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# 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 2015;■:1–12 © 2015 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



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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://srdr.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