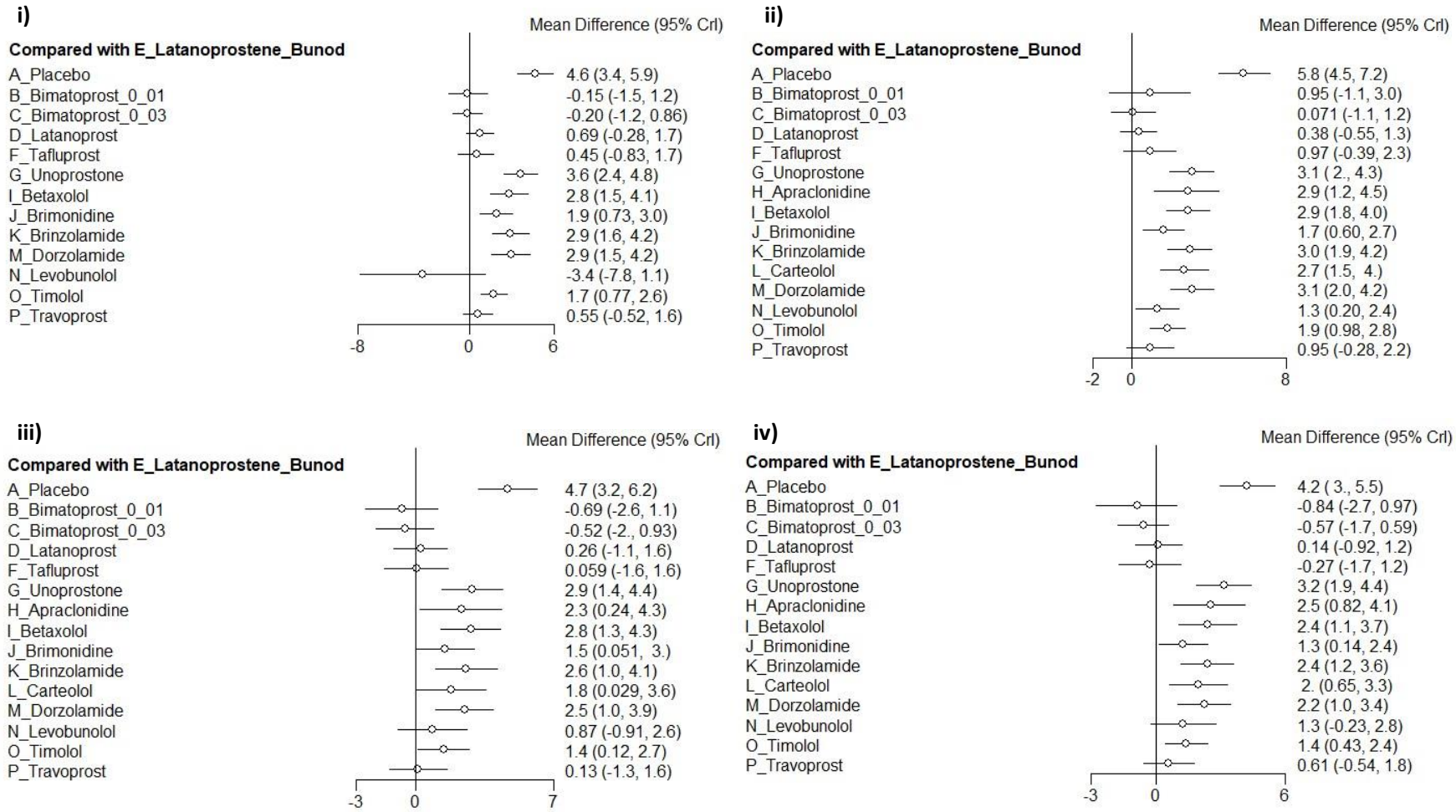


Figure 3. MD > 0 favors LBN. MD with a 95% CrI including 0 (crossing 0 in the forest plot) are not significant. PGAs = B, C, D, E, F and G i) Studies published from 2000 onward. ii) Studies with a washout period before randomization. iii) Studies that excluded prior glaucoma and cataract surgery. iv) Studies that excluded prior glaucoma laser.
If the treatment was included in the trial, LBN was still significantly more effective than placebo, unoprostone (PGA), apraclonidine, betaxolol, brimonidine, brinzolamide, carteolol, dorzolamide, and timolol for all these analyses. When compared with other PGAs, LBN was numerically more efficient than all PGAs in ii), numerically more efficient than latanoprost and tafluoprost in i) and iii) and numerically more efficient than latanoprost in iv).

Appendix L. Brooks-Gelman-Rubin Statistic

To verify the convergence of the model, the Brooks-Gelman-Rubin plot was obtained. Specifically, Gelman and Rubin (1992) proposed a general approach to monitoring convergence of MCMC output in which two or more parallel chains are run with starting values that are over dispersed relative to the posterior distribution. The convergence is assessed by comparing the estimated between-chains and within-chain variances for each model parameter. Large differences between these variances indicate nonconvergence. The method calculates a "potential scale reduction factor" that is the ratio of both variances. Approximate convergence is diagnosed when the factor of all chains is close to 1.[2] Brooks and Gelman (1998) generalized this method for observing the convergence of simulations by comparing between and within variance of multiple chains, in order to obtain a family of tests for convergence. They estimated a "shrink factor" at several points[3]. The Brooks-Gelman-Rubin plot shows the evolution of the "shrink factor" as the number of iterations increases. A "shrink factor" tending to 1 means convergence.[2]

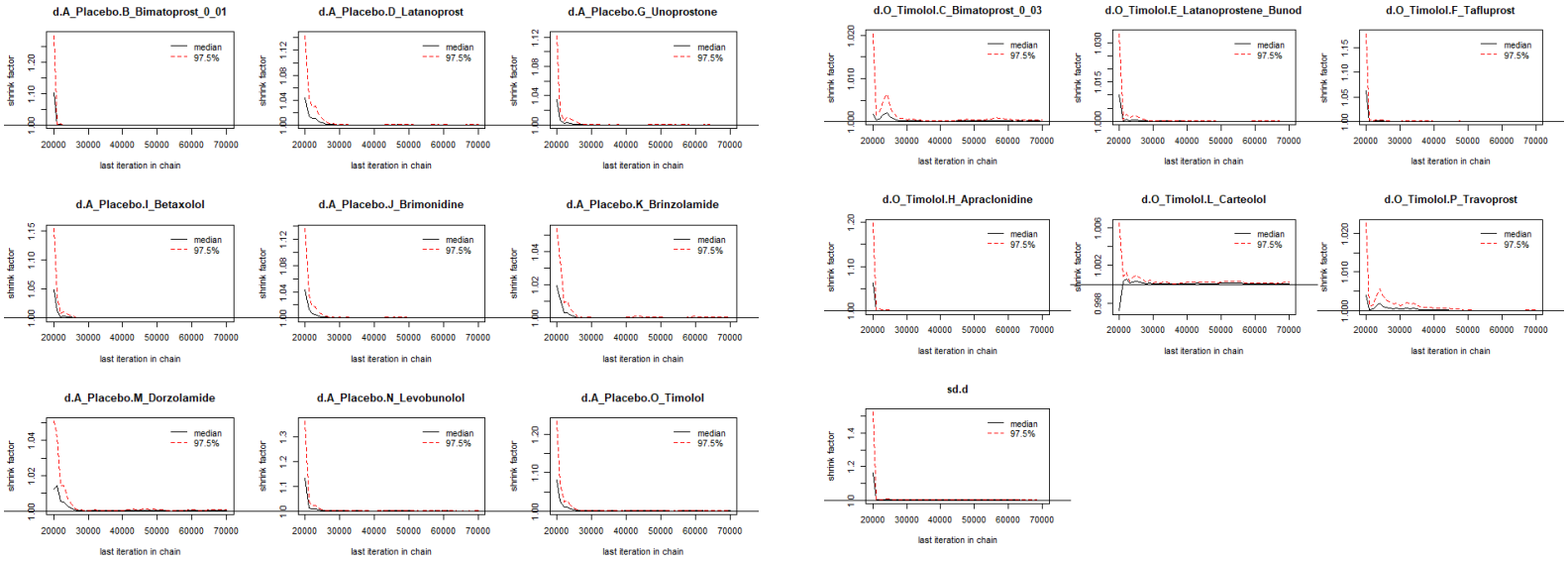


Figure 4. Brooks-Gelman-Rubin Plot. The plot illustrates that the NMA model converges after 20,000 burn-in.

[2] Gert van Valkenhoef JK. Package 'gemtc'. https://cran.r-project.org/web/packages/gemtc/gemtc.pdf. Published 2016. Accessed August 1, 2018.
[3] Gelman SPBA. General Methods for Monitoring Convergence of Iterative Simulations. *Journal of Computational and Graphical Statistics.* 1998.

Appendix A. Search Strategies

MEDLINE (OVID)

1. exp clinical trial/ [publication type]
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8.or/1-7
9. exp animals/
10. exphumans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma open angle'
14. exp ocular hypertension'
15. (open adj2 angle ajd2 glaucoma$).tw.
16. (POAG or OHT).tw.
17. (increes$ pr elevat$ or high$).tw.
18. (ocular or intra-ocular;).tw.
19. pressure.tw.
20. 17 and 18 and 19
21. 13 or 14 or 15 or 16 or 20
22. exp adrenergic beta antagonist/
23. exp timolol/
24. timolol$.tw.
25. exp metipranolol/
26. metipranolol$.tw.
27. exp carteolol/
28. carteolol$.tw.
29. exp levobunolol/
30. levobunolol$.tw.
31. exp betaxolol/
32. betaxolol$.tw.
33. exp carbonic anhydrase inhibitors/
34. (carbonic adj2 anhydrase adj2 inhibitor$).tw.
35. exp Acetazolamide/
36. acetazolamide$.tw.
37. brinzolamide$.tw.
38. dorzolamide%.tw.
39. exp Prostaglandins, Synthetic/
40. latanoprost$.tw.
41. travoprost$.tw.
42. bimatoprost$.tw.
43. unoprostone$.tw.
44. brimonidine$.tw.
45. exp antihypertensive agents1
46. exp pilocarpine/

47. pilocarpine$.tw.
48. exp epinephrine/
49. epinephrine$.tw.
50. dipivefrin$.tw.
51. exp Adrenergic alpha-2 Receptor Agonists/
52. ((adrenergic adj2 alpha$ ajd2 receptor$) or (adrenergic adj2 alpha$ ajd2 agonist$)).tw.
53. aoraclonidin$.tw.
54. tafluprost.tw.
55. monoprost$.tw.
56. latanoprostene bunod.tw.
57. ((drugs$ or medic$ or pharmacologic$) adj3 (treat$ or therap$ or intervent$)).tw.
58. 22 or 23 or 24 or 25 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59. 21 and 58
60. 12 and 59
61. limit 60 to yr “2014- Current

Embase

1 exp randomization/
2 randomized controlled trial/
3 double blind procedure/
4 single blind procedure/
5 random*.ti,ab.
6 1 or 2 or 3 or 4 or 5
7 (animal or animal experiment).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8 human/
9 7 and 8
10 (#7 not #9).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
11 (#6 not #10).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
12 exp clinical trial/
13 (clin* adj3 trial*).ab,ti.
14 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ab,ti.
15 exp placebo/
16 placebo*.ab,ti.
17 random*.ti,ab.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/

21 exp latin square design/
22 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 (#22 not #10).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
24 (#23 not #11).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control* or prospectiv* or volunteer*).ab,ti.
29 25 or 26 or 27 or 28
30 (#29 not #10).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
31 (#30 not (#11 or #23)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
32 11 or 24 or 31
33 exp open angle glaucoma/
34 exp intraocular hypertension/
35 ((open adj2 angle) and (angle adj2 glaucoma*)).ab,ti.
36 (poag or oht).ab,ti.
37 (((increas* or elevat* or high*) adj3 (ocular or 'intra ocular')) and pressure).ab,ti.
38 33 or 34 or 35 or 36 or 37
39 exp beta adrenergic receptor blocking agent/
40 exp timolol/
41 timolol*.ab,ti.
42 exp metipranolol/
43 metipranolol*.ab,ti.
44 exp carteolol/
45 carteolol*.ab,ti.
46 exp levobunolol/
47 levobunolol*.ab,ti.
48 exp betaxolol/
49 betaxolol*.ab,ti.
50 exp carbonate dehydratase inhibitor/
51 ((carbonic adj2 anhydrase) and (anhydrase adj2 inhibitor*)).ab,ti.
52 exp acetazolamide/
53 acetazolamide*.ab,ti.
54 brinzolamide*.ab,ti.
55 dorzolamide*.ab,ti.

56 exp latanoprost/
57 latanoprost*.ab,ti.
58 exp travoprost/
59 travoprost*.ab,ti.
60 exp bimatoprost/
61 bimatoprost*.ab,ti.
62 exp unoprostone isopropyl ester/
63 unoprostone*.ab,ti.
64 exp tafluprost/
65 tafluprost*.ab,ti.
66 exp monoprost/
67 monoprost*.ab,ti.
68 exp latanoprostene bunod/
69 exp brimonidine/
70 brimonidine*.ab,ti.
71 exp antihypertensive agent/
72 exp pilocarpine/
73 pilocarpin*.ab,ti.
74 exp adrenalin/
75 epinephrin*.ab,ti.
76 dipivefrin*.ab,ti.
77 exp alpha 2 adrenergic receptor stimulating agent/
78 ((adrenergic adj2 alpha*) and (alpha* adj2 agonist*)).ab,ti.
79 apraclonidin*.ab,ti.
80 ((drug* or medic* or pharmacologic*) adj3 (treat* or therap* or intervent*)).ab,ti.
81 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80
82 38 and 81
83 32 and 82

Appendix B. Eligibility Form

Reviewer Name:	Date:
First author, journal, year of publication:	
Study included	Study excluded

For each identified study, answer the following questions:

1. What was the diagnosis of the patients included in the clinical study?
   - Primary open angle glaucoma (POAG) -> 60% of patients
   - Ocular hypertension (OH) -> 60% of patients
   - POAG and / or OH -> 60% of patients
   - Other (exclude)
2. What is the treatment of interest assessed in this clinical trial?
   - Prostaglandin analogue
   - Beta blocker
   - Carbonic anhydrase inhibitor
   - Agonist adrenergic alpha-2 receptors
   - Other (exclude)
3. Does the treatment of interest is administered alone?
   - Yes
   - No, in combination (exclude)
4. What is the comparator in this clinical trial?
   - Active treatment alone
   - Placebo / no treatment
   - Combination (exclude)
5. Other (exclude)What was the study design?
   - Randomized parallel group
   - Crossover allowed (exclude)
   - Other (exclude)
6. Does the study was able to aim for the reduction of intraocular pressure?
   - Yes
   - No (exclude)
7. What was the follow-up time?
   - At least 28 days after randomization
   - Least than 28 days after randomization (exclude)
8. How many patients were included in the clinical study?
   - Over 10
   - Less than 10 (exclude)

Appendix C. References of Included Studies

1 Radius RL. Use of betaxolol in the reduction of elevated intraocular pressure. *Arch Ophthalmol.* 1983;101(6):898-900.
2 Berry DP, Van Buskirk EM, Shields MB. Betaxolol and timolol: a comparison of efficacy and side effects. *Archives of Ophthalmology.* 1984;102(1):42-45.
3 Bensinger RE, Keates EU, Gofman JD, Novack GD, Duzman E. Levobunolol: a three-month efficacy study in the treatment of glaucoma and ocular hypertension. *Archives of Ophthalmology.* 1985;103(3):375-378.
4 Berson FG, Cohen HB, Foerster RJ, Lass JH, Novack GD, Duzman E. Levobunolol compared with timolol for the long-term control of elevated intraocular pressure. *Arch Ophthalmol.* 1985;103(3):379-382.
5 Galin M, Cinotti A, Cinotti D, et al. Levobunolol vs timolol for open-angle glaucoma and ocular hypertension. *American journal of ophthalmology.* 1985;99(1):11-17.
6 Ober M, Scharrer A, David R, et al. Long-term ocular hypotensive effect of levobunolol: results of a one-year study. *British journal of ophthalmology.* 1985;69(8):593-599.
7 Stewart RH, Kimbrough RL, Ward RL. Betaxolol vs timolol: a six-month double-blind comparison. *Archives of Ophthalmology.* 1986;104(1):46-48.
8 Allen RC, Novack GD, Batoosingh AL. Long-term evaluation of 0.25% levobunolol and timolol for therapy for elevated intraocular pressure. *Arch Ophthalmol.* 1988;106:614-618.
9 Feghali J, Kaufman P, Radius R, Mandell A. A comparison of betaxolol and timolol in open angle glaucoma and ocular hypertension. *Acta ophthalmologica.* 1988;66(2):180-186.
10 Long DA, Johns GE, Mullen RS, et al. Levobunolol and betaxolol: a double-masked controlled comparison of efficacy and safety in patients with elevated intraocular pressure. *Ophthalmology.* 1988;95(6):735-741.
11 Seamone C, LeBlanc R, Saheb N, Novack G. Efficacy of twice-daily levobunolol in the treatment of elevated intraocular pressure. *Canadian journal of ophthalmology Journal canadien d'ophtalmologie.* 1988;23(4):168-170.
12 Epstein DL, Krug Jr JH, Hertzmark E, Remis LL, Edelstein DJ. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. *Ophthalmology.* 1989;96(10):1460-1467.
13 Kass MA, Gordon MO, Hoff MR, et al. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals. A randomized, double-masked, long-term clinical trial (1). *Journal of glaucoma.* 1993;2:1-2.
14 Schulzer M, Drance SM, Douglas GR. A comparison of treated and untreated glaucoma suspects. *Ophthalmology.* 1991;98(3):301-307.
15 Silverstone D, Zimmerman T, Choplin CN, et al. Evaluation of once-daily levobunolol 0.25% and timolol 0.25% therapy for increased intraocular pressure. *American journal of ophthalmology.* 1991;112(1):56-60.
16 Beehler CC, Stewart WC, MacDonald DK, et al. A comparison of the ocular hypotensive efficacy of twice-daily 0.25% levobunolol to 0.5% timolol in patients previously treated with 0.5% timolol. *Journal of glaucoma.* 1992;1(4):237-242.
17 Flammer J, Kitazawa Y, Bonomi L, et al. Influence of carteolol and timolol on IOP and visual fields in glaucoma: a multi-center, double-masked, prospective study. *European journal of ophthalmology.* 1992;2(4):169-174.
18 Azuma I, Masuda K, Kitazawa Y, Takase M, Yamamura H. Double-masked comparative study of UF-021 and timolol ophthalmic solutions in patients with primary

open-angle glaucoma or ocular hypertension. *Japanese journal of ophthalmology.* 1993;37(4):514-525.
19 Nagasubramanian S, Hitchings RA, Demailly P, et al. Comparison of apraclonidine and timolol in chronic open-angle glaucoma: a three-month study. *Ophthalmology.* 1993;100(9):1318-1323.
20 Wilkerson M, Cyrlin M, Lippa EA, et al. Four-week safety and efficacy study of dorzolamide, a novel, active topical carbonic anhydrase inhibitor. *Archives of Ophthalmology.* 1993;111(10):1343-1350.
21 Behrens-Baumann W, Kimmich F, Walt JG, Lue J. A comparison of the ocular hypotensive efficacy and systemic safety of 0.5% levobunolol and 2% carteolol. *Ophthalmologica.* 1994;208(1):32-36.
22 Ravalico G, Salvetat L, Toffoli G, Pastori G, Croce M, Parodi MB. Ocular hypertension: a follow-up study in treated and untreated patients. *New Trends in Ophthalmology.* 1994;9(2):97-101.
23 Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning: a comparison with timolol. *Ophthalmology.* 1995;102(12):1743-1752.
24 Schwartz B, Lavin P, Takamoto T, Araujo DF, Smits G. Decrease of optic disc cupping and pallor of ocular hypertensives with timolol therapy. *Acta Ophthalmologica.* 1995;73(S215):5-21.
25 Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. *Archives of Ophthalmology.* 1995;113(8):1009-1016.
26 Friström B. A 6-month, randomized, double-masked comparison of latanoprost with timolol in patients with open angle glaucoma or ocular hypertension. *Acta Ophthalmologica.* 1996;74(2):140-144.
27 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. *Archives of Ophthalmology.* 1996;114(8):929-932.
28 Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. *Survey of ophthalmology.* 1996;41:S27-S37.
29 Serle JB. A comparison of the safety and efficacy of twice daily brimonidine 0.2% versus betaxolol 0.25% in subjects with elevated intraocular pressure. *Survey of ophthalmology.* 1996;41:S39-S47.
30 Stewart WC, Laibovitz R, Horwitz B, Stewart RH, Ritch R, Kottler M. A 90-day study of the efficacy and side effects of 0.25% and 0.5% apraclonidine vs 0.5% timolol. *Archives of Ophthalmology.* 1996;114(8):938-942.
31 Watson P, Stjernschantz J. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. *Ophthalmology.* 1996;103(1):126-137.
32 Yamamoto T, Kitazawa Y, Noma A, et al. The effects of the beta-adrenergic-blocking agents, timolol and carteolol, on plasma lipids and lipoproteins in Japanese glaucoma patients. *Journal of glaucoma.* 1996;5(4):252-257.
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Appendix D. Baseline Characteristics

Table 1. Characteristics of the Selected Studies

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
1	1983	Placebo & Betaxolol	Inc.	Inc.	NA	Exc.	NA	≥26 in both eyes	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	1	40	NR
2	1984	Betaxolol & Timolol	Inc.	NA	NA	NA	Inc.	elevated IOPs	NR	Exc.	NA	Exc.	Yes	Yes	Multi (2)	USA	6	46	Other
3	1985	Placebo & Levobunolol	Inc.	Inc.	NA	NA	NA	NR	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	3	17	NR
4	1985	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	≥23 in each eye?	≥18	Exc.	NA	Exc.	Yes	Yes	Can't tell	NR	15	92	NR
5	1985	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	≥23	NR	Exc.	NA	Exc.	Yes	Yes	Can't tell	NR	15	85	NR
6	1985	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	≥23 in each eye	NR	NA	NA	NA	Yes	Yes	Multi (NR)	NR	12	67	NR
7	1986	Betaxolol & Timolol	Inc.	NA	NA	NA	NA	≥26 in at least one eye	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	6	29	NR
8	1988	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	NR	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	12	72	NR
9	1988	Betaxolol & Timolol	Inc.	Inc.	NA	NA	NA	average measurement >25.5 and no measurement <22	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (3)	USA	6	28	Responders
10	1988	Betaxolol & Levobunolol	Inc.	Inc.	NA	NA	Inc.	≥22 in at least one eye?	NR	NA	NA	NA	Yes	Yes	Can't tell	NR	3	73	NR
11	1988	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	≥21	NR	NA	NA	NA	Yes	Yes	Multi (2)	Canada	3	25	NR
12	1989	Placebo & Timolol	NA	Inc.	NA	NA	NA	≥22 and ≤28 in at least one eye	NR	Exc.	NA	Exc.	No	No	Single	USA	60	107	Intention-to-treat; Other
13		Placebo & Timolol										Exc.	Can't tell	No	Multi (2)	USA	61	124	NR
14	1991	Placebo & Timolol	NA	Inc.	NA	NA	NA	≥22	≥45 and ≤70	Exc.	NA	Exc.	Can't tell	No	Can't tell	NR	73	137	Intention-to-treat; Other
15	1991	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	exclude patients whose increased IOP was not controlled by a single drug therapy	NR	NA	NA	NA	Yes	Yes	Multi (NR)	NR	3	70	Other
16	1992	Levobunolol & Timolol	Can't tell	Inc.	NA	NA	Exc.	NR	NR	Exc.	Exc.	NA	Yes	Yes	Multi (7)	NR	2	128	NR
17	1992	Carteolol & Timolol	Inc.	NA	NA	NA	NA	>21	≥18 and ≤80	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	NR	12	144	Compilers or Adheres
18	1993	Timolol & Unoprostone	Inc.	Inc.	Exc.	Exc.	Exc.	≥22 and ≤35	NR	Exc.	NA	Exc.	Yes	Yes	Multi (18)	Japan	3	147	NR
19	1993	Apraclonidine & Timolol	Inc.	Inc.	NA	NA	NA	NR	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	NR	3	56	NR
20	1993	Placebo & Dorzolamide	Inc.	Inc.	NA	NA	NA	NR	NR	Exc.	NA	Exc.	Yes	Yes	Multi (3)	USA	1	42	Per protocol
21	1994	Carteolol & Levobunolol	Inc.	Inc.	NA	NA	Inc.	≥22	NR	NA	NA	NA	Yes	Yes	Multi (NR)	NR	3	52	NR
22	1994	Placebo & Levobunolol	NA	Inc.	NA	NA	NA	≥22 and ≤30	NR	NA	NA	NA	Can't tell	No	Can't tell	NR	24	46	NR
23	1995	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥22	≥40	Exc.	Exc.	Exc.	Yes	Yes	Multi (13)	Sweden & Denmark &	6	243	NR

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
																Finland & Norway			
24	1995	Placebo & Timolol	NA	Inc.	NA	NA	NA	≥21 and <35	NR	Exc.	Exc.	Exc.	Can't tell	No	Single	USA	24	74	NR
25	1995	Betaxolol & Timolol & Dorzolamide	Inc.	Inc.	NA	NA	NA	≥23	≥21 and ≤85	Exc.	NA	Exc.	Yes	Yes	Multi (34)	Costa Rica & Colombia & United States & Mexico & United Kingdom	12	516	Intention-to-treat; Per protocol
26	1996	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥22	>40	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	Sweden	6	20	NR
27	1996	Timolol & Latanoprost	Inc.	Inc.	NA	NA	NA	NR	NR	Exc.	Exc.	Exc.	No	Yes	Multi (35)	Japan	3	154	NR
28	1996	Brimonidine & Timolol	Inc.	Inc.	NA	NA	NA	post washout IOP ≥23 mmHg and <35 mmHg in each eye; Exc. IOP asymmetry of more than 5 mmHg	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	NR	12	647	Safety population or safety analysis
29	1996	Brimonidine & Betaxolol	Inc.	Inc.	NA	NA	NA	≥22 and ≤34, and difference between two eyes ≤5	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (13)	USA	3	177	Per protocol; Safety population or safety analysis
30	1996	Apraclonidine & Timolol	Inc.	Inc.	NA	NA	NA	≥22 and ≤35, and difference between two eyes ≤4	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (16)	USA	3	230	NR
31	1996	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥22	≥40	Exc.	Exc.	Exc.	Yes	Yes	Multi (14)	United Kingdom	6	255	NR
32	1996	Carteolol & Timolol	Inc.	Inc.	NA	NA	NA	NR	≥40 and ≤70	Exc.	NA	Exc.	Yes	No	Multi (3)	Japan	4	33	NR
33	1997	Levobunolol & Timolol	Inc.	Inc.	NA	NA	NA	≤20 in both eyes and difference between two eyes ≤4, and IOP fluctuation between both eyes ≤2 at baseline and 6 weeks prior to the study	≥20 and ≤75	Exc.	Exc.	Exc.	Yes	No	Multi (24)	Japan	3	58	Intention-to-treat
34	1997	Carteolol & Timolol	Inc.	Inc.	NA	NA	Exc.	≥22 and ≤34, and difference between two eyes <5	≥18 and ≤85	Exc.	Exc.	NA	Yes	Yes	Multi (13)	USA	3	176	Intention-to-treat
35	1998	Timolol & Dorzolamide	Inc.	Inc.	NA	Exc.	NA	NR	≥21 and ≤85	Exc.	Exc.	Exc.	No	Yes	Multi (27)	USA	3	220	Per protocol; Other
36	1999	Timolol & Dorzolamide	Inc.	Inc.	NA	Exc.	NA	≥22 at 9AM and 11AM	≥21	Exc.	Exc.	Exc.	Yes	No	Multi (22)	USA	3	149	Per protocol; Safety population or safety

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
																			analysis; Other
37	1998	Timolol & Latanoprost	Inc.	NA	NA	Exc.	Inc.	≥25 with IOP reducing therapy or ≥30 without IOP reducing therapy	≥18	Exc.	Exc.	Exc.	Yes	No	Multi (13)	Germany	1	37	NR
38	1998	Brimonidine & Timolol	Inc.	Inc.	NA	NA	Exc.	≥23 and ≤35, and difference between two eyes ≤5	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	NR	12	418	Per protocol; Safety population or safety analysis
39	1998	Betaxolol & Dorzolamide	Inc.	Inc.	NA	Exc.	NA	≥23 in at least one eye?	≥21	Exc.	NA	Exc.	Yes	Yes	Multi (24)	USA	3	310	Per protocol; At least receiving one treatment
40	1998	Timolol & Brinzolamide & Dorzolamide	Inc.	Inc.	Exc.	Exc.	Inc.	NR	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (42)	USA & Germany & France & Belgium & Portugal & the Netherlands & Iceland	3	491	Intention-to-treat; Per protocol; Responders; At least receiving one treatment; Safety population or safety analysis
41	1999	Carteolol & Timolol	Inc.	Inc.	NA	NA	Exc.	NR	NR	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	USA	3	107	Intention-to-treat
42	1999	Placebo & Brimonidine	NA	Inc.	NA	NA	NA	≥20 and ≤40	NR	Exc.	Exc.	Exc.	Yes	No	Single	USA	1	56	NR
43	2000	Timolol & Latanoprost	Inc.	Inc.	NA	NA	Inc.	NR	>40	NA	NA	NA	Can't tell	No	Multi (13)	Sweden	6	243	NR
44	2000	Dorzolamide & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	NR	NR	Exc.	Exc.	Exc.	Yes	Yes	Multi (12)	NR	3	213	NR
45	2000	Placebo & Brinzolamide & Dorzolamide	Inc.	Inc.	Exc.	Exc.	Inc.	≥24 and ≤36 at 8AM and ≥ 21 and ≤ 36 mmHg at 10AM and 6PM	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (24)	USA	3	395	Intention-to-treat; Per protocol; Safety population or safety analysis
46	2001	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥21	NR	Exc.	Exc.	Exc.	Yes	Yes	Multi (NR)	France	1	33	NR
47	2001	Brimonidine & Latanoprost	Inc.	Inc.	NA	NA	NA	≥22 and ≤34	≥18	Exc.	Exc.	Can't tell	Yes	Yes	Multi (5)	USA	3	125	Per protocol
48	2001	Latanoprost & Unoprostone	NA	Inc.	NA	NA	NA	≥21 and ≤29 in each eye	≥20 and ≤79	Exc.	Exc.	Exc.	No	No	Can't tell	NR	2	36	Safety population or safety analysis; Other
49	2001	Latanoprost & Unoprostone	Inc.	Inc.	NA	Exc.	NA	≥21	≥18	Exc.	Exc.	Exc.	Yes	Yes	Single	Brazil	2	105	Intention-to-treat; Per protocol

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
50	2002	Latanoprost & Unoprostone	Inc.	Inc.	NA	Exc.	Exc.	>21	≥21	Exc.	Exc.	Exc.	No	No	Multi (2)	Singapore	2	30	NR
51	2002	Placebo & Dorzolamide	Inc.	NA	NA	Inc.	NA	Exc. mean IOP of two eyes >30 or any IOP >35 in one eye	NR	Exc.	Exc.	Exc.	No	No	Single	Sweden	1	44	Intention-to-treat
52	2002	Timolol & Travoprost	Inc.	Inc.	NA	NA	Inc.	≥24 and ≤36	≥21	Exc.	Exc.	Exc.	Yes	Yes	Multi (44)	USA	6	605	Intention-to-treat; Per protocol; Safety population or safety analysis
53	2002	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥25 with IOP reducing therapy or ≥30 without IOP reducing therapy	≥18	Exc.	Exc.	Exc.	Yes	No	Multi (38)	USA	12	280	Intention-to-treat; Safety population or safety analysis
54	2002	Latanoprost & Unoprostone	Inc.	Inc.	NA	Exc.	NA	≥21	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (24)	USA	2	164	Intention-to-treat; Safety population or safety analysis
55	2002	Brimonidine & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	NR	NR	Exc.	Exc.	Exc.	Yes	Yes	Multi (30)	Germany & United Kingdom & Spain & Finland	6	375	Intention-to-treat
56	2002	Betaxolol & Timolol & Unoprostone	Inc.	Inc.	NA	NA	Inc.	NR	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (27)	Europe & Israel	24	552	Intention-to-treat
57	2002	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥25 with IOP reducing therapy or ≥30 without IOP reducing therapy	≥18	Exc.	Exc.	Exc.	Yes	No	Multi (37)	NR	6	296	Intention-to-treat; At least receiving one treatment
58	2002	Brimonidine & Latanoprost	Inc.	Inc.	NA	NA	NA	≥18 and ≤34, and difference between two eyes ≤5	≥21	NA	NA	NA	Yes	No	Multi (14)	USA	3	74	NR
59	2002	Latanoprost & Unoprostone	Inc.	Inc.	NA	Exc.	NA	≥21 and ≤27, and difference between two eyes <2	≥18	Exc.	NA	Exc.	Yes	Yes	Single	USA	1	50	NR
60	2002	Latanoprost & Unoprostone	NA	NA	NA	NA	NA	≥21 and <30	NR	Exc.	NA	Exc.	Yes	Yes	Multi (10)	Japan	2	44	NR
61	2003	Timolol & Latanoprost	Inc.	Inc.	Can't tell	Can't tell	Can't tell	NR	NR	Can't tell	Can't tell	Can't tell	Yes	Yes	Multi (17)	USA	6	248	Intention-to-treat; Responders
62	2003	Latanoprost & Travoprost	Inc.	NA	Exc.	Exc.	Exc.	>20	≥40 and ≤60	NA	NA	NA	No	No	Single	Italy	6	18	NR
63	2003	Brimonidine & Latanoprost	Inc.	Inc.	NA	NA	NA	NR	NR	Exc.	Exc.	Exc.	Yes	Yes	Can't tell	NR	3	38	NR
64	2003	Placebo & Betaxolol	NA	Inc.	NA	NA	NA	≥22 and ≤35	>35	NA	NA	NA	Can't tell	No	Single	United Kingdom	37	356	Intention-to-treat
65	2003	Bimatoprost 0.03% &	Inc.	Inc.	NA	Exc.	Inc.	≥21	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (45)	USA	3	410	Intention-to-treat; Per

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
		Latanoprost & Travoprost																	protocol; Safety population or safety analysis
66	2004	Betaxolol & Latanoprost	Inc.	NA	NA	NA	NA	NR	NR	Exc.	NA	Exc.	No	No	Can't tell	NR	3	31	NR
67	2004	Placebo & Unoprostone	Inc.	NA	NA	NA	NA	NR	NR	NA	NA	NA	Yes	No	Single	NR	2	50	NR
68	2004	Timolol & Bimatoprost 0.03%	Inc.	Inc.	Exc.	Exc.	Exc.	<16 on timolol for 12 months	≥40 and ≤60	NA	NA	NA	Can't tell	No	Single	Italy	6	38	NR
69	2004	Timolol & Bimatoprost 0.03% & Latanoprost	Inc.	Inc.	NA	NA	NA	≥22 and ≤34, and difference between two eyes ≤5	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (7)	USA	1	112	Intention-to-treat; Modified intention[to[treat; Safety population or safety analysis
70	2004	Timolol & Brinzolamide	Inc.	NA	NA	Exc.	NA	≥20 and ≤30	NR	NA	NA	NA	Yes	Yes	Single	Taiwan	1	48	NR
71	2005	Timolol & Travoprost	Inc.	Inc.	Exc.	Exc.	Exc.	NR	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (33)	USA	3	176	Intention-to-treat
72	2005	Brimonidine & Latanoprost	Inc.	Inc.	NA	Exc.	NA	≥22	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (23)	USA	6	301	Intention-to-treat; Per protocol; Safety population or safety analysis
73	2005	Placebo & Dorzolamide	NA	Inc.	NA	NA	NA	≥22 and ≤29 in at least one eye?	≥30 and ≤80	Exc.	NA	Exc.	Yes	Yes	Multi (18)	Belgium & Germany & Italy & Portugal	61	976	Intention-to-treat; Safety population or safety analysis
74	2006	Betaxolol & Latanoprost	Inc.	NA	NA	NA	NA	NR	NR	Exc.	Exc.	Exc.	No	No	Can't tell	NR	3	40	NR
75	2007	Bimatoprost 0.03% & Latanoprost & Travoprost	Inc.	Inc.	NA	NA	NA	≥22 and ≤36	≥18	Exc.	Exc.	Exc.	No	No	Can't tell	NR	6	60	Other
76	2007	Timolol & Bimatoprost 0.03%	Inc.	Inc.	NA	NA	Inc.	≥24 and ≤34	>18	Exc.	Exc.	Exc.	Yes	Yes	Can't tell	Spain	6	60	NR
77	2008	Bimatoprost 0.03% & Travoprost	Inc.	NA	NA	NA	Inc.	≤36	≥18	Exc.	Exc.	Exc.	No	No	Single	Turkey	6	82	NR
78	2008	Timolol & Bimatoprost	Inc.	Inc.	NA	Inc.	NA	≥18 with IOP reducing medication or ≥24 for treatment naïve patients in at least one eye	adults	Exc.	Exc.	Exc.	Yes	Yes	Multi (59)	USA & Canada	3	528	Intention-to-treat
79	2008	Timolol & Brinzolamide	Inc.	Inc.	NA	Exc.	Inc.	≥18 at 8AM or ≥21 at 10AM and ≤36 in at least one eye	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (35)	USA	6	346	Intention-to-treat; Per protocol

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
80	2008	Brimonidine & Timolol & Travoprost	Inc.	NA	NA	NA	Exc.	>21	NR	NA	NA	NA	Yes	No	Single	Brazil	1	50	NR
81	2008	Timolol & Bimatoprost	Can't tell	Inc.	Can't tell	Can't tell	Can't tell	≥22 and ≤34	NR	NA	NA	NA	Yes	Yes	Multi (15)	USA	49	113	Intention-to-treat; Per protocol; At least receiving one treatment; Safety population or safety analysis
82	2008	Bimatoprost 0.03% & Latanoprost & Travoprost	Inc.	NA	NA	Exc.	NA	>22	≥18	Exc.	NA	Exc.	No	No	Can't tell	NR	2	48	NR
83	2009	Bimatoprost 0.03% & Latanoprost	Can't tell	Inc.	Can't tell	Can't tell	Can't tell	≥17 and ≤22 in each eye	≥18	Exc.	NA	Exc.	Yes	No	Multi (8)	Australia	6	208	Intention-to-treat; Safety population or safety analysis
84	2009	Betaxolol & Levobunolol & Timolol	Inc.	NA	Inc.	NA	NA	NR	≥40 and ≤80	Exc.	NA	Exc.	Yes	No	Single	India	3	62	NR
85	2010	Bimatoprost 0.03% & Latanoprost & Travoprost	Inc.	Inc.	NA	NA	Inc.	>23 and <36	NR	Exc.	Exc.	Exc.	Yes	Yes	Multi (9)	Canada	6	83	Per protocol
86	2010	Placebo & Bimatoprost 0.01%	NA	Inc.	NA	NA	NA	difference between two eyes ≤5	≥18	Exc.	Exc.	NA	Yes	No	Multi (15)	USA	1	218	Modified intention-to-treat
87	2010	Timolol & Latanoprost	Inc.	Inc.	NA	Exc.	Inc.	≥26 and ≤36	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (58)	USA	3	265	Intention-to-treat; At least receiving one treatment; Eligible population; Safety population or safety analysis
88	2010	Bimatoprost 0.03% & Travoprost	Can't tell	Inc.	can't tell	can't tell	can't tell	inadequate IOP control after at least 30 days on latanoprost monotherapy, judged by the investigator	adults	Exc.	NA	Exc.	Yes	No	Multi (17)	NR	3	260	intention-to-treat
89	2010	Bimatoprost 0.03% & Travoprost	Inc.	Inc.	Exc.	Exc.	can't tell	≥21 and ≤35 in each eye	≥18	Exc.	NA	Exc.	Yes	Yes	Multi (NR)	Egypt	6	72	NR
90	2010	Latanoprost & Tafluprost	Inc.	Inc.	NA	NA	Inc.	≥22 and ≤34 in at least one eye	≥18	Exc.	NA	Exc.	Yes	Yes	Multi (3)	Italy & Finland	1	36	Intention-to-treat; At least receiving one

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
																			treatment; Safety population or safety analysis
91	2012	Timolol & Tafluprost	Inc.	Inc.	NA	NA	Inc.	≥23 and ≤36, and difference between two eyes < 5	≥18	Exc.	NA	Exc.	Yes	Yes	Multi (50)	USA & Spain & Switzerland	3	610	Per protocol; At least receiving one treatment
92	2013	Bimatoprost 0.01% & Travoprost	Inc.	Inc.	NA	NA	NA	NR	≥18	Exc.	NA	Exc.	Yes	Yes	Multi (15)	Canada & United States	3	109	Intention-to-treat; Per protocol; Safety population or safety analysis
93	2013	Timolol & Latanoprost	Inc.	Inc.	Exc.	Exc.	Exc.	≤18	≥18 and ≤90	NA	NA	NA	Yes	No	Multi (45)	France	3	143	Per protocol; other
94	2013	Brimonidine & Brinzolamide	NA	Inc.	Exc.	Exc.	Exc.	≥24 and ≤36at 8AM, or≥21 AND ≤36 in both eyes at all time points	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (66)	USA	3	405	Intention-to-treat; Safety population or safety analysis
95	2013	Brimonidine & Brinzolamide	Inc.	Inc.	NA	Exc.	NA	≥24 and ≤36at 8AM, or≥21 AND ≤36 in both eyes at all time points	≥18	Exc.	Exc.	Exc.	Yes	Yes	Multi (65)	USA	6	419	Intention-to-treat safety population or safety analysis
96	2014	Timolol & Bimatoprost 0.03% & Latanoprost & Levobetaxolol	Inc.	NA	Exc.	Exc.	Exc.	IOP≥ 21 mm Hg for 1 or 2 eyes	≥ 18	Exc.	Exc.	Exc.	No	No	Single	NR	3	140	comparaison
97	2015	Latanoprost & Tafluprost	Inc.	Inc.	Inc.	Exc.	Exc.	NR	≥ 18	Exc.	Exc.	Exc.	No	No	NR	Italie	12	67	Post-hoc
98	2015	Placebo & Latanoprost	Inc.	NA	Exc.	Exc.	Exc.	IOP ≥ 30 mmHg Exc.	≥ 20	Exc.	Exc.	Exc.	Yes	No	Multi (10)	UK	24	461	comparaison
99	2015	Latanoprost & Latanoprostene bunod	Inc.	Inc.	Exc.	Exc.	Exc.	IOP of 22-32 mmHg, IOP of ≥24 mmHg for at least 2 of the 3-time points during the visit 3	≥ 18	NA	NA	NA	No	yes	Multi (23)	USA & European Union	1	165	comparaison
100	2016	Timolol & Tafluprost	Inc.	Inc.	Exc.	Exc.	Exc.	IOP ≥24 and ≤36 mm Hg at least one eye at 8 h, and be < 5 mmHg difference in mean (or median) IOP between the eyes at all the hour time points.	18-80	Exc.	Exc.	Exc.	Yes	Yes	Multi	India	2,5	167	Non-inferiority

Ref.	Year	Drugs compared	Primary open angle glaucoma (POAG)*	Ocular hypertension (OTH) or glaucoma suspect*	Normal/Low tension glaucoma*	Angle closure glaucoma*	Secondary glaucoma*	IOP*	Age, years*	Prior glaucoma surgery*	Prior glaucoma laser*	Prior cataract surgery*	Allowed ocular hypotensive medication at enrollment*	Reported using a washout period before randomization*	Mult/single center trial (# of recruiting centers)*	Countries in which participants were recruited*	Maximal planned length of followup, months*	Total number of participants or eyes included in analysis	Types of analysis*
101	2016	Timolol & Latanoprostene bunod	Inc.	Inc.	Exc.	Exc.	Exc.	IOP≥ 26 mm Hg at a minimum of 3 h (8 AM, 12 PM, and 4 PM), ≥ 24 mm Hg at a minimum of 1-time point, and ≥ 22 mm Hg at 1 time point, IOP ≤36 mm Hg at all times point in both eyes	≥ 18	Exc.	Exc.	Exc.	No	yes	Multi (46)	USA & European Union	3	387	Non-inferiority
102	2016	Timolol & Latanoprost	Inc.	NA	Exc.	Exc.	Exc.	IOP≥ 21 mm Hg in each eye	≥ 40	Exc.	Exc.	Exc.	No	yes	Single	India	3	110	Superiority
103	2016	Timolol & Latanoprostene bunod	Inc.	Inc.	Exc.	Exc.	Exc.	IOP ≥ 26 mmHg at a minimum of 1-time point, ≥ 24 mmHg at least 1 time point, ≥ 22 mmHg at 1 point in the same eye, IOP ≤ 36 mmHg in both eyes baseline	≥ 18	Exc.	Exc.	Exc.	No	yes	Multi	USA & Europe	3	413	Non-inferiority
104	2018	Bimatoprost 0.01% & Latanoprost & Travoprost & Levobetaxolol	Inc.	NA	Exc.	Exc.	Exc.	IOP ≥ 20 mmHg after 1 month of treatment: Exc.	≥ 18	Exc.	Exc.	Exc.	No	No	Single	Lebanon	6	32	comparison
105	2019	Bimatoprost 0.01% & Latanoprost	Inc.	Exc.	Exc.	Exc.	Exc.	IOP > 20 mmHg at 8 am	≥ 18	Exc.	NA	Exc.	No	No	Single	Pakistan	1	240	Comparison
106	2019	Brimonidine & Timolol	Inc.	Exc.	Exc.	Exc.	Exc.	Treated with IOP <21 mmHg in both eyes	≥ 20	Exc.	Exc.	Exc.	Yes	No	Single	Japan	24	56	Comparison

* Information taken directly from Li *et al.* (2016) publication for years before 2014 (all reference numbers except 105-106)
Ref.: Reference
Exc.: Excluded
Inc.: Included
NA: Not applicable
NR: Not reported
IOP: Intraocular pressure

Appendix D. Baseline Characteristics

Table 2. Characteristics of Included Studies per Treatment Arm

Characteristics (mean* (range))	Placebo	Bimatoprost 0.01%	Bimatoprost 0.03%	Latanoprost	Latanoprostene Bunod	Tafluprost	Unoprostone
Age (years)	63.7 (53.6, 74.0) [3]	52.1 (30.4, 65.1) [5]	61.1 (48.3, 69.0) [4]	62.0 (32.0, 69.0) [4]	64.3 (60.8, 65.0) [5]	62.3 (56.7, 68.5) [4]	62.7 (54.0, 64.2) [4]
% Female	48.5 (34.0, 75.0) [3]	60.1 (50.0, 64.3) [5]	54.9 (35.0, 65.8) [4]	52.7 (14.3, 84.2) [4]	59.7 (58.3, 68.7) [5]	51.7 (0.4, 0.7) [5]	51.3 (48.1, 63.2) [4]
Baseline IOP	23.3 (18.0, 28.7) [5]	21.0 (16.8, 26.1) [5]	23.2 (17.0, 27.2) [5]	23.8 (15.8, 28.3) [5]	26.6 (26.0, 26.7) [5]	24.5 (18.5, 26.7) [5]	23.9 (19.1, 25.7) [5]

Characteristics (mean (range))	Apraclonidine	Betaxolol	Brimonidine	Brinzolamide	Carteolol	Dorzolamide	Levobunolol
Age (years)	59.9 (59.8, 60.5) [5]	63.0 (49.6, 66.5) [4]	63.3 (53.6, 67.4) [5]	63.1 (42.4, 65.0) [3]	60.2 (54.2, 70.3) [5]	63.5 (61.3, 72.0) [3]	60.8 (55.9, 65.8) [4]
% Female	56.8 (54.5, 57.2) [5]	48.9 (39.0, 65.0) [4]	55.0 (46.2, 75.0) [5]	56.1 (40.0, 57.6) [5]	63.5 (33.3, 100.0) [5]	53.7 (42.0, 56.9) [3]	53.8 (40.0, 62.9) [4]
Baseline IOP	25.5 (25.5, 25.7) [5]	25.7 (23.1, 31.2) [5]	24.4 (12.7, 25.8) [5]	25.9 (24.7, 27.1) [5]	24.2 (20.8, 25.2) [5]	25.3 (22.5, 28.1) [5]	25.7 (18.3, 33.5) [5]

Characteristics (mean (range))	Timolol	Travoprost
Age (years)	62.0 (41.9, 70.5) [4]	62.3 (46.1, 65.9) [5]
% Female	53.3 (23.4, 100.0) [4]	51.3 (44.4, 78.9) [5]
Baseline IOP	25.1 (12.9, 33.8) [5]	24.9 (16.4, 29.6) [5]

* Weighted average of the mean by number of patients.

[1] Characteristics reported in < 25% of n (arm specific)
[2] Characteristics reported in 25%-50% of n related to this treatment arm
[3] Characteristics reported in 50%-75% of n related to this treatment arm
[4] Characteristics reported in 75%-100% of n related to this treatment arm
[5] Characteristics reported in 100 % of n related to this treatment arm

Appendix E. Risk of Bias Table

Information were taken directly from *Li et al.* (2016) publication, except references number 105-106

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
1	NR	NR	NR/CT	NR/CT	Yes	Yes	No
2	Randomly numbered with a unique code by a third party	Each patient, in sequence, was assigned a study number corresponding to a test drug... The code was broken at the end of the study.	Yes	Yes	No	NR	No
3	NR	NR	NR/CT	NR/CT	Yes	Yes	Yes
4	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
5	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
6	NR	NR	NR/CT	NR/CT	Yes	NR	No
7	NR	NR	Yes	NR/CT	Yes	Yes	Yes
8	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
9	NR	Patients were then randomly assigned in a double-masked fashion to one of two	NR/CT	NR/CT	Yes	Yes	No
10	NR	NR	NR/CT	NR/CT	Yes	NR	Yes
11	NR	NR	Yes	Yes	No	NR	No
12	The treatment assignment was done in stratified groups based on the patient's baseline IOP and the number of eyes which were entered in the study.	The randomization list was kept by the research secretary, and the examining physician did not know to which group a newly recruited patient would be assigned	No	Yes	No	Yes	No
13	NR	NR	NR/CT	NR/CT	Yes	Yes	No
14	NR	NR	No	NR/CT	No	Yes	No
15	NR	NR	Yes	NR/CT	Yes	NR	No
16	NR	NR	Yes	NR/CT	No	NR	Yes
17	Participating patients were distributed randomly, i.e. each new patient entering the study received the next-numbered, masked bottle.		NR/CT	NR/CT	Yes	Yes	No
18	The containers were confirmed as indistinguishable, and allotted in a randomized manner by the controller. The key code table was retained by the controller.		Yes	NR/CT	Yes	NR	No
19	NR	NR	Yes	NR/CT	Yes	Yes	Yes
20	NR	NR	NR/CT	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
21	NR	NR	NR/CT	NR/CT	Yes	Yes	Yes
22	NR	NR	NR/CT	NR/CT	No	NR	No
23	The patients were allocated to treatment	NR	Yes	NR/CT	Yes	Yes	Yes

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	groups according to a computer generated scheme prepared by Pharmacia.						
24	Subjects were then places on either placebo or timolol drops in both eyes twice a day in a double masked manner using randomized number tables.	NR	Yes	Yes	No	Yes	Yes
25	NR	NR	Yes	NR/CT	Yes	Yes	Yes
26	NR	NR	NR/CT	NR/CT	Yes	Yes	No
27	NR	NR	Yes	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
28	NR	NR	Yes	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
29	NR	NR	NR/CT	NR/CT	Yes	NR	No
30	NR	NR	Yes	NR/CT	Yes	Yes	Reported none of the authors has any financial relationship
31	The patients were allocated to different treatment groups according to a pregenerated randomization list.	NR	NR/CT	NR/CT	Yes	Yes	Yes
32	Envelope method		NR/CT	NR/CT	No	NR	Reported none of the authors has any financial relationship
33	NR	NR	NR/CT	NR/CT	Yes	NR	No
34	NR	NR	NR/CT	NR/CT	Yes	Yes	No
35	Patients with an IOP of greater than or equal to 24 mm Hg in at least one eye (the same eye) at hours 0 and 2 were then randomly assigned, according to a computer-generated allocation schedule.	NR	Yes	NR/CT	Yes	NR	Yes

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
36	Patients randomly (according to a computer-generated allocation schedule) received one of the following masked treatment regimens for 3 months	All study medication was packaged in identical bottles by allocation number	Yes	NR/CT	Yes	Yes	Yes
37	The patients were allocated to the treatment groups according to a computer-generated list prepared by Pharmacia & Upjohn (Uppsala, Sweden)	NR	NR/CT	NR/CT	Yes	Yes	Yes
38	Randomization schedules were generated for each site using SAS (Version 6.08; SAS Institute, Cary, NC) procedure, PROC PLAN.	Patients were assigned sequentially to masked treatment according to a randomization schedule generated by the study sponsor (Allergan Inc). Each bottle of test medication was coded with a shipment number and labeled with a study number. Each time a bottle was dispensed to a patient, the tearoff portion of the label was attached to the patient's case-report form.	Yes	Yes	No	Yes	Reported none of the authors has any financial relationship
39	NR	NR	Yes	NR/CT	Yes	Yes	Yes
40	Computer-generated randomization code	All clinical supplies were labeled based on a computer-generated randomization code and dispensed in numerical sequence to patients at each investigational site.	Yes	NR/CT	Yes	Yes	Yes
41	NR	NR	NR/CT	NR/CT	Yes	Yes	No
42	NR	NR	NR/CT	NR/CT	Yes	NR	No
43	NR	NR	No	No	Yes	Yes	No
44	NR	NR	No	No	No	Yes	No
45	NR	NR	Yes	NR/CT	Yes	Yes	No
46	The randomization was stratified for centre and performed in blocks of six consecutive patients within each centre.	NR	NR/CT	NR/CT	Yes	NR	Reported none of the authors has any financial relationship
47	NR	NR	Yes	NR/CT	Yes	Yes	Reported none of the authors has

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
							any financial relationship
48	Patients were randomized using computer-generated numbers (0= receive latanoprost in the right eye and unoproste in the left eye, 1= receive unoprostone in the right eye and latanoprost in the left eye).	NR	No	Yes	No	NR	No
49	Patients were dispensed study medication that was packaged in identical bottles according to a computer-generated randomization list provided by Pharmacia & Upjohn, Sweden.	Patients were dispensed study medication that was packaged in identical bottles according to a computer-generated randomization list provided by Pharmacia & Upjohn, Sweden. Disclosure envelopes were kept in a locked cabinet at the study site. In the event of an emergency requiring identification of the masked treatment, the envelope could be opened. No enveloped were opened during the trial.	Yes	NR/CT	Yes	Yes	No
50	On the baseline day, the patients were randomized (by block randomisation) to two parallel study groups.	NR	No	Yes	No	No	Yes
51	The method used for preparing the allocation schedule was based on blocked randomization in blocks of eight allocation numbers.	The method used for preparing the allocation schedule was based on blocked randomization, in blocks of eight allocation numbers. During the study the assignment codes were kept in sealed envelopes in a locked space at the study location, and were delivered with unbroken seals on completion of trial.	Yes	Yes	No	Yes	No
52	Patients who met all study eligibility criteria were assigned a patient number	Medication description was concealed from the patient, investigator, and	Yes	Yes	No	Yes	Reported none of the authors has

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	and sequentially randomly assigned to one in an equal (1:1:1) ratio by means of a computer generated randomization schedule prepared by the Alcon Biostatistics Department. Randomization was stratified by site to ensure balanced treatment within each site.	clinical study staff. Masked medication was packaged in identical Drop-Tainers and provided to the investigators along with sealed envelopes containing the medication description for each patient.					any financial relationship
53	Patients were allocated to 1 of 3 treatment groups according to a computer-generated randomization code list. A single block randomization list was generated for the entire study.	Drug was issued according to patient numbers that were given in consecutive order at baseline. Medications were provided in identical coded bottles. Study medication was shipped to the individual study sites in sets such that each set was a multiple of the block size used in generating the randomization.	NR/CT	NR/CT	Yes	Yes	No
54	Randomization codes were generated and medical supplies were prepared by Pharmacia clinical Supply Logistics (Kalamazoo, Michigan, USA).	Each center received prepackaged clinical supplies with patients numbers, which were allocated sequentially.	No	NR/CT	No	Yes	Yes
55	NR	NR	NR/CT	NR/CT	Yes	Yes	No
56	Computer-generated randomization schedule	Medication identity was concealed in individually sealed envelopes stored at the study sites.	Yes	NR/CT	Yes	Yes	No
57	NR	NR	Yes	NR/CT	Yes	Yes	Reported none of the authors has any financial relationship
58	The randomization code was maintained at the central coordination center.	NR	Yes	NR/CT	Yes	Yes	No
59	NR	NR	No	NR/CT	Yes	Yes	Yes
60	The central Registration System controller randomly allocated patients into these two groups by assigning patients into blocks in sequence of registration to the center, which was determined by the investigators. Each block consisted of six patients for a set of treatments		NR/CT	NR/CT	NR/CT	NR	No

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	(three latanoprost, three unoprostone) where the order of treatments within the block had been randomized.						
61	NR	NR	NR/CT	NR/CT	Yes	Yes	Yes
62	NR	NR	Yes	Yes	Yes	Yes	No
63	NR	NR	No	No	No	NR	Reported none of the authors has any financial relationship
64	The chief pharmacist at Moorfields Eye Hospital, who had no other direct involvement with the trial, randomised one of the patients in each pair to treatment with either betaxolol drops or placebo drops. The fellow member of the pair was then allocated to the alternative treatment arm. Randomisation was carried out by means of randomisation tables.	Each patient was assigned drops coded either A, B, C or D that corresponded to their trial number.	Yes	Yes	No	Yes	Reported none of the authors has any financial relationship
65	NR	NR	No	Yes	No	Yes	No
66	NR	NR	No	Yes	Yes	NR	No
67	NR	NR	NR/CT	NR/CT	No	NR	No
68	At the baseline visit (day 0), eligible patients were randomly assigned, using a computer-generated randomization code list, to 1 of 2 treatment groups.	NR	No	No	No	NR	No
69	The randomization schedule was generated using a SAS (version 6.12) program and stored in a locked cabinet until the study was completed.		No	No	Yes	Yes	Yes
70	A computer-generated list of random assignments decided which treatment patients would receive.	The list was sealed and could be opened only after the completion of the study protocol or after any serious adverse event occurred.	NR/CT	NR/CT	Yes	NR	No
71	Computer-generated	Assign patient numbers sequetially; opaque syndiotactic polypropylene oval bottles.	Yes	NR/CT	Yes	Yes	No
72	Randomization was performed by centralized allocation by Voice Processing plus, inc., via an interactive phone registration system.		NR/CT	Yes	No	Yes	Yes
73	Randomization was obtained at the	Bottles of drug and placebo were given to	Yes	Yes	No	Yes	No

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	Coordinating Center. Each clinical center had its own randomization list that was stratified for pseudoexfoliation, pigmentary dispersion syndrome, and diabetes mellitus.	each center according to the randomization list. Patients were given a bottle marked with a code label. The allocation code was secured at the Coordinating Center at the office of the Project Coordinator.					
74	NR	NR	NR/CT	NR/CT	Yes	NR	No
75	NR	NR	NR/CT	Yes	Yes	NR	No
76	NR	NR	NR/CT	Yes	No	No	Reported none of the authors has any financial relationship
77	Randomization was achieved by asking the participants to choose any numbers between 1 to 10; even and odd numbers were assigned to bimatoprost (n=41) and travoprost (n=49) groups respectively.	NR	NR/CT	Yes	No	NR	No
78	Patients were randomized in a ratio of 2:1:1 to the FC (q.d., mornings), BIM 0.03% (q.d., evenings), or TIM 0.5% (b.i.d.) using a computer-generated randomization llist (PROC PLAN, SAS Version 8.2, Cary, NC).	NR	NR/CT	NR/CT	Yes	Yes	Yes
79	NR	White plastic dropper bottles, each labeled with a unique patient number.	Yes	NR/CT	Yes	Yes	Yes
80	NR	NR	Yes	NR/CT	Yes	Yes	Yes
81	A list of random numbers	Standard containers were used and they were concealed with a study specific cover and all kept in a standard opaque black medicine vial	Yes	NR/CT	Yes	NR	No
82	Randomization lists were used to preallocate treatment kits to each patient number by personnel not involved with the management of the study.		No	No	No	Yes	No
83	Allocation was based on computer-generated random numbers and was concealed by using sequentially numbered opaque sealed envelopes.		NR/CT	NR/CT	No	NR	Reported none of the authors has

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
							any financial relationship
84	Fifty opaque envelopes containing random numbers (drugs in code forms), generated with the help of table of randomization, were prepared in advance by an investigator who was not related to the study. Whenever, a study participant was found to be eligible, an envelope was opened by another person in the department and the patient was put on the allocation plan as found inside the envelope in coded form.		Yes	No	No	NR	No
85	A randomization schedule, balanced for ethnicity and drug assignment, was produced for each participating site by the biostatistician.	NR	No	Yes	No	No	No
86	The randomization sequence was computer-generated.	The randomization code was retained by the study sponsor and made available to the investigators only after the study had ended.	Yes	No	Yes	Yes	Yes
87	Randomization codes were generated by Pfizer according to standard operating procedures and were kept at Global Pharmacy Operations (New York, New York).	NR	NR/CT	Yes	No	Yes	Yes
88	The randomisation code was computed-generated	NR	No	NR/CT	Yes	Yes	Yes
89	NR	NR	NR/CT	NR/CT	No	No	Reported none of the authors has any financial relationship
90	Patients were randomized using Proc Plan, SAS for Windows (version 8.; SAS Institute Inc., Cary, NC)	NR	Yes	NR/CT	Yes	Yes	Yes
91	Patients were assigned to treatment using a computer generated randomized allocation schedule prepared by a statistician at Merck	Personnel at each study site used an interactive voice response system to determine which masked treatment containers should be given to which patient.	Yes	Yes	No	Yes	Yes
92	NR	NR	No	NR/CT	Yes	Yes	Yes
93	NR	NR	No	No	No	NR	Yes
94	A list of sequential patient numbers was generated	A list of sequential patient numbers was generated	Yes	NR/CT	No	Yes	Yes

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	by a member of the sponsor programming group (SAS Institute) not involved in the conduct of the study.	by a member of the sponsor programming group (SAS Institute) not involved in the conduct of the study. Study medications were provided in identical bottles. Staff members who provided the study medications to patients did not discuss those medications with other site personnel.					
95	NR	NR	Yes	NR/CT	Yes	Yes	Yes
96	Computer-generated random table numbers with an equal allocation of 35 patients into each study group	NR	Yes	Yes	Yes	NR	No
97	List of random numbers	NR	NR	Yes	No	Yes	Yes
98	Randomly allocated participants (1:1) in permuted blocks of varying sizes (block sizes range from 4 to 10), stratified by participating center, to either latanoprost 0·005% or latanoprost vehicle eye drops (placebo) alone once a day in both eyes.	The randomisation schedule, drawn up by the research and development statisticians at Moorfields Eye Hospital on a randomisation website, was sent to the Pharmaceutical Manufacturing Unit, which labelled the bottles with the participant study identification number only.	Yes	Yes	Yes	Yes	Yes
99	NR	Because the active control bottle (Xalatan) was visibly different than the investigational bottles, a designee at each study site, other than the investigator, was responsible for the dispensing study treat-ment at Visit 3, instructing patients on proper installation of study medication, and retrieval of materials at the end of the study. Attempts were made to mask the subjects by removing commercial labelling, replacing with	No	No	Yes	Yes	Yes

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
		identical investigational labels and packaging in identical kit boxes.					
100	Computer-generated	Subjects received masked kits for 2 weeks of study medication via an interactive voice response system using a computer-generated random allocation schedule.	Yes	NR/CT	Yes	Yes	No
101	Computer-generated	A statistician created a randomization schedule prior to any study enrolment not otherwise involved in the study using SAS (SAS Institute, Cary, North Carolina, USA; Version 9.2). Allocation of study drug was completed through the use of IRT (Interactive Response Technology), which determined which kit to assign to each subject. Adults with OAG or OHT from 46 clinical sites (United States and European Union) were randomized 2:1 to LBN instilled once daily (QD) in the evening and vehicle in the morning or timolol instilled twice a day (BID) for 3 months.	Yes	Yes	Yes	Yes	Yes
102	Enrolled patients were randomly divided into two groups by block randomization	NR	No	No	No	NR	No
103	Study drug was dispensed via an Interactive Response Technology system. Randomization schedules were created by a designated unmasked statistician using SAS Version 9.2 (SAS Institute, Inc., Cary, NC).	For masking purposes, each treatment was labeled with identical investigational labels and packaged in identical kit boxes. Eligible subjects were randomized 2:1 to receive LBN 0.024% qPM and vehicle every morning or timolol 0.5% BID for 3 months.	Yes	NR/CT	Yes	Yes	No
104	Included patients were randomly assigned to	NR	No	No	No	NR	No

Ref.	Random sequence generation	Allocation concealment	Masking of participants	Masking of IOP assessor	Reported single, double or triple masking, but did not specify the role of person who was masked	Funded by pharmaceutical industry	Reported financial relationship
	receive one of the four PGAs: bimatoprost 0.01% (with BAK 0.02%), latanoprost 0.005% (with BAK 0.02%), travoprost 0.004% (with 0.001% polyquad), and tafluprost 0.0015% (preservative-free).						
105	Randomized in permuted blocks of size 2 by the study drug coordinator at a ratio of 1:1. Managed and retained independently until study completion.	No	No	No	No	Yes	No
106	Lottery method	NR	No	No	No	No	No

Appendix F. Mean difference (MD) in Intraocular Pressure at 3 months (95% Credible Interval [95% CrI]).

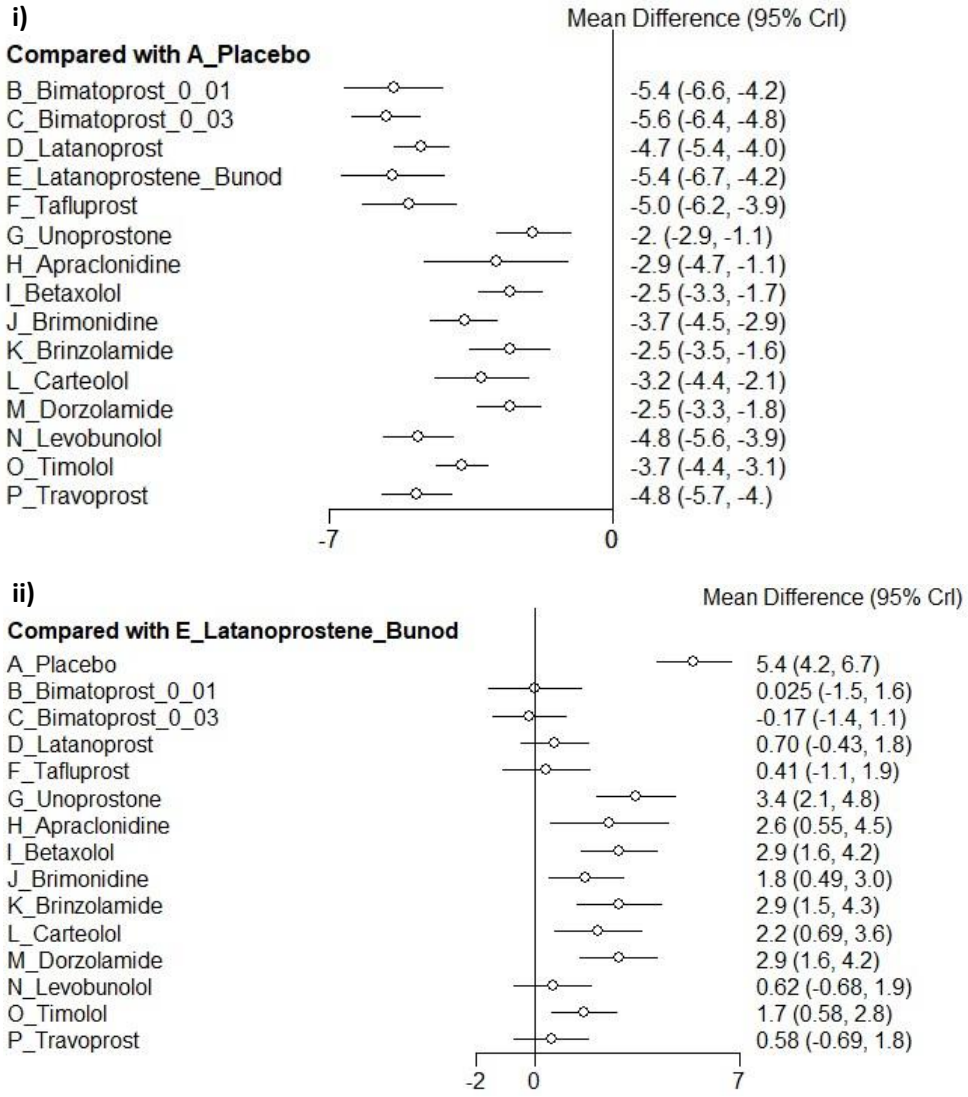
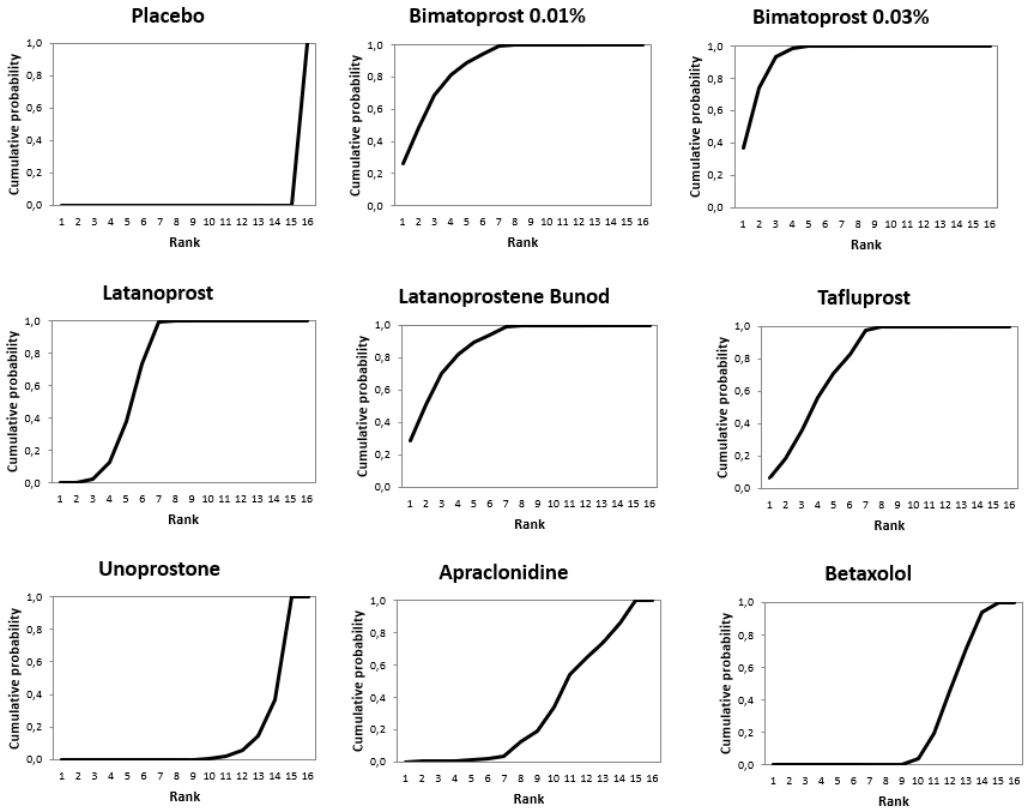


Figure 1. MD with a 95% CrI including 0 (crossing 0 in the forest plot) are not significant. PGAs = B, C, D, E, F and G
i) All treatments compared to placebo, MD > 0 favors placebo. ii) All treatments compared to LBN, MD > 0 favors placebo.

Appendix G. Cumulative Ranking Probabilities Plot

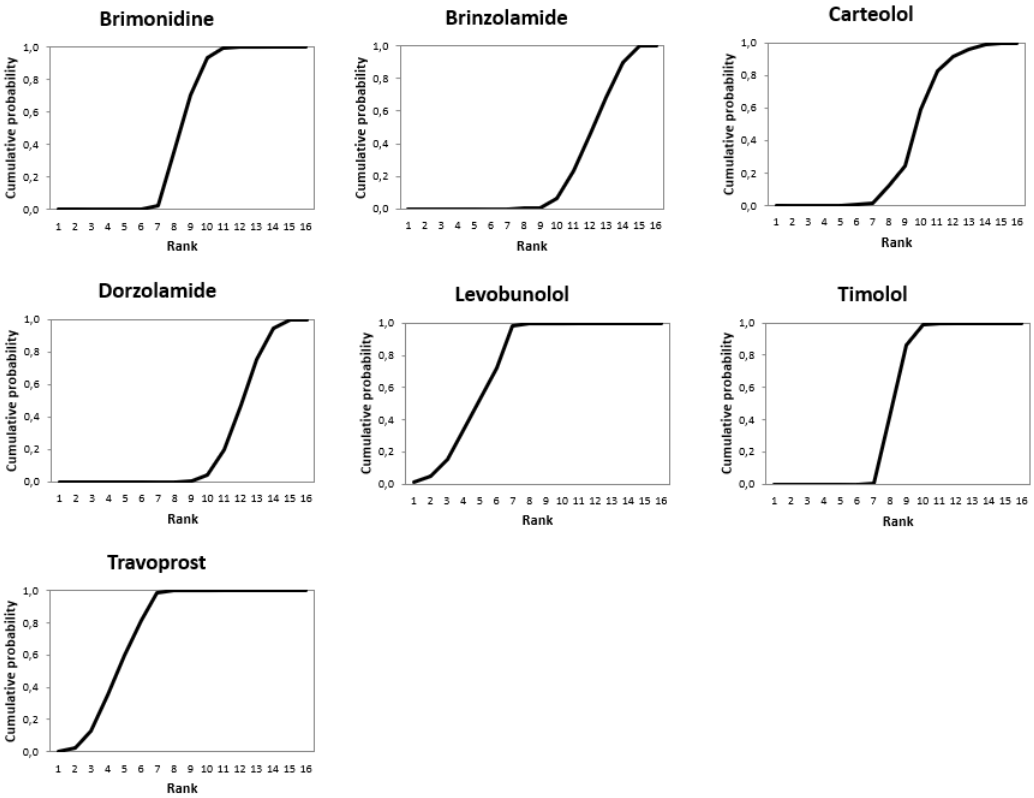
The surface under the cumulative ranking (SUCRA) probabilities for each treatment represents the average proportion of treatments worse than this treatment. Higher is the SUCRA (bigger surface under the cumulative ranking curve), better is the rank of this treatment.



SUCRA:

Placebo	0.0%
Bimatoprost 0.01%	87.2%
Bimatoprost 0.03%	93.5%
Latanoprost	68.4%
Latanoprostene Bunod	87.6%
Tafluprost	77.9%
Unoprostone	10.6%
Apraclonidine	30.1%
Betaxolol	22.2%

PGA



SUCRA:

Brimonidine	46.7%
Brinzolamide	22.3%
Carteolol	37.8%
Dorzolamide	22.7%
Levobunolol	71.8%
Timolol	48.5%
Travoprost	72.7%

PGA

Appendix H. Studies Identified as Possibly Causing Heterogeneity

As mentioned in the Cochrane Handbook[1], although a random effect model was used for the NMA, which assumes heterogeneity between studies, this does not mean that the problem of heterogeneity is eliminated. To quantify inconsistency across studies, the parameter "I^2" has been developed. I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Cochrane Handbook developed a rough guide for interpretation of I^2: less than 40% might not be important, 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity and 75% to 100% represented considerable heterogeneity.

All comparisons with I^2 higher than 65% were investigated. Based on Cochrane Handbook for a systematic review of intervention, "*If results of smaller studies are systematically different from results of larger ones, which can happen as a result of publication bias or within-study bias in smaller studies, then a random-effect meta-analysis will exacerbate the effects of the bias. In this situation, it may be wise to perform a sensitivity analysis in which small studies are excluded*." Therefore, if the investigation did not find any reason for the heterogeneity and smaller trials differed from larger ones, I^2 was tested without trials with the smallest cohort.

Comparison with I^2 higher than 65%	Reference* number of studies identified as possibly causing heterogeneity and explications	I^2 with all studies	I^2 without studies identified
Placebo vs. dorzolamide	Study 73: Baseline criteria for the IOP were stricter compared to other studies	76%	0%
Bimatoprost 0.01% vs travoprost	Study 104 (small cohorts compared to the other)	80%	NA
Bimatoprost 0.03% vs travoprost	Study 82: small cohort compared to others and MR completely different from the others	86%	29%
Latanoprost vs. travoprost	Study 82: small cohort compared to others and MR completely different from the others	87%	0%
Apraclonidine vs. timolol	Study 19: small cohort compared to the other	89%	NA
Betaxolol vs. levobunolol	Study 84: small cohort compared to the other + MR and SD very big comparatively to other trials	84%	NA
Betaxolol vs. timolol	Study 84: small cohort compared to the other + MR and SD very big comparatively to other trials	67%	0%
Brimonidine vs. latanoprost	Studies 47; 58; 63: small cohort compared to others	78%	16%
Timolol vs. latanoprost	Studies 26; 37; 46; 69; 96; 102: small cohort compared to others	76%	45%
Timolol vs. unoprostone	Study 18: small cohort compared to the other	87%	NA

MR: Mean reduction of IOP after 3 months
SD: Standard deviation of the MR
* See Reference in **Appendix B**.

[1] The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. http://handbook-5-1.cochrane.org/. Published 2011. Accessed August 5, 2018.

Appendix I. Sensitivity Analyses

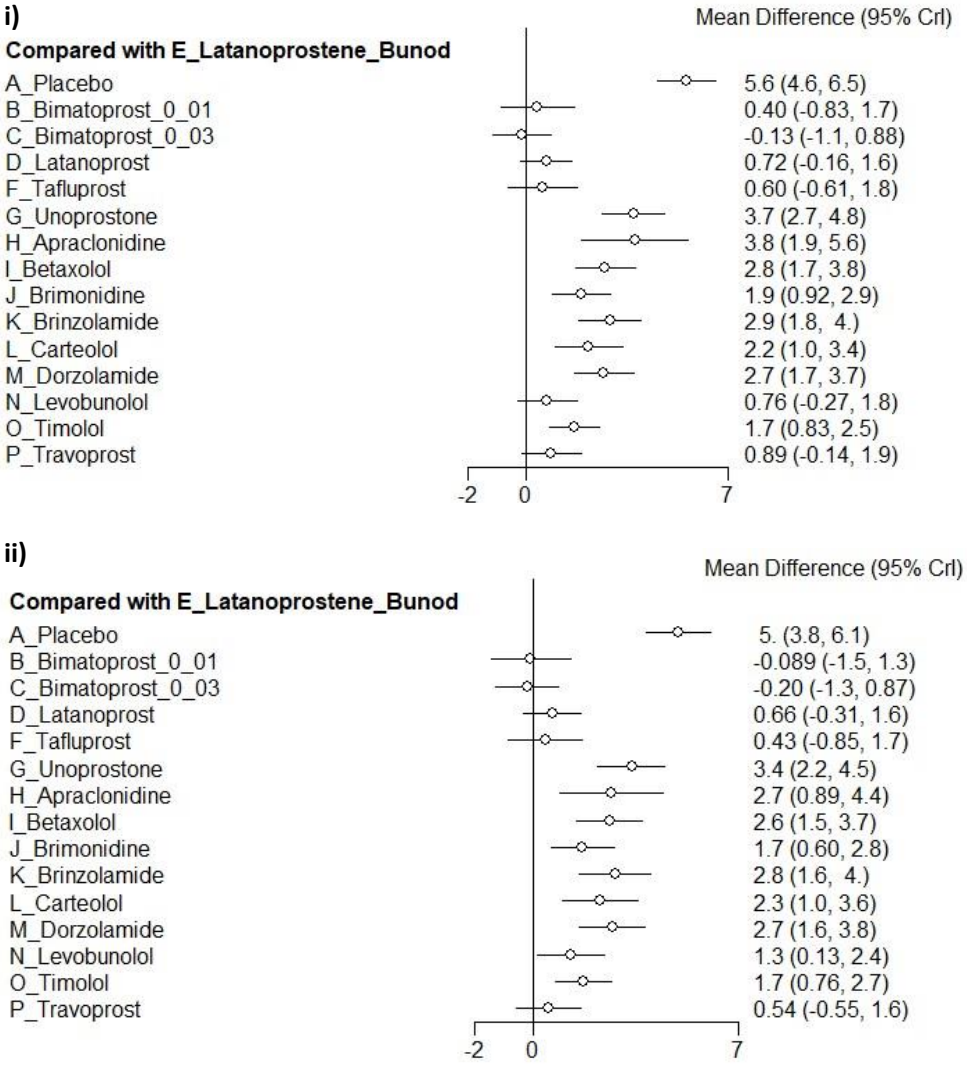
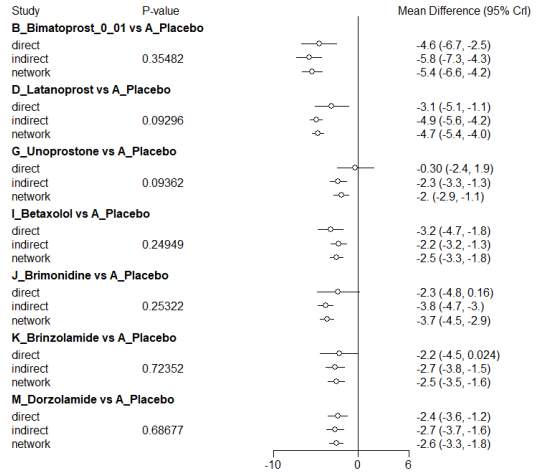
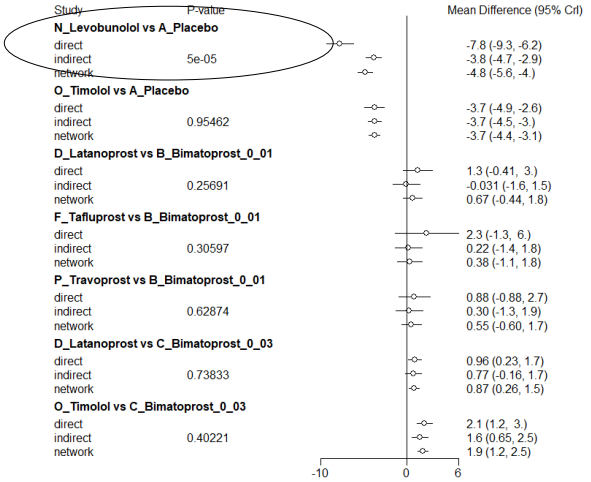


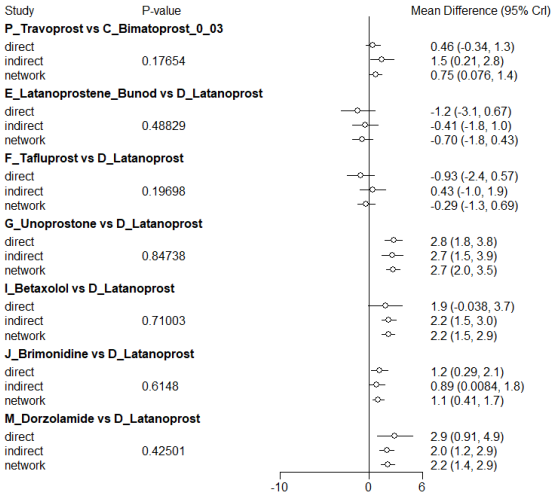
Figure 2. MD > 0 favors LBN. MD with a 95% CrI including 0 (crossing 0 in the forest plot) are not significant. PGAs = B, C, D, E, F and G
i) All Treatments Compared with Latanoprostene Bunod (without trials identified as possibly causing heterogeneity). ii) All Treatments Compared with Latanoprostene Bunod (without studies identified as causing inconsistency)

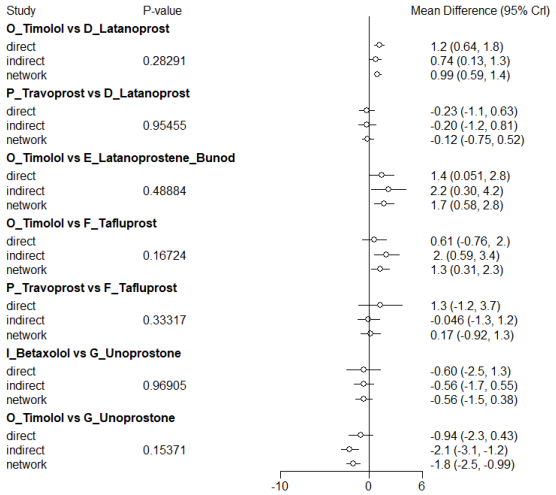
Appendix J. Inconsistency (Node-Splitting Approach Results)

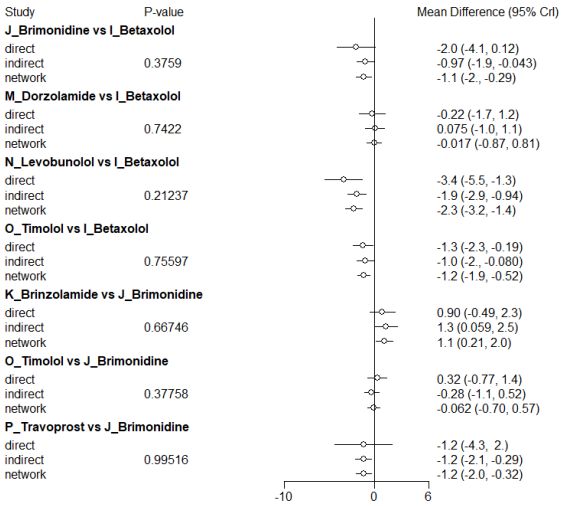
Inconsistent nodes are circled (p-value < 0.05)

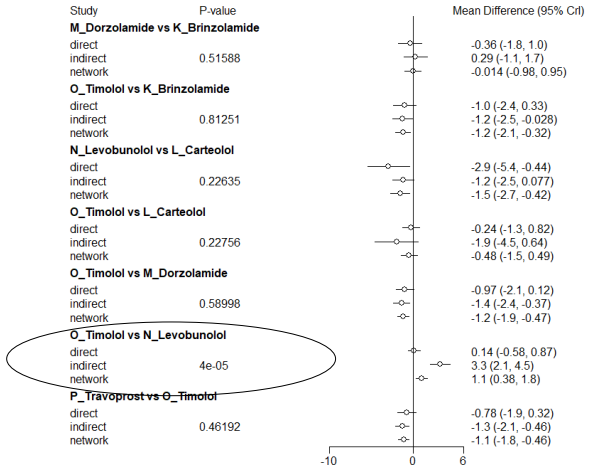









Study
P-value
Mean Difference (95% CrI)
J_Brimonidine vs I_Betaxolol
direct
indirect 0.3759
network
-2.0 (-4.1, 0.12)
-0.97 (-1.9, -0.043)
-1.1 (-2., -0.29)
M_Dorzolamide vs I_Betaxolol
direct
indirect 0.7422
network
-0.22 (-1.7, 1.2)
0.075 (-1.0, 1.1)
-0.017 (-0.87, 0.81)
N_Levobunolol vs I_Betaxolol
direct
indirect 0.21237
network
-3.4 (-5.5, -1.3)
-1.9 (-2.9, -0.94)
-2.3 (-3.2, -1.4)
O_Timolol vs I_Betaxolol
direct
indirect 0.75597
network
-1.3 (-2.3, -0.19)
-1.0 (-2., -0.080)
-1.2 (-1.9, -0.52)
K_Brinzolamide vs J_Brimonidine
direct
indirect 0.66746
network
0.90 (-0.49, 2.3)
1.3 (0.059, 2.5)
1.1 (0.21, 2.0)
O_Timolol vs J_Brimonidine
direct
indirect 0.37758
network
0.32 (-0.77, 1.4)
-0.28 (-1.1, 0.52)
-0.062 (-0.70, 0.57)
P_Travoprost vs J_Brimonidine
direct
indirect 0.99516
network
-1.2 (-4.3, 2.)
-1.2 (-2.1, -0.29)
-1.2 (-2.0, -0.32)
-10
0
6


Study
P-value
Mean Difference (95% CrI)
M_Dorzolamide vs K_Brinzolamide
direct
indirect 0.51588
network
-0.36 (-1.8, 1.0)
0.29 (-1.1, 1.7)
-0.014 (-0.98, 0.95)
O_Timolol vs K_Brinzolamide
direct
indirect 0.81251
network
-1.0 (-2.4, 0.33)
-1.2 (-2.5, -0.028)
-1.2 (-2.1, -0.32)
N_Levobunolol vs L_Carteolol
direct
indirect 0.22635
network
-2.9 (-5.4, -0.44)
-1.2 (-2.5, 0.077)
-1.5 (-2.7, -0.42)
O_Timolol vs L_Carteolol
direct
indirect 0.22756
network
-0.24 (-1.3, 0.82)
-1.9 (-4.5, 0.64)
-0.48 (-1.5, 0.49)
O_Timolol vs M_Dorzolamide
direct
indirect 0.58998
network
-0.97 (-2.1, 0.12)
-1.4 (-2.4, -0.37)
-1.2 (-1.9, -0.47)
O_Timolol vs N_Levobunolol
direct
indirect 4e-05
network
0.14 (-0.58, 0.87)
3.3 (2.1, 4.5)
1.1 (0.38, 1.8)
P_Travoprost vs O_Timolol
direct
indirect 0.46192
network
-0.78 (-1.9, 0.32)
-1.3 (-2.1, -0.46)
-1.1 (-1.8, -0.46)
-10
0
6

Appendix K. Supplementary Analyses

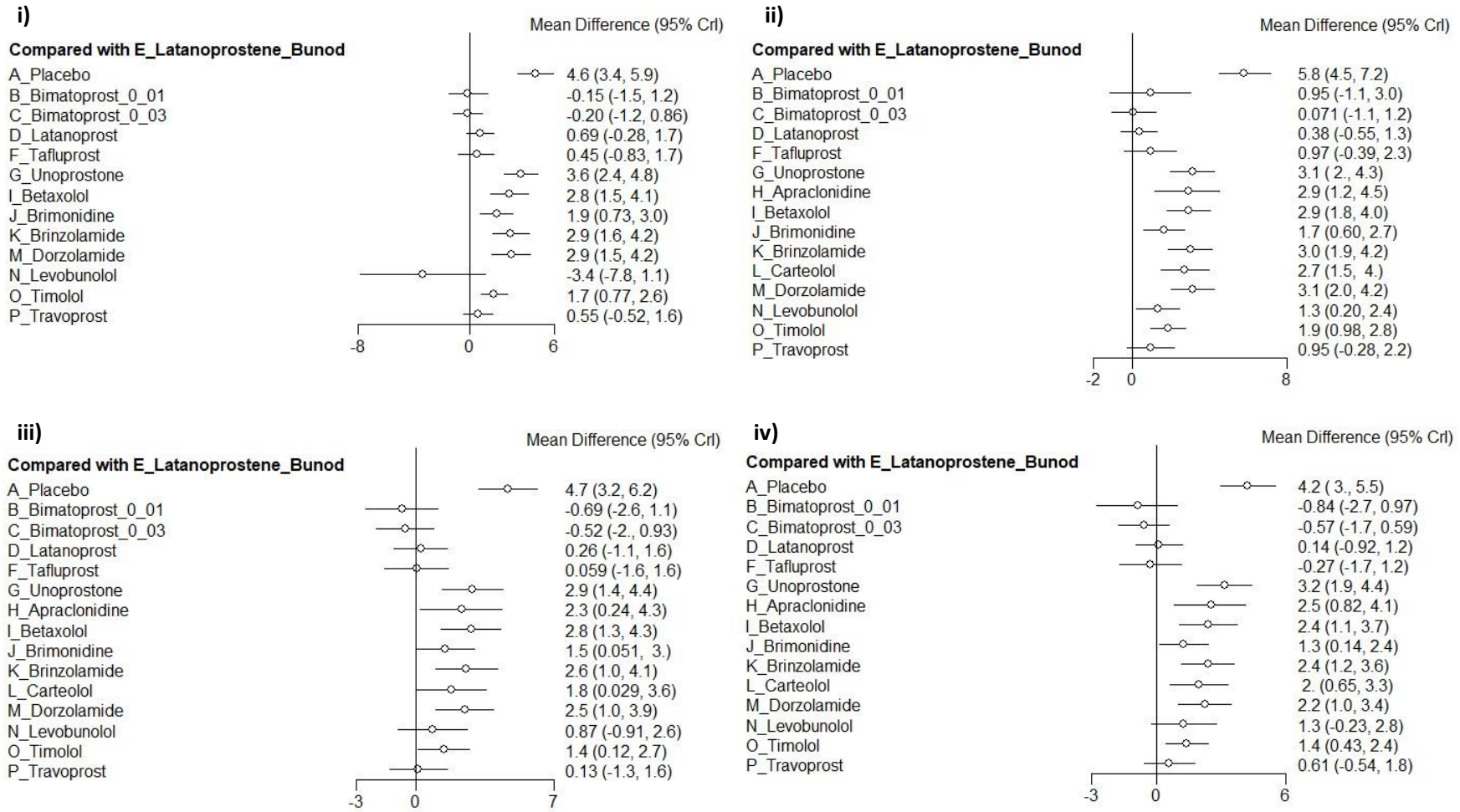


Figure 3. MD > 0 favors LBN. MD with a 95% CrI including 0 (crossing 0 in the forest plot) are not significant. PGAs = B, C, D, E, F and G i) Studies published from 2000 onward. ii) Studies with a washout period before randomization. iii) Studies that excluded prior glaucoma and cataract surgery. iv) Studies that excluded prior glaucoma laser.
If the treatment was included in the trial, LBN was still significantly more effective than placebo, unoprostone (PGA), apraclonidine, betaxolol, brimonidine, brinzolamide, carteolol, dorzolamide, and timolol for all these analyses. When compared with other PGAs, LBN was numerically more efficient than all PGAs in ii), numerically more efficient than latanoprost and tafluoprost in i) and iii) and numerically more efficient than latanoprost in iv).

Appendix L. Brooks-Gelman-Rubin Statistic

To verify the convergence of the model, the Brooks-Gelman-Rubin plot was obtained. Specifically, Gelman and Rubin (1992) proposed a general approach to monitoring convergence of MCMC output in which two or more parallel chains are run with starting values that are over dispersed relative to the posterior distribution. The convergence is assessed by comparing the estimated between-chains and within-chain variances for each model parameter. Large differences between these variances indicate nonconvergence. The method calculates a "potential scale reduction factor" that is the ratio of both variances. Approximate convergence is diagnosed when the factor of all chains is close to 1.[2] Brooks and Gelman (1998) generalized this method for observing the convergence of simulations by comparing between and within variance of multiple chains, in order to obtain a family of tests for convergence. They estimated a "shrink factor" at several points[3]. The Brooks-Gelman-Rubin plot shows the evolution of the "shrink factor" as the number of iterations increases. A "shrink factor" tending to 1 means convergence.[2]

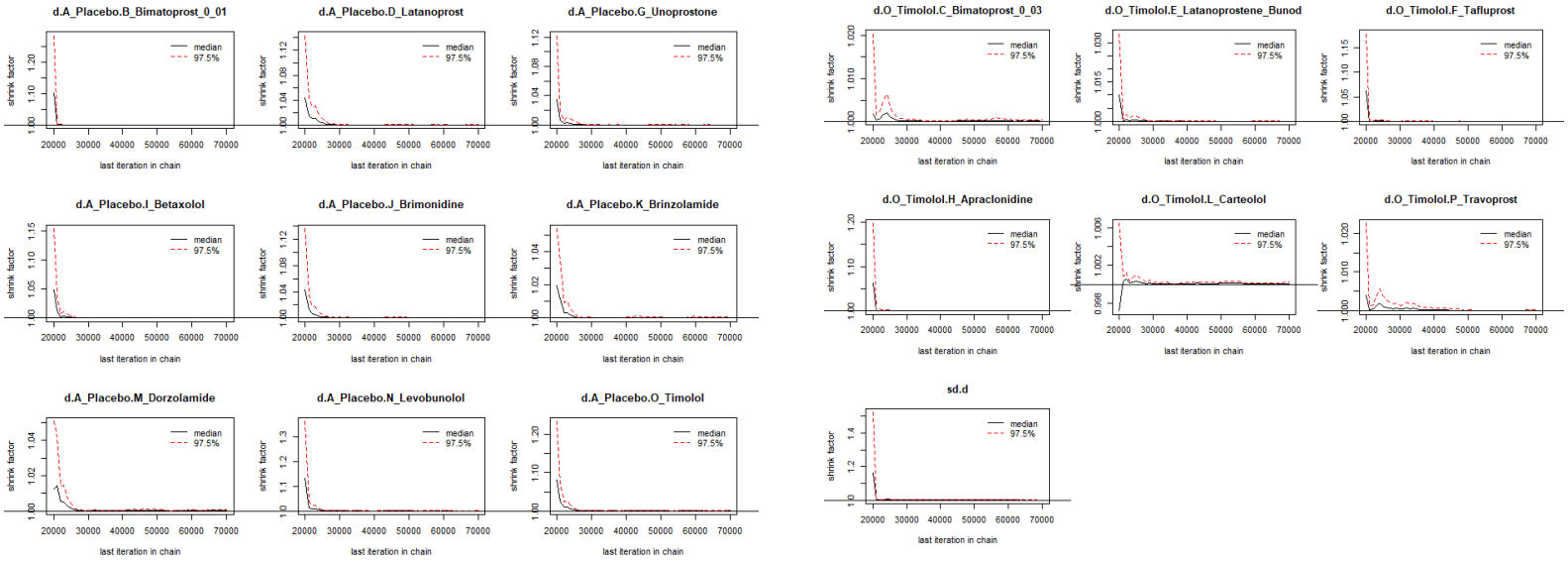


Figure 4. Brooks-Gelman-Rubin Plot. The plot illustrates that the NMA model converges after 20,000 burn-in.

[2] Gert van Valkenhoef JK. Package 'gemtc'. https://cran.r-project.org/web/packages/gemtc/gemtc.pdf. Published 2016. Accessed August 1, 2018.
[3] Gelman SPBA. General Methods for Monitoring Convergence of Iterative Simulations. *Journal of Computational and Graphical Statistics.* 1998.