

Comparative Effectiveness of First-Line Medications for Primary Open-Angle Glaucoma

A Systematic Review and Network Meta-analysis

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Topic: Primary open-angle glaucoma (POAG) is a highly prevalent condition worldwide and the most common cause of irreversible sight loss. The objective is to assess the comparative effectiveness of first-line medical treatments in patients with POAG or ocular hypertension through a systematic review and network meta-analysis, and to provide relative rankings of these treatments.

Clinical Relevance: Treatment for POAG currently relies completely on lowering the intraocular pressure (IOP). Although topical drops, lasers, and surgeries can be considered in the initial treatment of glaucoma, most patients elect to start treatment with eye drops.

Methods: We included randomized controlled trials (RCTs) that compared a single active topical medication with no treatment/placebo or another single topical medication. We searched CENTRAL, MEDLINE, EMBASE, and the Food and Drug Administration's website. Two individuals independently assessed trial eligibility, abstracted data, and assessed the risk of bias. We performed Bayesian network meta-analyses.

Results: We included 114 RCTs with data from 20 275 participants. The overall risk of bias of the included trials is mixed. The mean reductions (95% credible intervals) in IOP in millimeters of mercury at 3 months ordered from the most to least effective drugs were as follows: bimatoprost 5.61 (4.94; 6.29), latanoprost 4.85 (4.24; 5.46), travoprost 4.83 (4.12; 5.54), levobunolol 4.51 (3.85; 5.24), tafluprost 4.37 (2.94; 5.83), timolol 3.70 (3.16; 4.24), brimonidine 3.59 (2.89; 4.29), carteolol 3.44 (2.42; 4.46), levobetaxolol 2.56 (1.52; 3.62), apraclonidine 2.52 (0.94; 4.11), dorzolamide 2.49 (1.85; 3.13), brinzolamide 2.42 (1.62; 3.23), betaxolol 2.24 (1.59; 2.88), and unoprostone 1.91 (1.15; 2.67).

Conclusions: All active first-line drugs are effective compared with placebo in reducing IOP at 3 months. Bimatoprost, latanoprost, and travoprost are among the most efficacious drugs, although the within-class differences were small and may not be clinically meaningful. All factors, including adverse effects, patient preferences, and cost, should be considered in selecting a drug for a given patient. *Ophthalmology* 2016;123:129-140 © 2016 by the American Academy of Ophthalmology.



Supplemental material is available at www.aaojournal.org.

Glaucoma is an acquired disease of the optic nerve with characteristic optic nerve head changes and associated visual field defects.¹⁻⁴ It is the second leading cause of blindness worldwide.⁵ Approximately three-quarters of all glaucoma occurs in individuals with open angles, and open-angle glaucoma is the most common form of glaucoma in nearly all countries.⁵ Although some forms of open-angle glaucoma occur secondary to other phenomena, the majority is idiopathic and therefore is referred to as primary open-angle glaucoma (POAG). Data based on the US population suggest that POAG affects 2 to 3 million Americans aged 40 years or older.⁶⁻⁸ The risk of developing POAG increases with increased intraocular pressure (IOP), age, a family history of glaucoma, use of steroids, and having ancestry of

the West African diaspora (e.g., African Americans or African Caribbeans).¹⁻⁸ Because IOP is the only known modifiable risk factor, treatment for POAG has focused on lowering IOP, which is proven to slow disease progression and decrease the rate of visual field loss, and may protect against loss of visual function and blindness.¹⁻⁴

Medical treatment (e.g., topical eye drops) is considered a reasonable first line of therapy in published guidelines for the treatment of POAG.^{1,2} Clinicians usually prescribe a single medication chosen from 1 of 4 drug classes: beta-blockers, carbonic anhydrase inhibitors, alpha-2 adrenergic agonists, and prostaglandin analogs. Among them, prostaglandin analogs have a reputation for lowering IOP more than other classes.¹⁻⁴ However, existing practice guidelines

and systematic reviews supporting guideline recommendations have not yet addressed the comparative effectiveness and safety of *any* 2 drugs (or *any* 2 classes of drugs) or provided a ranked order of the drugs (or classes of drugs) in terms of effectiveness and safety.^{1–4} This is because conventional randomized controlled trials (RCTs) and quantitative synthesis of such trials (i.e., meta-analysis) typically focus on 1-at-a-time, pairwise comparisons (e.g., active drug vs. placebo). A direct comparison between 2 active drugs, one doctors may be most interested in, is often lacking. Naïve methods of making such comparisons are common but often subject to bias.^{9,10}

Network meta-analysis, an extension to standard pairwise meta-analysis, enables simultaneous “all-way” comparisons of multiple healthcare interventions for a condition through combining direct evidence from individual trials and indirect evidence gleaned using statistical techniques across trials.^{10–14} Treatment effects estimated from network meta-analyses usually have improved precision compared with pairwise meta-analyses, and inferences can be drawn even for comparisons not directly evaluated in individual trials.^{10–14} Network meta-analysis also can provide relative rankings for multiple competing interventions to inform decision-making.^{15,16} The objective of this article is to assess the comparative effectiveness of first-line medical treatments for lowering IOP in patients with POAG or ocular hypertension through a systematic review and network meta-analysis and to provide relative rankings of these treatments.

Methods

We followed a prospective protocol in performing this systematic review. The reporting conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for network meta-analysis (<http://www.equator-network.org/reporting-guidelines/prisma/>; accessed August 19, 2015).

Eligibility Criteria for Considering Studies for This Review

Trials were eligible for our network meta-analysis if they were reported to be randomized parallel group trials (i.e., crossover trials were not eligible) and 60% or more of randomized participants had a diagnosis of POAG or ocular hypertension, as defined by the trialists. Trials were eligible if they evaluated first-line topical medical interventions from 1 of 4 drug classes—beta-blockers, carbonic anhydrase inhibitors, alpha-2 adrenergic agonists, and prostaglandin analogs—to reduce IOP or progression of visual field damage, and compared a single active treatment with no treatment/placebo or another single active topical medical treatment.

We excluded trials enrolling fewer than 10 participants in each group. We also excluded trials evaluating combination medical treatments because they are generally prescribed for patients who have failed a single first-line treatment. We required no maximum or minimum duration of treatment; however, participants had to be followed for an outcome for at least 28 days after randomization.

We prespecified difference in mean IOP measured by any method at 3 months in continuous millimeters of mercury (mmHg) unit as our primary outcome. If more than 1 IOP measure was available, we used the following order of priority in selecting IOP data for analysis: mean diurnal IOP, 24-hour mean IOP, peak IOP,

morning IOP, and trough IOP. When a trial’s duration was shorter or longer than 3 months, we used the IOP that was measured at the follow-up time point closest to 3 months. We prespecified visual field as our secondary outcome. Because visual field tends to be measured and aggregated differently across trials, we included visual field outcome as defined and reported in individual trials at any follow-up time point. Only those trials providing sufficient information (i.e., measures of treatment effect and the associated precision) were included in our statistical analysis.

Search Methods for Identifying Studies

We searched the Cochrane Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, and EMBASE on November 17, 2009, and updated the search on March 11, 2014. We did not impose any date or language restrictions in the electronic searches. We searched the US Food and Drug Administration’s website (<https://www.accessdata.fda.gov/scripts/cder/drugsatfda/>) in April 2014 for drugs potentially eligible for our review. The full search strategies are described in Appendix 1 (available at www.aaojournal.org).

Study Selection

Two individuals independently assessed the titles and abstracts identified by the searches for potential eligibility, and the full-text articles were retrieved for those that appeared relevant. Two individuals independently assessed full-text articles for final eligibility. Non-English language reports were assessed by a single individual who was a native or fluent speaker of the language. We resolved discrepancies in classification of eligibility of the full-text article through discussion or consultation with a third person.

Data Collection and Risk of Bias Assessment

For each included trial, 2 individuals independently extracted data on the study design, participant and intervention characteristics, outcomes, risk of bias, and quantitative results for treatment effects using electronic forms developed and maintained in the Systematic Review Data Repository (<http://srdc.ahrq.gov/>).^{17,18} We graded each of the following methodological domains at “low,” “high,” or “unclear” risk of bias using the Cochrane Risk of Bias Tool: sequence generation and allocation sequence concealment (both items related to selection bias), masking of participants and outcome assessors (information bias), funding for the trial, and financial relationship reported by the authors.¹⁹ We compared the data extracted by 2 individuals and resolved discrepancies through discussion or consultation with a third person.

Data Synthesis and Analysis

Qualitative Synthesis. We evaluated clinical and methodological heterogeneity among studies, and examined the participant characteristics and risk of bias of included trials that could affect the interpretation of cumulative evidence using qualitative synthesis.²⁰

Quantitative Synthesis. We first conducted pairwise meta-analyses for every treatment comparison with at least 2 trials (i.e., direct comparisons) with an outcome measured and aggregated in a similar fashion using a random-effects model. We first assumed a comparison-specific statistical heterogeneity and then a common heterogeneity across all comparisons.²¹ We used STATA 13 (StataCorp LP, College Station, TX) for pairwise meta-analyses.

We then fitted a Bayesian random-effects network meta-analysis model following the approach by Lu and Ades^{22,23} and accounted for the correlation among the multi-arm trials. We used noninformative priors and fitted the model using Markov chain

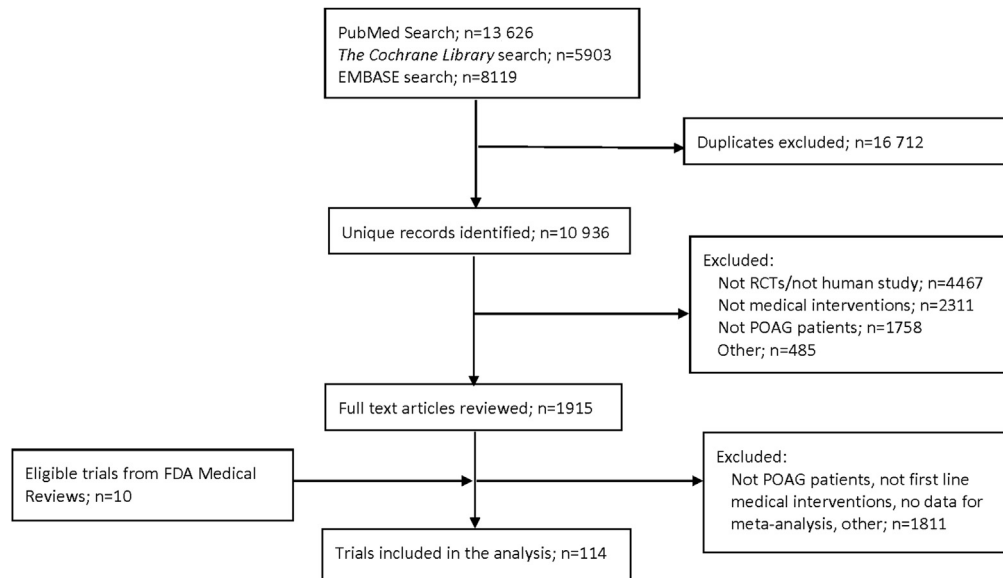


Figure 1. Selection of studies. Our search was broad and included all medical interventions for glaucoma. We reviewed a large number of full-text articles because some of them will be used in different but related systematic reviews, for example, combination drug therapy for glaucoma. FDA = Food and Drug Administration; POAG = primary open-angle glaucoma; RCT = randomized controlled trial.

Monte Carlo algorithms, executed using the “gemtc” R package, which recalls JAGS in R for Markov chain Monte Carlo sampling.²⁴ We used 4 parallel chains and obtained 50 000 samples after a 20 000-sample burn-in in each chain. To check convergence, we used the Gelman and Rubin²⁵ diagnostic and trace plots.²⁶

Evaluation of the Assumption for Network Meta-analysis. Network meta-analysis is valid when there are no important differences among the trials other than the treatments being compared.^{13,27} This assumption implies that participants included in the network hypothetically could be randomized to any of the treatments.¹³ We used our qualitative synthesis to inform our assessment of this assumption underlying network meta-analysis. We considered treatments defined in our research question to be comparable, in that any of them could, in theory, be used as a first-line treatment for patients with POAG or ocular hypertension.

We further assessed statistical disagreement of direct and indirect evidence, known as *inconsistency*, using 3 approaches: loop-specific approach, node-splitting approach, and a comparison of Bayesian model fit with and without assuming consistency in the network.^{28–32} For investigating loop-specific inconsistency, we used STATA 13 (StataCorp LP, College Station, TX).^{16,33} For the node-splitting approach, we used the “gemtc” package in R.^{29,30} For the comparison of model fit, we fitted 2 Bayesian network meta-analysis models with and without assuming consistency implemented in the “gemtc” package in R.²⁴ We evaluated the fit of these 2 models using the Deviance Information Criterion.³⁴ We qualitatively checked the influence of selected trial characteristics (e.g., funding source, large effect size) when statistically significant inconsistency was detected. We conducted sensitivity analysis by removing studies that seemed to introduce statistical inconsistency.²⁷

Measures of Association. We calculated the mean difference of IOP between 2 treatments with 95% confidence intervals or credible intervals. Because “mean differences based on changes from baseline can usually be assumed to be addressing the same underlying intervention effects as analyses based on final measurements”³⁵ in RCTs, change scores and final measurements were combined in

the analysis. Because glaucoma drugs are expected to lower IOP, a larger negative mean difference means that the first drug used in the comparison reduced IOP more.

We combined different concentrations of the same medication in the primary analysis, and separated bimatoprost and timolol into 2 concentrations (bimatoprost 0.03% or bimatoprost 0.01%; timolol 0.5% or timolol <0.5%) in an ad hoc sensitivity analysis. Bimatoprost 0.03% was the only concentration available on the market when we started this project in 2009. It was discontinued by the end of year 2012 in the United States and replaced by bimatoprost 0.01% (a concentration approved in the United States in late 2010). Bimatoprost 0.03% is still available in some countries. For timolol, for which both higher and lower concentrations are available, clinicians are interested in knowing whether a lower concentration works as well as the 0.5% concentration because the side effects may be less with a lower concentration.

We also generated probabilities of each treatment taking each possible rank (e.g., the probability of timolol being ranked as the most efficacious treatment, the second-most efficacious treatment, and so on, to the worst treatment) and the cumulative ranking probabilities, known as a “Surface under the Cumulative Ranking curve” (SUCRA) plot.^{15,16} The SUCRA values show the relative probability of an intervention being among the best options. Rankings based on SUCRA values account better for the uncertainty in the estimated treatment effect.^{15,16} All rankings used “placebo/vehicle/no treatment” as the reference group.

Results

We identified 10 936 unique records from our searches, of which 114 RCTs were eligible to be included in our network meta-analysis (Fig 1; references to these RCTs are presented in Appendix 2, available at www.aaojournal.org). Included trials were published between 1983 and 2013, with more than half published after 2000 (Appendix 3, available at www.aaojournal.org; Table 1). These trials randomized a total of 20 275 participants with a sample size ranging from 17 to 976 (median, 113.5; interquartile

Table 1. Summary Estimates for Intraocular Pressure at 3 Months Derived from Pairwise Meta-analysis Based on Direct Comparisons from 114 Trials*

Column 1	Column 2	No. of Studies	Comparison-Specific Heterogeneity				
			Mean Difference [†]	95% CI, Lower	95% CI, Upper	Tau-Squared	I-Squared
Placebo vs.	Brimonidine	1	−2.30	−3.99	−0.61	NA	NA
	Betaxolol	3	−2.38	−3.78	−0.98	1.11	73%
	Levobunolol	2	−7.52	−8.50	−6.50	NA	NA
	Timolol	5	−3.68	−4.72	−2.63	0.71	52%
	Levobetaxolol	1	−3.00	−4.53	−1.47	NA	NA
	Brinzolamide	2	−2.17	−3.23	−1.10	0.00	0%
	Dorzolamide	4	−1.91	−2.92	−0.90	0.51	51%
	Bimatoprost	1	−4.60	−5.60	−3.60	NA	NA
	Unoprostone	1	−0.20	−1.56	1.16	NA	NA
Apraclonidine vs.	Timolol	2	−0.84	−3.75	2.08	3.73	84%
Brimonidine vs.	Betaxolol	1	1.94	0.84	3.04	NA	NA
	Timolol	4	0.17	−0.70	1.03	0.55	81%
	Brinzolamide	2	1.01	0.50	1.53	0.00	0%
	Latanoprost	5	−1.36	−2.21	−0.50	0.73	78%
	Travoprost	1	−1.20	−3.77	1.37	NA	NA
Betaxolol vs.	Levobunolol	2	−4.73	−10.01	0.55	12.25	83%
	Timolol	9	−1.57	−2.20	−0.93	0.33	41%
	Levobetaxolol	1	−2.00	−3.54	−0.46	NA	NA
	Dorzolamide	2	−0.30	−0.96	0.36	0.00	0%
	Latanoprost	2	−1.06	−2.62	0.51	0.33	25%
	Unoprostone	1	0.60	0.09	1.11	NA	NA
Carteolol vs.	Levobunolol	1	−2.90	−4.59	−1.22	NA	NA
	Timolol	4	0.03	−0.61	0.68	0.11	24%
Levobunolol vs.	Timolol	11	−0.03	−0.44	0.39	0.01	3%
Timolol vs.	Levobetaxolol	3	1.25	0.27	2.23	0.52	73%
	Brinzolamide	3	1.10	0.50	1.70	0.00	0%
	Dorzolamide	7	0.94	0.41	1.47	0.22	43%
	Bimatoprost	7	−2.08	−2.47	−1.70	0.05	19%
	Latanoprost	14	−1.27	−1.70	−0.84	0.37	64%
	Travoprost	6	−0.90	−1.27	−0.52	0.00	0%
	Tafluprost	1	−0.30	−0.72	0.12	NA	NA
	Unoprostone	3	1.35	0.42	2.27	0.57	86%
Brinzolamide vs.	Dorzolamide	2	−0.58	−1.15	0.00	0.00	0%
Dorzolamide vs.	Latanoprost	1	−2.90	−3.70	−2.10	NA	NA
Bimatoprost vs.	Latanoprost	6	0.87	0.01	1.73	0.82	76%
	Travoprost	8	0.59	−0.13	1.30	0.73	74%
Latanoprost vs.	Travoprost	7	−0.06	−0.46	0.34	0.00	0%
	Tafluprost	1	−0.90	−3.40	1.60	NA	NA
	Unoprostone	6	3.07	2.51	3.63	0.01	2%

NA = not available.

*There are 101 two-arm trials, 12 three-arm trials, and 1 four-arm trial (total 114 trials).

[†]Mean difference is calculated using the IOP of the drug in column 2 − column 1.

Glaucoma drugs are expected to lower IOP; therefore, mean difference >0 favors the drug in column 1, and mean difference <0 favors the drug in column 2.

Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

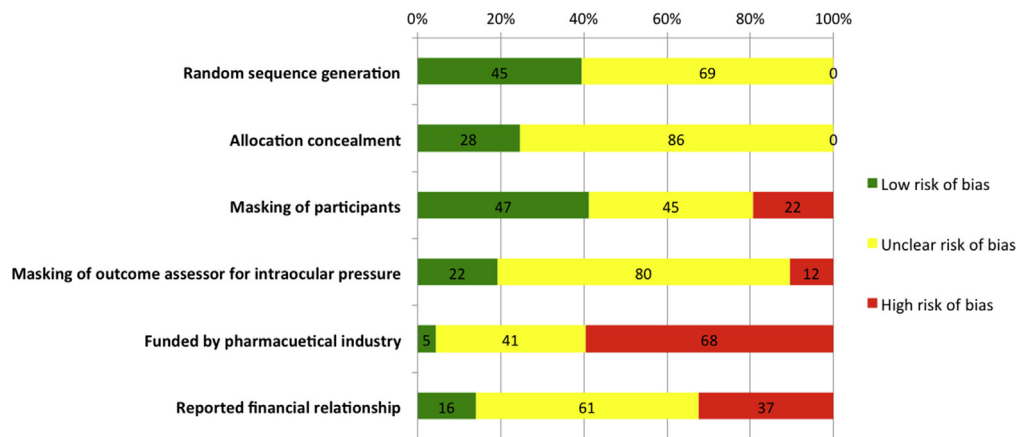


Figure 2. Risk of bias figure.

range, 50–260). Seventy-eight RCTs (68%) were multicenter trials. Of the 85 trials reporting the region(s) where participants were recruited, 47 (55%) recruited participants from North America, 20 (24%) recruited participants from Europe, 17 (20%) recruited participants from Asia, 4 (5%) recruited participants from Latin America, 4 (5%) recruited participants from Oceania, and 2 (2%) recruited participants from Africa (a trial could recruit participants from >1 region).

Ninety-one trials (80%) allowed enrolling participants if they were taking ocular hypotensive medication at the time of enrollment, and of these, 75 (82%) reported using a washout period before randomization. Twelve trials (11%) reported using a run-in period before randomization, with 11 of 12 trials using an active drug in the run-in period. The reported median follow-up time for participants after randomization was 3 months (interquartile range, 2.8–6 months).

The overall risk of bias of the included RCTs is mixed at best (Fig 2; Table 2 in Appendix 3, available at www.aaojournal.org). Forty-five trials (39%) and 28 trials (25%) were rated at low risk of bias for random sequence generation and allocation concealment, respectively; the remaining trials (69 and 86, respectively) were rated at “unclear risk of bias” on each of these 2 domains. Forty-seven trials (41%) reported masking of study participants (rated at “low risk of bias”); 22 trials (19%) reported that the study participants were not masked (rated at “high risk of bias”); and the remaining 45 trials (39%) were rated at “unclear risk of bias.” Twenty-two trials (19%) reported masking of outcome assessors for IOP (rated at “low risk of bias”); 12 trials (11%) reported that the outcome assessor for IOP was not masked (rated at “high risk of bias”); and the remaining 80 trials (70%) were rated at “unclear risk of bias.” Seventy-one trials (62%) reported receiving funding for the research, of which 68 (96%) were funded by the pharmaceutical industry and 7 (10%) were funded by the government (a trial could receive >1 source of funding). Thirty-seven trials (32%) reported that at least 1 author had a financial conflict of interests.

The included trials compared 15 interventions (14 active drugs and “placebo/vehicle/no treatment”) (Fig 3). Of the 39 direct comparisons, 12 (31%) are based on 1 trial and 8 (21%) are based on 2 trials. The median number of trials for each direct comparison is 2 (interquartile range, 1–5.5). Timolol was the most often used comparator and was studied in 70 trials (61%). A total of 101 trials (89%) had 2 treatment arms, 12 trials (11%) had 3 arms, and the remaining trial (1%) had 4 arms.

Table 1 shows the results based on direct comparisons. Brimonidine, betaxolol, levobunolol, timolol, levobetaxolol, brinzolamide, dorzolamide, bimatoprost, and unoprostone have been compared directly with placebo in 20 comparisons. When a

comparison-specific heterogeneity is assumed, all drugs except unoprostone lower IOP at 3 months; the IOP reduction point estimates (using the measure under placebo arm minus the measure under the active drug) range from 1.91 to 7.52 mmHg. Levobetaxolol, brinzolamide, dorzolamide, bimatoprost, latanoprost, travoprost, tafluprost, and unoprostone have been compared directly with timolol in 44 comparisons. When a comparison-specific heterogeneity is assumed, bimatoprost, latanoprost, and travoprost lowered IOP more than timolol at 3 months; the difference in IOP compared with timolol ranged from 0.30 to 2.08 mmHg. The results assuming a common heterogeneity are comparable to the results assuming a comparison-specific heterogeneity (results not shown).

Table 2 shows the results based on a Bayesian network meta-analysis that combines direct and indirect comparisons. All active drugs are shown to be more effective than placebo in lowering IOP at 3 months. The mean reductions (95% credible intervals) in IOP in mmHg at 3 months, ordered from the most to least effective drugs based on the SUCRA values, were as follows: bimatoprost 5.61 (4.94; 6.29), latanoprost 4.85 (4.24; 5.46), travoprost 4.83 (4.12; 5.54), levobunolol 4.51 (3.85; 5.24), tafluprost 4.37 (2.94; 5.83), timolol 3.70 (3.16; 4.24), brimonidine 3.59 (2.89; 4.29), carteolol 3.44 (2.42; 4.46), levobetaxolol 2.56 (1.52; 3.62), apraclonidine 2.52 (0.94; 4.11), dorzolamide 2.49 (1.85; 3.13), brinzolamide 2.42 (1.62; 3.23), betaxolol 2.24 (1.59; 2.88), and unoprostone 1.91 (1.15; 2.67). Bimatoprost, when the 2 concentrations (0.03% and 0.01%) are not differentiated, resulted in a statistically significant lower IOP than any other active drug except tafluprost, although the pairwise differences in lowering IOP at 3 months among bimatoprost, latanoprost, travoprost, and tafluprost are small and may not be clinically meaningful.

The ranking probabilities for any drug at any possible position are presented in Figure 4, ordered from the least effective drug to the most effective. The ranking probabilities are consistent with our estimates of treatment effect. For example, the probabilities of bimatoprost being ranked as the first, second, and third most efficacious drug for lowering IOP at 3 months are 95.3%, 4.6%, and 0.1%, respectively. The probabilities of latanoprost being ranked as the first, second, and third most efficacious drug in lowering IOP at 3 months are 0.1%, 36.1%, and 42.6%, respectively. The cumulative ranking probabilities, displayed in the SUCRA plot, are presented in Figure 5. The larger the surface area under the curve and the faster the curve rises, the higher ranking the drug.^{15,16} On the basis of the SUCRA values derived from trials included in our network meta-analysis, bimatoprost seems to be the most efficacious drug in lowering IOP at 3

Table 2. Summary Estimates for Intraocular Pressure at 3 Months Derived from Network Meta-analysis of 114 Trials*

Placebo	-2.52 (-4.11; -0.94)	-3.59 (-4.29; -2.89)	-2.24 (-2.88; -1.59)	-3.44 (-4.46; -2.42)	-4.51 (-5.24; -3.8)	-3.7 (-4.24; -3.16)	-2.56 (-3.62; -1.52)	-2.42 (-3.23; -1.62)	-2.49 (-3.13; -1.85)	-5.61 (-6.29; -4.94)	-4.85 (-5.46; -4.24)	-4.83 (-5.54; -4.12)	-4.37 (-5.83; -2.94)	-1.91 (-2.67; -1.15)
2.52 (0.94; 4.11)	Apraclonidine	-1.08 (-2.65; 0.52)	0.28 (-1.29; 1.87)	-0.92 (-2.64; 0.81)	-2 (-3.58; -0.39)	-1.18 (-2.67; 0.31)	-0.05 (-1.81; 1.72)	0.09 (-1.55; 1.75)	0.03 (-1.54; 1.62)	-3.1 (-4.65; -1.53)	-2.33 (-3.85; -0.79)	-2.31 (-3.88; -0.73)	-1.85 (-3.85; 0.15)	0.61 (-0.99; 2.23)
3.59 (2.89; 4.29)	1.08 (-0.52; 2.65)	Brimonidine	1.35 (0.67; 2.04)	0.15 (-0.87; 1.17)	-0.92 (-1.69; -0.16)	-0.11 (-0.64; 0.42)	1.03 (-0.05; 2.1)	1.17 (0.4; 1.92)	1.1 (0.4; 1.8)	-2.02 (-2.69; -1.35)	-1.25 (-1.8; -0.72)	-1.24 (-1.92; -0.55)	-0.78 (-2.23; 0.65)	1.69 (0.92; 2.45)
2.24 (1.59; 2.88)	-0.28 (-1.87; 1.29)	-1.35 (-2.04; -0.67)	Betaxolol	-1.2 (-2.21; -0.19)	-2.28 (-3.01; -1.55)	-1.46 (-1.99; -0.94)	-0.32 (-1.38; 0.72)	-0.18 (-1.03; 0.65)	-0.25 (-0.91; 0.4)	-3.37 (-4.06; -2.7)	-2.61 (-3.2; -2.02)	-2.59 (-3.3; -1.89)	-2.13 (-3.58; -0.7)	0.33 (-0.42; 1.08)
3.44 (2.42; 4.46)	0.92 (-0.81; 2.64)	-0.15 (-1.17; 0.87)	1.2 (0.19; 2.21)	Carteolol	-1.08 (-2.07; -0.09)	-0.26 (-1.14; 0.61)	0.88 (-0.42; 2.16)	1.02 (-0.11; 2.14)	0.95 (-0.07; 1.96)	-2.17 (-3.16; -1.18)	-1.41 (-2.35; -0.47)	-1.39 (-2.4; -0.38)	-0.93 (-2.54; 0.66)	1.53 (0.47; 2.59)
4.51 (3.8; 5.24)	2 (0.39; 3.58)	0.92 (0.16; 1.69)	2.28 (1.55; 3.01)	1.08 (0.09; 2.07)	Levobunolol	0.81 (0.25; 1.38)	1.95 (0.86; 3.04)	2.09 (1.2; 2.99)	2.03 (1.28; 2.77)	-1.1 (-1.83; -0.36)	-0.33 (-0.99; 0.33)	-0.31 (-1.06; 0.44)	0.14 (-1.32; 1.6)	2.61 (1.79; 3.43)
3.7 (3.16; 4.24)	1.18 (-0.31; 2.67)	0.11 (-0.42; 0.64)	1.46 (0.94; 1.99)	0.26 (-0.61; 1.14)	-0.81 (-1.38; -0.25)	1.14 (0.19; 2.07)	1.28 (0.56; 1.99)	1.21 (0.69; 1.73)	1.21 (-2.38; -1.44)	-1.91 (-1.5; -0.79)	-1.15 (-1.63; -0.63)	-1.13 (-2.02; 0.67)	-0.67 (-2.02; 0.67)	1.79 (1.18; 2.41)
2.56 (1.52; 3.62)	0.05 (-1.72; 1.81)	-1.03 (-2.1; 0.05)	0.32 (-0.72; 1.38)	-0.88 (-2.16; 0.42)	-1.95 (-3.04; -0.86)	-1.14 (-2.07; -0.19)	Levobetaxolol	0.14 (-1.03; 1.32)	0.07 (-0.99; 1.14)	-3.05 (-4.09; -1.99)	-2.28 (-3.28; -1.27)	-2.27 (-3.32; -1.19)	-1.81 (-3.45; -0.18)	0.66 (-0.45; 1.78)
2.42 (1.62; 3.23)	-0.09 (-1.75; 1.55)	-1.17 (-1.92; -0.4)	0.18 (-0.65; 1.03)	-1.02 (-2.14; 0.11)	-2.09 (-2.99; -1.2)	-1.28 (-1.99; -0.56)	-0.14 (-1.32; 1.03)	Brinzolamide	-0.07 (-0.85; 0.71)	-3.19 (-4.03; -2.36)	-2.42 (-3.18; -1.66)	-2.41 (-3.26; -1.55)	-1.95 (-3.47; -0.44)	0.52 (-0.39; 1.43)
2.49 (1.85; 3.13)	-0.03 (-1.62; 1.54)	-1.1 (-1.8; -0.4)	0.25 (-0.4; 0.91)	-0.95 (-1.96; 0.07)	-2.03 (-2.77; -1.28)	-1.21 (-1.73; -0.69)	-0.07 (-1.14; 0.99)	0.07 (-0.71; 0.85)	Dorzolamide	-3.12 (-3.8; -2.44)	-2.36 (-2.95; -1.76)	-2.34 (-3.05; -1.63)	-1.88 (-3.32; -0.45)	0.58 (-0.19; 1.36)
5.61 (4.94; 6.29)	3.1 (1.53; 4.65)	2.02 (1.35; 2.69)	3.37 (2.7; 4.06)	2.17 (1.18; 3.16)	1.1 (0.36; 1.83)	1.91 (1.44; 2.38)	3.05 (1.99; 4.09)	3.19 (2.36; 4.03)	3.12 (2.44; 3.8)	Bimatoprost	0.77 (0.27; 1.26)	0.78 (0.26; 1.3)	1.24 (-0.18; 2.65)	3.71 (2.97; 4.44)
4.85 (4.24; 5.46)	2.33 (0.79; 3.85)	1.25 (0.72; 1.8)	2.61 (2.02; 3.2)	1.41 (0.47; 2.35)	0.33 (-0.33; 0.99)	1.15 (0.79; 1.5)	2.28 (1.27; 3.28)	2.42 (1.66; 3.18)	2.36 (1.76; 2.95)	-0.77 (-1.26; -0.27)	Latanoprost	0.02 (-0.5; 0.53)	0.48 (-0.91; 1.83)	2.94 (2.33; 3.55)
4.83 (4.12; 5.54)	2.31 (0.73; 3.88)	1.24 (0.55; 1.92)	2.59 (1.89; 3.3)	1.39 (0.38; 2.4)	0.31 (-0.44; 1.06)	1.13 (0.63; 1.63)	2.27 (1.19; 3.32)	2.41 (1.55; 3.26)	2.34 (1.63; 3.05)	-0.78 (-1.3; -0.26)	-0.02 (-0.53; 0.5)	Travoprost	0.46 (-0.98; 1.87)	2.92 (2.17; 3.68)
4.37 (2.94; 5.83)	1.85 (-0.15; 3.85)	0.78 (-0.65; 2.23)	2.13 (0.7; 3.58)	0.93 (-0.66; 2.54)	-0.14 (-1.6; 1.32)	0.67 (-0.67; 2.02)	1.81 (0.18; 3.45)	1.95 (0.44; 3.47)	1.88 (0.45; 3.32)	-1.24 (-2.65; 0.18)	-0.48 (-1.83; 0.91)	-0.46 (-1.87; 0.98)	Tafuprost	2.46 (1.01; 3.95)
1.91 (1.15; 2.67)	-0.61 (-2.23; 0.99)	-1.69 (-2.45; -0.92)	-0.33 (-1.08; 0.42)	-1.53 (-2.59; -0.47)	-2.61 (-3.43; -1.79)	-1.79 (-2.41; -1.18)	-0.66 (-1.78; 0.45)	-0.52 (-1.43; 0.39)	-0.58 (-1.36; 0.19)	-3.71 (-4.44; -2.97)	-2.94 (-3.55; -2.33)	-2.92 (-3.68; -2.17)	-2.46 (-3.95; -1.01)	Unoprostone

*Posterior means (95% Bayesian credible intervals) are calculated by column – row under the Lu and Ades²² homogeneous random effects model assuming consistency. Mean difference <0 favors the drug in the column, and mean difference >0 favors the drug in the row.

Color coding:

White	Placebo/vehicle/no treatment
Purple	Alpha-2 adrenergic agonist
Yellow	Beta-blocker
Orange	Carbonic anhydrase inhibitor
Turquoise	Prostaglandin analog

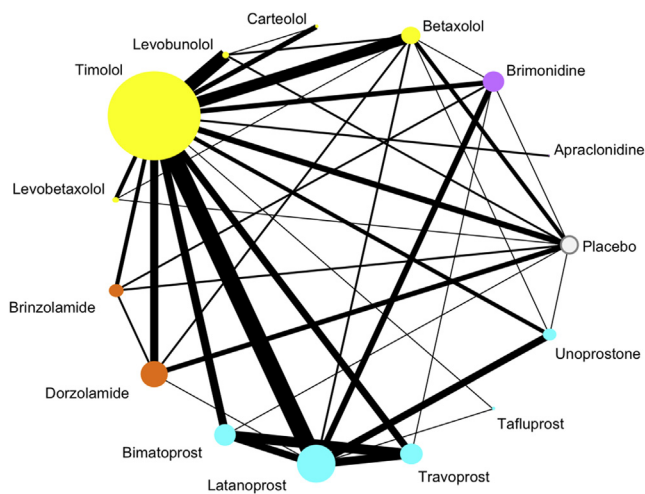


Figure 3. Network graph. Each node represents 1 drug. The drugs are color-coded by class. The size of the node is proportional to the number of participants randomized to that drug. The edges represent direct comparisons, that is, when there is a line connecting 2 drugs, the 2 drugs have been compared directly with each other in a trial. The width of the edge is proportional to the number of trials. Total number of studies = 114. Number of published studies = 104 (11 three-arm studies). Number of Food and Drug Administration studies = 10 (1 three-arm study, 1 four-arm study). Total number of patients contributing to this network = 20 275. Color coding: white = placebo/vehicle/no treatment; purple = alpha-2 adrenergic agonist; yellow = beta-blocker; orange = carbonic anhydrase inhibitor; turquoise = prostaglandin analog.

months. Of note, the 2 alpha-agonists, apraclonidine and brimonidine, had different effectiveness profiles with brimonidine ranking close to timolol, whereas apraclonidine was lower.

Sensitivity Analysis

Of the 17 bimatoprost trials included in our network, 15 evaluated bimatoprost 0.03% and 2 evaluated bimatoprost 0.01%. Of the 70 timolol trials included in our network, 65 evaluated timolol 0.5% and 5 evaluated a timolol concentration lower than 0.5%.

The mean differences in IOP at 3 months comparing bimatoprost 0.03% or bimatoprost 0.01% with placebo are 5.77 (5.04; 6.50) and 4.74 (1.91; 3.19), respectively. The mean difference in IOP between bimatoprost 0.03% and bimatoprost 0.01% is small (1.04 [−0.30; 2.39]), and this difference is not statistically significant (Appendix 4, available at www.aaojournal.org). The mean differences in IOP at 3 months comparing timolol 0.5% or timolol <0.5% with placebo are similar and comparable to the estimate for timolol under our main analysis, in which the 2 concentrations are combined (Appendix 4, available at www.aaojournal.org).

The relative rankings of the top 3 drugs changed in the sensitivity analysis. By using the SUCRA values, the top ranked drugs are bimatoprost 0.03%, followed by latanoprost, travoprost, and bimatoprost 0.01% (Appendix 4, available at www.aaojournal.org). Bimatoprost 0.03% is no longer manufactured or sold in the United States (although it is still available in some countries), and the patent expired in August 2014.

Inconsistency

We used several methods for assessing inconsistency between direct and indirect evidence. By using the loop-specific approach, we found 4 of 37 (11%) triangle loops (i.e., any 3 drugs connected

in Fig 3 forms a triangle loop) that showed evidence of statistical inconsistency. By using the node-splitting approach, we found 2 statistically significant inconsistency nodes. We could not find any qualitative reasons to explain the inconsistency and elected to address the inconsistency by fitting an “inconsistency” model to the data and to conduct a sensitivity analysis by removing studies that seemed to introduce statistical inconsistency. The inconsistency model did not improve our model fit and did not change our conclusions. Results of the inconsistency model and sensitivity analysis are presented in Appendix 4 (available at www.aaojournal.org).

Visual Field

Twenty-three of the 114 trials (20%) reported visual field outcomes, of which 13 (57%) presented both a point estimate and some form of precision estimate (Appendix 5, available at www.aaojournal.org). Because of the heterogeneity in how the visual field was measured, aggregated, and reported at different follow-up times, however, no pairwise or network meta-analysis of visual field data was possible. Not a single trial reported a difference or ratio between treatment groups with respect to visual field outcomes, although some trials provided group-level data and treatment effect could be calculated on the basis of the group level data.

Discussion

By using a systematic review and network meta-analysis, we estimated the pairwise comparative effectiveness of 14 first-line IOP-lowering drugs used in patients with POAG or ocular hypertension. All drugs examined were significantly more effective than placebo in lowering IOP at 3 months. Drugs in the prostaglandin class were more efficacious than drugs in other classes, although the within-class differences were generally small (bimatoprost vs. travoprost, latanoprost, or tafluprost). Bimatoprost 0.01% is no more effective than latanoprost or travoprost in lowering IOP at 3 months. Brimonidine lowered IOP more than apraclonidine; and unoprostone and betaxolol lowered IOP the least.

Our analyses confirmed existing beliefs of the comparative effectiveness of glaucoma drugs and revealed interesting new findings.^{1–4} Both the American Academy of Ophthalmology Preferred Practice Patterns and the UK-based National Institute for Health and Care Excellence guidelines recommend prostaglandins as the initial medical therapy for POAG and ocular hypertension.^{1,2} Our estimate of the efficacy of latanoprost against placebo in lowering IOP, derived entirely from indirect evidence (we found no direct comparison between latanoprost and placebo) (Fig 3), is consistent with a major RCT that was published after our search date.³⁶ Unexpected results were that brimonidine, an alpha-agonist, performed as well as levobetaxolol and carteolol, and better than betaxolol (3 beta-blockers).

Relative IOP reduction needs to be weighed against other factors in a given decision framework. The best-ranking drug in lowering IOP at 3 months (i.e., bimatoprost 0.03%) is no longer sold, being replaced on the market by a lower concentration (i.e., bimatoprost 0.01%). In some developing countries, timolol is the only accessible and affordable option among the top ranked drugs, as reflected in prescription patterns. For example, beta-blockers constitute as much as 90% of prescriptions for POAG in India,³⁷ whereas in the

Ranks	Placebo	Unoprostone	Betaxolol	Brimonidine	Dorzolamide	Apraclonidine	Levobunolol	Carteolol	Brimonidine	Timolol	Tafuprost	Levobunolol	Travoprost	Latanoprost	Bimatoprost
1	0	0	0	0	0	0	0	0	0	0	0.042	0.002	0.001	0.001	0.953
2	0	0	0	0	0	0.001	0	0	0	0	0.155	0.082	0.356	0.361	0.046
3	0	0	0	0	0	0.001	0	0.001	0	0	0.081	0.129	0.361	0.426	0.001
4	0	0	0	0	0	0.003	0	0.008	0.003	0	0.167	0.424	0.215	0.18	0
5	0	0	0	0	0	0.014	0.002	0.069	0.067	0.074	0.333	0.343	0.065	0.032	0
6	0	0	0	0	0	0.031	0.006	0.178	0.248	0.437	0.079	0.018	0.002	0	0
7	0	0	0	0.001	0.001	0.033	0.014	0.17	0.339	0.379	0.061	0.002	0	0	0
8	0	0	0.002	0.019	0.013	0.082	0.063	0.379	0.285	0.102	0.055	0	0	0	0
9	0	0.006	0.033	0.143	0.152	0.206	0.245	0.136	0.055	0.006	0.018	0	0	0	0
10	0	0.021	0.101	0.214	0.283	0.125	0.21	0.037	0.004	0	0.005	0	0	0	0
11	0	0.049	0.194	0.219	0.281	0.095	0.147	0.013	0	0	0.002	0	0	0	0
12	0	0.108	0.289	0.191	0.178	0.097	0.13	0.006	0	0	0.001	0	0	0	0
13	0	0.265	0.285	0.144	0.075	0.119	0.111	0.002	0	0	0	0	0	0	0
14	0.001	0.551	0.097	0.068	0.017	0.192	0.072	0.001	0	0	0	0	0	0	0
15	0.999	0	0	0	0	0.001	0	0	0	0	0	0	0	0	0

Histogram of ranking probabilities for each drug (the warmer the color, the better the rank).

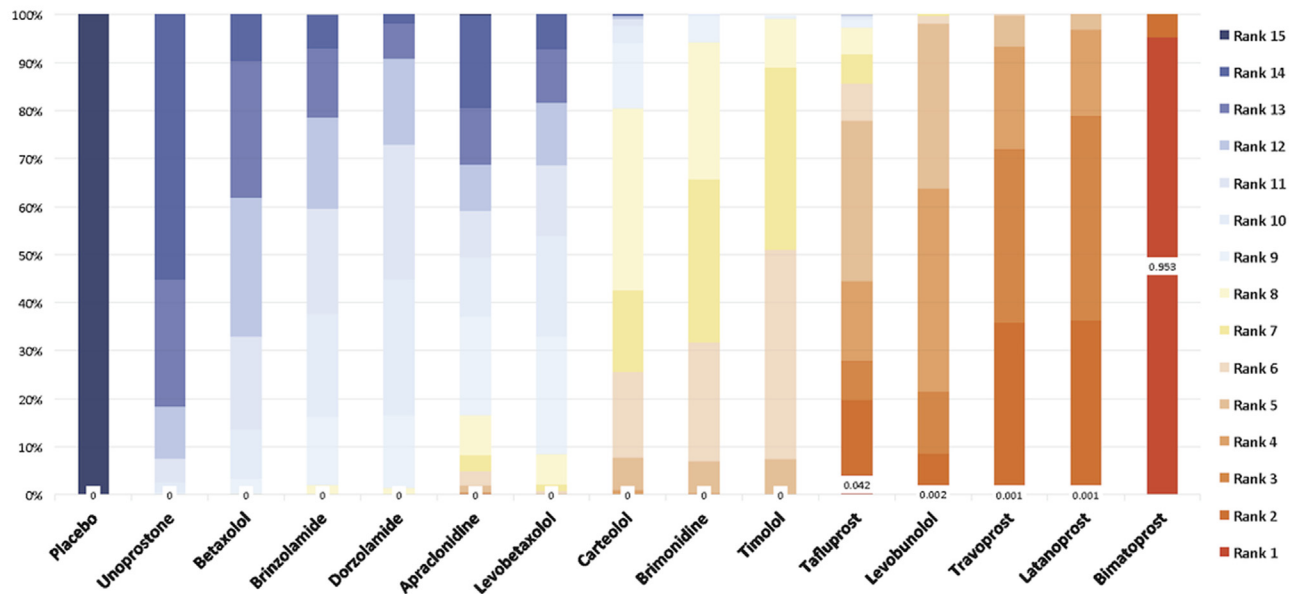


Figure 4. Ranking probabilities for any drug at any position.

United Kingdom and United States, latanoprost is the most prescribed drug.^{38,39} Drug safety and side effects are other important considerations. Prostaglandins have been associated with eyelash lengthening and iris color change, adverse side effects that some patients may find bothersome.^{3,4} Among prostaglandins, latanoprost has been reported to have a lower risk of conjunctival hyperemia (redness) than travoprost or bimatoprost.^{3,4} Our study ranks the relative IOP reduction for all drugs, one aspect of the decision framework, and thus does not define which medications are best for initial treatment.

Although IOP is a surrogate outcome, it is typically used in glaucoma trials, including trials submitted to regulatory agencies for market approval, as an outcome measure that quantifies intervention effectiveness.^{40,41} This is because IOP reduction correlates with preservation of visual field, yet definite or most meaningful outcomes such as change in visual field and optic nerve damage are not easy to quantify and effects on patient-centered outcomes such as visual function (e.g., whether a patient can drive and read) and blindness require a long follow-up time to observe.^{40,41} Because preservation of visual function is the primary aim of glaucoma treatment, visual field outcome is a more

meaningful gauge of the effectiveness of glaucoma treatment than IOP. Unfortunately, only 11% of trials included in our sample reported any analyzable visual field data and the data were measured and reported in many different ways, making a pairwise meta-analysis or a network meta-analysis impossible. The short length of follow-up time of most trials (median 3 months), in contrast to what is needed (e.g., 5 years of observing visual field change³⁶), also precludes meaningful assessments of visual field outcome.

Visual field was used as the primary outcome in a Cochrane systematic review of medical interventions for POAG.⁴² Findings from this pairwise review concluded that treating ocular hypertension with any drug is more effective than placebo or no treatment in reducing the onset of visual field defects.⁴² When individual drugs were examined, no drug showed a significant visual field protection, although the review also found positive but weak evidence for a beneficial effect of beta-blockers as a class.

An evidence synthesis such as the network meta-analysis we have done does not overcome the underlying fact that some studies we included were at high or unclear risk of bias, had small sample size, had short follow-up time, and used IOP, a surrogate outcome to assess treatment effect.

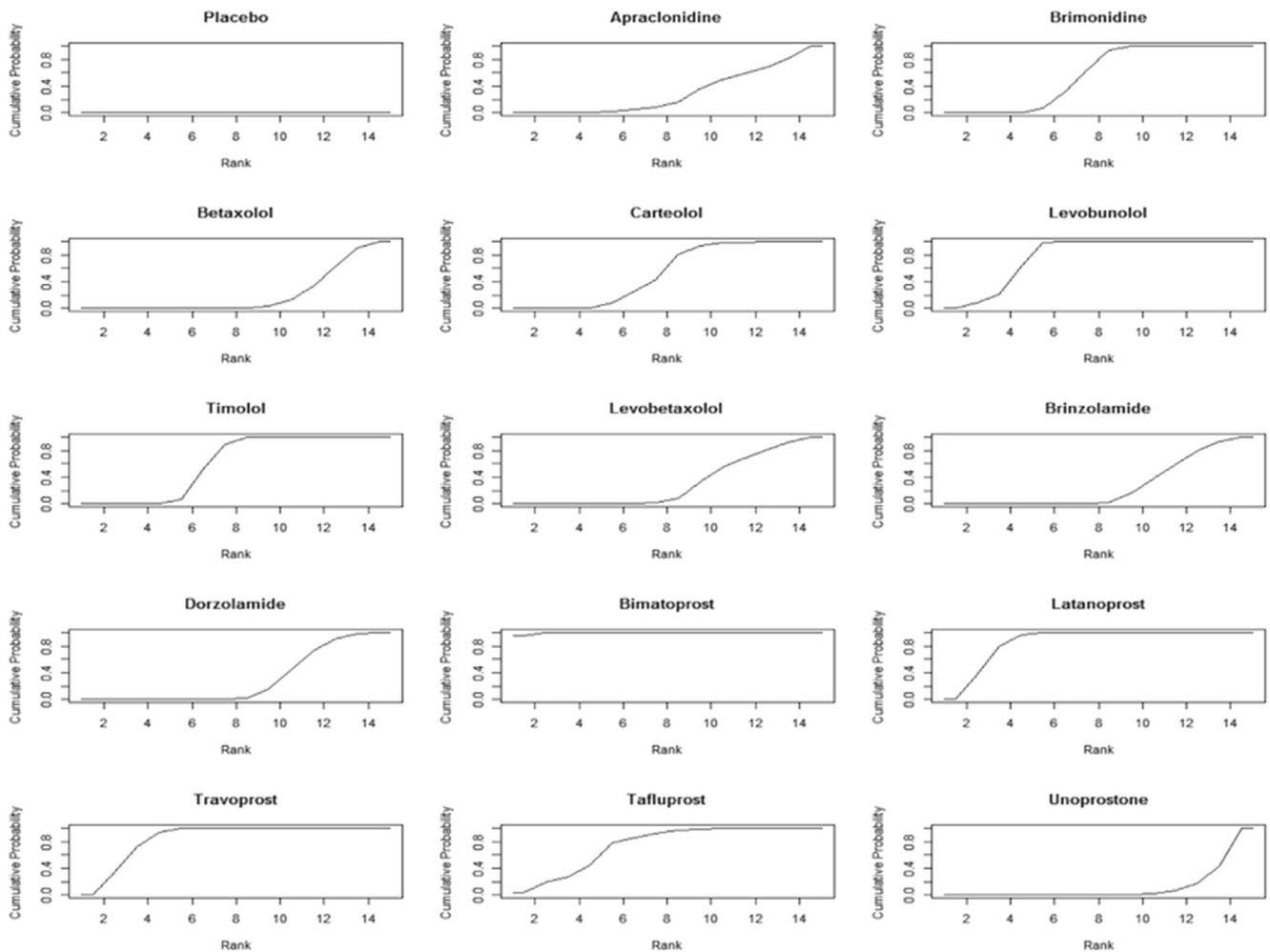


Figure 5. Cumulative ranking probabilities for each drug. The Surface under the Cumulative Ranking curve (SUCRA) value represents the surface underneath the cumulative ranking curve and is the posterior probabilities for each drug to be among the n-best options.^{15,16} The larger the SUCRA value, the higher the ranking probabilities for the drug among the drugs compared. Rankings based on SUCRA values account better for the uncertainty in the estimated treatment effects.^{15,16} SUCRA values normalized to %: placebo (0.01), apraclonidine (30.55), brimonidine (57.09), betaxolol (21.62), carteolol (53.44), levobunolol (77.96), timolol (60.39), levobetaxolol (31.56), brinzolamide (27.67), dorzolamide (30.36), bimatoprost (99.66), latanoprost (86.56), travoprost (85.76), tafluprost (74.79), and unoprostone (12.44).

Others have found that high or unclear risk of bias for random sequence generation, allocation concealment, and masking of patients and outcome assessors does not seem to affect network meta-analysis results materially.⁴³ This finding was based on an empirical meta-epidemiologic study of 32 networks including more than 600 RCTs.⁴³ Some researchers have posited that the biases may mitigate through a common comparator.^{43–45} For example, if there is sponsorship bias in favor of the company's own products, by connecting the trials through placebo, the indirect evidence might be less biased.^{44,45}

The findings of this study provide critical information to answer the doctors' and patients' question "What works best?" among all alternative topical medical treatments for POAG and ocular hypertension. By using indirect evidence, we filled in gaps in the literature about the comparative effectiveness of any 2 glaucoma drugs. As illustrated in Table 1, direct evidence obtained from RCTs was available for only 39 of 105

comparisons (37%) that we made. Conventional pairwise meta-analyses, summarizing these RCTs, can only answer questions where RCTs exist and can only examine pairs of interventions.⁹ This does not support real-world clinical decision-making because each meta-analysis takes into account only one part of the overall range of choice. It is also worth noting that 43% of pairwise meta-analyses published up to February 2012 on glaucoma medications used problematic statistical analyses, calling conclusions from these meta-analyses and systematic reviews into question.⁹ One common error was that the review authors pooled data by treatment group rather than analyzing the between-group effect estimates, breaking the randomized nature of trials.⁹ We used 3 approaches to examine the inconsistency assumption for our network meta-analysis and found that this assumption is likely to hold in our analysis.

Network meta-analysis exploits all available direct evidence and uses statistical methods to obtain indirect

evidence to form a coherent knowledge base, providing information for comparisons between pairs of drugs that may have never been evaluated in individual trials. The network meta-analysis methodology itself has been validated and matured over recent years, and its utility and added value have been demonstrated.^{46–51} Furthermore, we offered a comprehensive summary of a large amount of data and in most cases provided more precise estimates of treatment effect than the corresponding pairwise meta-analyses (by comparing estimates in Tables 1 and 2 for the same comparison). Compared with a previous network meta-analysis on glaucoma drugs published in 2009,⁵² our analysis included 4 times as many trials. Finally, ranking probabilities create a new metric for clinicians to use when choosing therapy. In some cases, the absolute difference in IOP reduction might be small and may not be clinically meaningful; but on the other hand, ranking allows one to put options in context, for example, in conjunction with considerations such as side effects, patient preference, and cost.

In conclusion, we found that all active first-line drugs are effective compared with placebo and that prostaglandins were more efficacious in lowering IOP at 3 months than beta-blockers, alpha-agonists, or carbonic anhydrase. Bimatoprost, latanoprost, and travoprost are among the most efficacious drugs, although the within-class differences were small and may not be clinically meaningful. Most trials did not measure or report visual field or other patient-centered outcomes, such as visual function and blindness. All factors, including side effects, patient preferences, and cost, should be considered in selecting a drug for a given patient.

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Abbreviations and Acronyms:

IOP = intraocular pressure; **POAG** = primary open-angle glaucoma; **RCT** = randomized controlled trial; **SUCRA** = Surface under the Cumulative Ranking curve.

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