

Title: Network Meta-Analysis for Clinical Practice Guidelines – A Case Study on First-Line Medical Therapies for Primary Open-Angle Glaucoma

Short Title: Network Meta-Analysis for Clinical Practice Guidelines

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56 None of the authors have any commercial conflict of interest to declare.

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Abstract

Background:

Network meta-analysis compares multiple treatment options for the same condition and may be useful for developing clinical practice guidelines.

Purpose:

To compare treatment recommendations for first-line medical therapy for primary open angle-glaucoma (POAG) from major updates of American Academy of Ophthalmology's (AAO) guidelines with the evidence available at the time, using network meta-analysis.

Data Sources:

We searched MEDLINE, EMBASE, and *The Cochrane Library* on March 11, 2014 for randomized controlled trials (RCTs) of glaucoma monotherapies compared with placebo/vehicle/no treatment or other monotherapies. We searched the AAO website in August 2014 to identify AAO POAG guidelines.

Study Selection:

Eligible RCTs were selected by two independent reviewers and guidelines were selected by one person.

Data Extraction:

One person abstracted recommendations from guidelines and a second person verified. Two people independently abstracted data from included RCTs.

Data Synthesis:

We grouped guidelines together based on literature search dates, and analyzed RCTs that existed at 1991, 1995, 1999, 2004, and 2009. The outcome of interest is intraocular pressure

81 (IOP) at 3 months. Only the latest guideline made a specific recommendation--prostaglandins.
82 Network meta-analyses showed that all treatments were superior to placebo in lowering IOP at
83 3 months. The mean reduction (95% credible interval) for the highest-ranking class compared
84 with placebo were as follows: 1991: beta blockers, 4.01 (0.48-7.43); 1995: alpha-2 adrenergic
85 agonists, 5.64 (1.73-9.50); 1999: prostaglandins, 5.43 (3.38-7.38); 2004: prostaglandins, 4.75
86 (3.11-6.44); 2009: prostaglandins, 4.58 (2.94-6.24).

87 **Limitations:**

88 When comparisons are informed by a small number of studies, the treatment effects and
89 rankings may not be stable.

90 **Conclusions:**

91 For timely recommendations when multiple treatment options are available, guidelines
92 developers should consider network meta-analysis.

93 Introduction

94 In 2011, the Institute of Medicine defined clinical practice guidelines as “statements that
95 include recommendations intended to optimize patient care, that are informed by a systematic
96 review of evidence and an assessment of the benefits and harms of alternative care options”
97 (1). Historically, guidelines primarily represented the opinions of individual authors or the
98 consensus of experts (2). With the advent of evidence-based healthcare, guidelines have
99 increasingly used systematic reviews and meta-analyses of randomized controlled trials (RCTs)
100 to form the basis of recommendations (2–4). Standard meta-analytic techniques can be used if
101 the guideline addresses pairwise comparisons, for example, treatment A versus treatment B. If
102 a guideline is attempting to address the question of which treatment is best among multiple
103 options, however, standard meta-analysis may not be adequate. By contrast, network meta-
104 analysis - a method that uses information from both direct and indirect comparisons and makes
105 inferences about the comparative effectiveness of all the treatments of interest in a single
106 analysis (5,6) - is particularly suited in such situations.

107
108 Clinical conditions for which guidelines could benefit from network meta-analysis the most are
109 those with numerous treatment options, for example, first-line medical treatment for primary
110 open-angle glaucoma (POAG). POAG, highly prevalent in the United States (US) and worldwide,
111 is an eye condition in which optic nerve damage leads to gradual and painless visual field
112 reduction over time (7,8). Because optic nerve damage is difficult to measure, and changes in
113 visual field takes years to develop, treatment effectiveness is generally determined by

reduction in intraocular pressure (IOP), a modifiable risk factor for POAG over a period of a few months (7,9).

The American Academy of Ophthalmology's (AAO) POAG Preferred Practice Pattern (PPP) has been particularly influential in the US (7,10–17). The first version of this guideline was published in 1989, with major revisions being published approximately every 3 to 5 years. When the AAO PPP guideline was first developed by AAO's Glaucoma Panel, evidence was gathered based on the panel members' knowledge - members submitted what they considered seminal works and these works were distributed among the rest of the panel (18). Since 1996, the panel has been using a more systematic approach, carrying out a formal search of the relevant scientific literature and rating the strength of evidence for recommendations (7,13–17).

The objective of this study is to compare the evidence base for first-line medical treatments for POAG with the recommendations for each major revision of the AAO PPP by using cumulative network meta-analysis (i.e., conducting a series of network meta-analysis on a systematically assembled set of RCTs published up to several distinct time periods). Previously Antman and Lau demonstrated, by comparing the results from cumulative pairwise meta-analyses with recommendations given by experts, that meta-analysis can improve the timeliness of guidance (19,20). Using this previous work as a model, we evaluated whether network meta-analysis can provide additional benefit in developing clinical practice guidelines. The data for our cumulative network meta-analysis are from a systematic review and network meta-analysis we previously published (21). This study is not intended as criticism of guideline developers for not using

statistical methods that were undeveloped at times in the past, but as an example to show how network meta-analysis may be able to benefit future guideline recommendations.

Methods

Guideline identification and extraction

We searched the AAO website (www.aao.org) and contacted the AAO's librarian to identify all versions of AAO's PPPs in August 2014. One member of the team (BR) reviewed each version of the guideline, identified statements concerning first-line POAG medical treatment, that is as topical monotherapy for lowering IOP (22), and identified among them the recommendations. We defined recommendations as statements that used the following words "recommend," "should," "appropriate," "necessary," "must", or other words that suggested a particular practice such as prescribing a medication. A second individual (TL) verified the abstraction and the classification of whether a statement was really a "recommendation". We then categorized recommendations by drug name and class of medical treatment (e.g., latanoprost, prostaglandins), and extracted the quantitative estimates of effect (e.g., reduction of IOP) when provided. We also extracted the ratings of strength of evidence for each recommendation (e.g., level I indicates basis is "a high-quality large RCT" or a "systematic review" and level III indicates basis is "consensus of experts") (7,13–17).

When two or more consecutive guideline versions reported the same literature search years or, in absence of reporting search years, they presented identical recommendations regarding

medical treatment, we grouped them together. This is to facilitate the comparison of the guidelines recommendations with the results from our cumulative network meta-analyses.

Systematic review and cumulative network meta-analyses

We identified all available RCTs from a systematic review our group recently conducted (21). In this review, we searched the following databases: Cochrane Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, and EMBASE on March 11, 2014 (see Appendix 1 for the full search strategy), and included RCTs evaluating first-line topical monotherapies for POAG or ocular hypertension compared to no treatment, placebo, or other topical monotherapies. The process of title and abstract screening, full-text screening, data abstraction, and risk of bias evaluation has been described previously (21). All data were extracted into the Systematic Review Data Repository (23,24).

For this manuscript, we used the latest guideline in each set to define eligible studies for each network meta-analysis. Eligible studies are those published either up to the stopping year for the literature search reported in the guideline(s) or, if such a point was not reported, the year before the guideline(s) was/were published, to allow for lag time between publication and inclusion of evidence in the guideline. The primary outcome was the mean IOP at 3 months as a continuous variable in units of mmHg, which corresponds to the primary effectiveness endpoint on which guideline recommendations were made (7). We prioritized using mean change in IOP from baseline values, but also accepted mean IOP at 3 months when the change score was not reported (25).

179

180 Our analysis did not distinguish between drug concentrations, and comparisons were based on
181 the active ingredient and class of that ingredient. We first examined direct comparisons using
182 random-effects model meta-analysis assuming comparison-specific heterogeneity and a
183 common heterogeneity across all comparisons at both the drug and class level. To assess the
184 statistical heterogeneity, we examined the I^2 and τ^2 values for these models. Analyses for
185 direct comparisons were conducted in Stata version 13 (StataCorp) using the *metan* command.

186

187 We fitted Bayesian random-effects network meta-analysis models using WinBUGS 1.4.3 (26–
188 28). We used a three-level hierarchical model with components at the following levels: study,
189 individual drug, and drug class. This model accounts for the within-study correlation of multi-
190 arm trials and also incorporates class effect (26,27,29). A valid network analysis requires the
191 assumption of transitivity, that is, there are no systematic differences among the trials other
192 than the treatments being compared (5). This assumption can be tested by assessing
193 inconsistency, the statistical disagreement between direct and indirect comparisons (5). See
194 Appendix 2 for further details.

195

196 We examined mean differences in IOP (and 95% credible intervals) between pairs of individual
197 drugs and drug classes (21). We also ranked each drug or class (i.e., the probability of a drug
198 being the most effective treatment, the second best, etc.). We examined the hierarchy of
199 treatment rankings by using the surface below the cumulative ranking curve (SUCRA) (30,31). A
200 SUCRA value (or percentage) gives the probability that a treatment is among the most effective

treatments, with a value of 1 (or 100%) meaning that a treatment is certain to be the most effective of treatments in the network, and 0 (or 0%) meaning that a treatment is certain to be the least effective. Rankings based on SUCRA values are considered to take into account uncertainty in estimated treatment effects better than general ranking probabilities (30,31).

Guidelines and network meta-analysis comparison

We compared information extracted from each guideline set to the results of the corresponding network meta-analysis. We assessed whether the recommended drugs or drug classes and effectiveness estimates in the guideline match with the highest-ranking drug or drug class, determined by SUCRA values, from the network meta-analysis.

Comparison with published pair-wise meta-analyses

To determine if network meta-analysis gives incremental information to guideline developers that cannot be gained from pairwise meta-analyses, we examined the results of published, high-quality systematic reviews and pairwise meta-analyses identified previously (32). We matched the pairwise results to the network meta-analysis results based on which interventions were compared and the year of publication. We examined agreement of the findings from the two approaches qualitatively. For example, when the 95% confidence interval covers the null value, we concluded that one drug is not superior to another drug.

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Results

Guideline identification and extraction

We identified 9 versions of the AAO's POAG PPP: 1989, 1990, 1992, 1996, 2000, 2003, 2005, 2006, and 2010 (7,10–17). Based on literature search years and recommendations relevant to POAG medical therapies, we grouped the guidelines together into 5 “sets”: 1989-1992, 1996, 2000-2003, 2005-2006, and 2010. Of these guideline sets, only 2010 made recommendations about a specific first-line medical therapy (Appendix Table 1). The 2010 guideline stated, based on a meta-analysis of 11 trials (33), that “Prostaglandin analogs are the most effective drugs at lowering IOP and can be considered as initial medical therapy.” No other guideline made specific recommendations at a class or drug level for POAG, though all guidelines recommended medical treatment, in general, as initial therapy. For example, the 2005-2006 guidelines, without citing any literature, stated, “in many instances, topical medications constitute effective initial therapy.” Related recommendations were about considerations in choosing initial care, or for monitoring the effect of medical interventions on IOP.

The 1989-1992 and 1996 guideline sets did not report search years; the 2000-2003, 2005-2006; and 2010 sets did: the stopping years were 1999, 2004, and 2009, respectively. Accordingly, five

244 separate network meta-analyses were conducted using studies published up to 1991, 1995,
245 1999, 2004, and 2009. From here on, we refer to the network meta-analyses based on the last
246 trial publication date. For example, we refer to the network meta-analysis of trials published up
247 to 1995 as the 1995 network meta-analysis.

249 *Network meta-analysis*

250 *Search result, general study characteristics, and risk of bias*

251 Of the 10,936 unique records previously identified (21), 91 RCTs met the eligibility criteria for
252 the current study (Appendix Figure 1; see also reference list in Appendix 3). The first trial was
253 published in 1983 and the latest in 2009 (see Appendix Table 2 for the characteristics of the
254 trial networks for each analysis year). Later networks include trials that were generally larger,
255 more often multi-center, and of shorter duration than trials included in earlier networks. The
256 proportion of trials categorized with unclear risk of bias appears to decrease in later networks,
257 indicating that reporting of trial quality may have improved over time. The risk of bias of
258 included studies is reported in Appendix Table 2.

260 *Interventions*

261 Overall, included trials studied 12 drugs from four classes (alpha-2 adrenergic agonists, beta
262 blockers, prostaglandins, and carbonic anhydrase inhibitors) as well as placebo/vehicle/no
263 treatment (Appendix Figure 2a-e). Up to 1991, three active drugs (betaxolol, levobunolol, and
264 timolol) from one class (beta blockers) and placebo were studied in RCTs. By 1995, an
265 additional five drugs (apraclonidine, carteolol, dorzolamide, latanoprost, and unoprostone),

with at least one drug from each class, were studied in trials. The 1999 network includes a total of 10 active drugs with the addition of brimonidine and brinzolamide. Both the 2004 and 2009 networks include all active drugs. Many direct comparisons between drugs, such as latanoprost versus placebo, have not been made in trials, even by 2009, and for the direct comparisons that have been made there are often only one or two trials (Appendix Figure 3).

Network meta-analysis outcomes

The results of our network meta-analyses indicate that all interventions were superior to placebo/vehicle/no treatment in lowering 3-month IOP for all analysis years (Figure 1a-b; Appendix Figure 4a-j). The mean reduction (95% credible interval) for the class with the highest ranking SUCRA value compared with placebo/vehicle/no treatment at each analysis year was as follows: 1991: beta blockers, 4.01 (0.48; 7.43); 1995: alpha-2 adrenergic agonists, 5.64 (1.73; 9.50); 1999: prostaglandins, 5.43 (3.38; 7.38); 2004: prostaglandins, 4.75 (3.11; 6.44); 2009: prostaglandins, 4.58 (2.94; 6.24). The drug with the highest ranking at each analysis year was as follows: 1991: levobunolol, 4.53 (3.31; 5.79); 1995: levobunolol, 5.36 (4.30; 6.41); 1999: latanoprost, 5.89 (4.66; 7.14); 2004: bimatoprost, 5.87 (4.67; 7.06); 2009: bimatoprost, 5.87 (4.96; 6.77). Point estimates for drug and class effects appear to attenuate and the credible intervals become narrower over time (Figure 1a-b).

Rankings based on cumulative ranking probabilities from SUCRA plots were generally consistent with effect estimates (Figure 2a-b; Appendix Figure 4). The only time at which the highest cumulative rank did not match with treatment effect was in the 1995 network, in which

apraclonidine had the highest mean effect but levobunolol had the highest cumulative ranking. In the 2004 and 2009 networks, rankings remained stable for both drugs and classes. Sometimes, when two drugs were included at the same time point, they crossed in cumulative rank at subsequent points (Figure 2a-b).

Guideline and network meta-analysis comparison

A summary of the comparison between AAO clinical practice guideline recommendations and network meta-analytic findings is provided in Table 1. Based on our cumulative network-meta-analyses, quantitative evidence of treatment effect could have informed recommendations on specific treatments at both the drug and class level for all guideline sets had network meta-analysis methods been available. Though the 2010 guideline recommended prostaglandins as first-line treatment for POAG, the AAO PPP might have made this recommendation earlier on the basis of network meta-analysis results (Table 1). The first prostaglandin drug was approved by the US Food and Drug Administration in 1996 and was first mentioned in the 1996 PPP as a treatment option (13).

Comparison with published pair-wise meta-analyses

Compared to the 78 drug comparisons that we were able to make in our network meta-analysis, we were able to identify only six pairwise comparisons from four published high-quality systematic reviews and meta-analyses (34–37) (Figure 3; see Appendix Table 3 for the characteristics of comparisons from identified systematic reviews). As all identified systematic reviews had literature searches conducted in 2005 or 2006, we compared their results to those

from our 2009 network meta-analysis. Of these six comparisons, the network meta-analysis findings were different for two. In both cases (latanoprost versus brimonidine and bimatoprost versus travoprost), there were two pairwise systematic reviews on the same topic, with one arriving at the same conclusion as our network meta-analysis and one arriving at a different conclusion (34,35). For example, the mean IOP reduction (95% credible or confidence interval) for latanoprost versus brimonidine from each source were as follows: our analysis: 1.22 (0.56; 1.88) (latanoprost superior); Hodge et al.: 1.10 (0.57; 1.63) (latanoprost superior) (37); and Li et al.: 1.04 (-0.91; 3.01) (no superiority shown) (34).

Discussion

We identified five sets of guidelines from AAO's POAG PPPs. Specific treatment recommendations were made only in the last update (2010 guideline). Using cumulative network meta-analyses of the RCTs available at the time, we were able to determine which drug and drug class were with the greatest IOP-lowering effect at the time of each major revision. Both the final 2010 guideline and the corresponding network meta-analysis indicate that prostaglandins should be considered first-line treatment in terms of IOP reduction. It is worth noting that, had network meta-analysis been available to guideline developers, prostaglandins, which are now the standard treatment, may have been recommended as early as the 2000 update.

The AAO's POAG PPPs up to 2010 did not give recommendations at the drug level. This may be because the guideline producers did not want to appear to favor a particular drug

manufacturer, since some glaucoma drugs, such as bimatoprost, are still under patent. The cultures of other clinical areas or different glaucoma guideline groups may lead them to have different approaches to making treatment recommendations (e.g., at the drug level rather than at the class level) (9). Our results indicate that drugs within a class generally have similar effects on IOP. A notable exception is unoprostone, which was the least effective drug in the 2004 and 2009 network meta-analyses despite the high ranking of all other prostaglandins. Indeed, there is uncertainty as to whether unoprostone should be classified as a prostaglandin analogue (38,39).

Systematic reviews underpin trustworthy clinical practice guidelines (1), however, with the increasing number of competing alternatives available for a given condition, traditional pairwise meta-analysis techniques do not meet the need. This is because pairwise meta-analysis compares only interventions that have been directly evaluated in individual trials. As illustrated in Appendix Figure 2a-e, direct evidence obtained from RCTs was only available for one third of all possible pairwise comparisons of first-line medical treatments for POAG, which limited the potential of evidence synthesis and treatment recommendations. Additionally, as shown in our example, fewer than 10% of the 78 possible pairwise comparisons in 2009 were evaluated in published, high-quality, pairwise systematic reviews, and the conclusions were discordant for two of the six comparisons.

Without information for all possible direct comparisons, it would be difficult for guideline developers to compare all interventions to one another and form coherent recommendations

on the basis of pairwise meta-analysis alone. Since Antman and Lau's landmark cumulative meta-analysis over 20 years ago (19,20), the statistical methods for systematic review have evolved to allow us to extend their methodology to the comparison of multiple treatments in a single analysis to facilitate timely recommendations. Network meta-analysis allows all treatments to be compared to one another and ranked, facilitating the selection of a preferred treatment for a specific condition. Even older interventions, now rarely used, can be included in the analyses to assess whether their disuse was well founded or whether their use might be resurrected in certain circumstances.

There are several considerations before adopting findings from network meta-analysis in making guideline recommendations. First, it may not be appropriate to make a recommendation on the basis of only the initial studies of a new treatment, since their estimates may be less certain and may overestimate the true treatment effect. In our example, the estimated treatment effects fade over time, which is consistent among different drugs and classes (Figure 1a-b). This phenomenon of diminishing effects has been noted in previous studies (40,41), with potential explanations being time-lag bias, publication bias, small study effects, change in study quality, and heterogeneity in the clinical population (41,42).

Secondly, a network meta-analysis conducted as part of guidelines development should consider both effectiveness and safety outcomes, as both are important to patients, their caregivers, and their doctors (6,43,44). Our analysis, conducted mainly to explore the potential

utility of the methodology of network meta-analysis, considered only one factor, intraocular pressure, an effectiveness outcome relevant to the recommendation process.

Finally, caution should be exercised by guidelines producers and clinicians in applying the findings of any network meta-analysis, related to the potential limitations of the statistical methodology. For example, the validity of the results of a network meta-analysis depends on the validity of the assumptions being made; the results depend on the network definitions applied; and the treatment rankings are associated with uncertainty. Although these issues have been discussed extensively in the network meta-analysis literature (5,6,45,46), they may not be familiar to guidelines producers and clinicians.

In recent years, network meta-analysis has begun to be recognized as a useful tool for guideline developers. The Endocrine Society commissioned a network meta-analysis to inform recommendations of treatment for its 2012 clinical practice guideline for osteoporosis in men (47,48). The National Institute for Health and Clinical Excellence (NICE) in the UK also used network meta-analysis for developing recommendations for its 2013 neuropathic pain treatment guideline (49) and 2014 bipolar disorder guideline (50). Based on these examples and our experience, we provide recommendations for guideline developers who seek to conduct or use a network meta-analysis (see Box with elaboration below).

What guideline developers should know about network meta-analysis?

- Always work with statisticians and methodologists who understand the methods for network analysis from the outset.
- Define treatment networks explicitly. The nodes in the networks should represent available treatment options in clinical practice.
- Analyze outcomes that matter to patients.
- Use the ranking statistics that account for the uncertainty in ranking, and interpret ranking together with the size of treatment effect.
- Interpret the findings carefully when there are insufficient data, a large amount of heterogeneity/inconsistency, or data of poor quality.

First, always work with statisticians and methodologists who understand the methods for network analysis from the outset. Network meta-analysis methods can be complex and include many nuances. The validity of the finding relies on a careful assessment of the transitivity assumption when forming the network and later in the analysis. Whether conducting or commissioning a network meta-analysis, developers should ensure that the review team includes experts in network meta-analysis methodology.

Second, define treatment networks explicitly. The nodes in the networks should represent available treatment options in clinical practice. In network meta-analyses of drug interventions, for example, nodes may be defined as each dose of each drug, any dose of each drug with all doses merged, or each class with all drugs merged, depending on the question of interest and the biological or clinical appropriateness of merging the different treatments. In addition, so that the analysis is most clinically informative, all potential treatment options that are suitable or indicated for patients with a given condition should be considered. Finally, even if an intervention is not of direct clinical interest (e.g., placebo), it may still be included in the

analysis to inform the comparisons. Similar to a pair-wise meta-analysis, depending on how interventions are defined and which studies are included, the findings from network meta-analysis may vary.

Third, analyze outcomes that matter to patients. Patients may value treatment safety as much as or more than treatment effectiveness. Analyses that consider both effectiveness and safety outcomes allow for better understanding of treatment applicability in clinical settings. In addition, clinical outcomes and patient-reported outcomes usually are more important to patients than surrogate outcome. For example, the effectiveness outcome in our analysis, IOP, is understood as a surrogate outcome for visual function with conflicting evidence supporting their relationship (51–53). Despite this, IOP served as the basis for recommendations in the AAO PPPs and was the primary determinant of effectiveness in trials, while more relevant outcomes, such as visual field, were often not even measured in these primary studies.

Fourth, use the ranking statistics that account for the uncertainty in ranking, and interpret ranking together with the size of treatment effect. Ranking based on SUCRA values is preferred to crude ranking since it summarizes the estimated probabilities for all possible ranks (30,31). Even when using an appropriate measure, however, the highest-ranking treatment may have a modest or insignificant clinical effect, and therefore rankings need to be interpreted in the context of the size of treatment effect.

Fifth, interpret the findings carefully when there are insufficient data, a large amount of heterogeneity/inconsistency, or data of poor quality. When comparisons are informed by a small number of studies, the treatment effects and rankings may not be stable. The guideline developers should consider the potential for clinical or methodological heterogeneity/inconsistency and risk of bias that may affect the results, and apply appropriate caution in the interpretation of the findings.

Conclusion

Our example of IOP in POAG showed that, had network meta-analysis been available, the AAO POAG PPP may have recommended prostaglandins, the current first-line treatment, earlier. When many different treatment options are available, guideline developers may wish to go beyond pairwise meta-analyses because pairwise meta-analyses are limited by treatments that have been compared directly in individual studies. Guideline developers should consider working with trained methodologists to conduct network meta-analysis of all relevant outcomes, and using the results of network meta-analyses to inform future clinical recommendations.

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635 **Figure 1. Network meta-analysis treatment effect estimates relative to placebo for each**
636 **analysis year**
637 a. Individual drugs vs. placebo
638
639 b. Classes vs placebo
640

641 **Figure 2. Relative ranking over time based on surface under the cumulative ranking curve**
642 **(SUCRA) value**
643 a. Drug rankings
644
645 b. Class rankings
646
647 Legend for figure 2
648 SUCRA percentage is the probability a treatment has of being among the most effective
649 treatments in the network (e.g. 100% if certainly the most effective, 0% if certainly the least)
650

Figure 3. Comparison between network meta-analysis and published pair-wise meta-analysis results

Legend for figure 3

The network meta-analysis results are from the 2009 network.

* Hodge WG, Lachaine J, Steffensen I, et al. The efficacy and harm of prostaglandin analogues for IOP reduction in glaucoma patients compared to dorzolamide and brimonidine: a systematic review. *Br J Ophthalmol*. 2008;92(1):7-12

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‡ Li N, Chen XM, Zhou Y, Wei ML, Yao X. Travoprost compared with other prostaglandin analogues or timolol in patients with open-angle glaucoma or ocular hypertension: Meta-analysis of randomized controlled trials. *Clin Exp Ophthalmol*. 2006;34(8):755-764

§ Aptel F, Cucherat M, Denis P. Efficacy and tolerability of prostaglandin analogs: a meta-analysis of randomized controlled clinical trials. *J Glaucoma*. 2008;17(8):667-673

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Table 1. Comparison between the American Academy of Ophthalmology Preferred Practice Pattern Guidelines recommendations and network meta-analysis results

Guideline sets	Guideline first-line therapy recommendation (estimated IOP reduction)	Best ranking* drug class and drug IOP reduction mmHg (95% credible interval) relative to placebo/vehicle/no treatment	
		Class	Drug
1989, 1990, 1992	NR	Beta blockers 4.01 (0.48 to 7.43)	Levobunolol 4.53 (3.31 to 5.79)
1996	NR	Alpha agonists 5.64 (1.73 to 9.50)	Levobunolol 5.36 (4.30 to 6.41)
2000, 2003	NR	Prostaglandins 5.43 (3.38 to 7.38)	Latanoprost 5.89 (4.66 to 7.14)
2005, 2006	NR	Prostaglandins 4.75 (3.11 to 6.44)	Bimatoprost 5.87 (4.67 to 7.06)
2010	Prostaglandins 25-33%	Prostaglandins 4.58 (2.94 to 6.24)	Bimatoprost 5.87 (4.96 to 6.77)

IOP: Intraocular pressure

NR: No recommendation

* Ranking based on surface under the cumulative ranking curve values

Appendix Table 1. Recommendations from the American Academy of Ophthalmology Preferred Practice Pattern Guidelines for Primary Open-Angle

Guideline(s)	Years of literature searched	Recommendations* relevant to first-line topical medical treatment	Does recommendation concern a specific medical treatment?	Interpretation of recommendation	Guideline rating for strength of evidence
1989, 1990, 1992	None specified	"While the choice of initial therapy depends on numerous considerations, in most instances one begins with topical medications."	No	Recommendation for medical treatment as initial therapy	None
1989, 1990, 1992	None specified	"To determine the effectiveness of topical therapy, it is necessary to distinguish between the therapeutic impact of an agent on IOP and ordinary background fluctuations of IOP."	No	Recommendation for monitoring the effects of intervention on IOP	None
1996	"Since 1985"	"The choice of initial therapy depends on numerous considerations, and discussion of treatment should include all options."	No	Recommendation for considerations in choosing initial care	III
1996	"Since 1985"	"In most instances, topical medications are initial therapy."	No	Recommendation for medical treatment as initial therapy	III
1996	"Since 1985"	"To determine the effectiveness of topical therapy, it is necessary to distinguish between the therapeutic impact of an agent on IOP and ordinary background fluctuations of IOP."	No	Recommendation for monitoring the effects of intervention on IOP	None
2000, 2003	1995-1999	"The choice of initial therapy depends on numerous considerations, and discussion of treatment should include all options."	No	Recommendation for considerations in choosing initial care	III

2000, 2003	1995-1999	"In most instances, topical medications constitute initial therapy."	No	Recommendation for medical treatment as initial therapy	III
2000, 2003	1995-1999	"To determine the effectiveness of topical therapy, it is necessary to distinguish between the therapeutic impact of an agent on IOP and ordinary background fluctuations of IOP."	No	Recommendation for monitoring the effects of intervention on IOP	None
2005, 2006	1999-2004	"The choice of initial therapy depends on numerous considerations, and discussion of treatment with the patient should include appropriate options."	No	Recommendation for considerations in choosing initial care	III
2005, 2006	1999-2004	"In many instances, topical medication constitute effective initial therapy. "	No	Recommendation for medical treatment as initial therapy	None
2005, 2006	1999-2004	"To determine the effectiveness of topical therapy, it is necessary to distinguish between the therapeutic impact of an agent on IOP and ordinary background fluctuations of IOP."	No	Recommendation for monitoring the effects of intervention on IOP	None
2010	2004-2009	"The choice of initial therapy depends on numerous considerations, and discussion of treatment with the patient should include the relative risks and benefits of the three options."	No	Recommendation for considerations in choosing initial care	III
2010	2004-2009	To determine the effectiveness of topical therapy, it is necessary to distinguish between the therapeutic impact of an agent on IOP and ordinary background fluctuations of IOP."	No	Recommendation for monitoring the effects of intervention on IOP	None

2010	2004-2009	"Prostaglandin analogs are the most effective drugs at lowering IOP and can be considered as initial therapy unless other considerations such as cost, side effects, intolerance, or patient refusal preclude this."	Yes	Recommendation for prostaglandin class as initial medical therapy	I†
------	-----------	--	-----	---	----

IOP: Intraocular Pressure

* Any statement which uses "recommend," "should," "appropriate," "necessary," "must", or words suggesting a particular practice such as prescribing a medication is considered a recommendation

† Stewart WC, Konstas AG, Nelson LA, Kruff B. Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines.

Appendix Table 2. Characteristics and risk of bias of networks

Characteristics of the Trial Network	Analysis year				
	1991	1995	1999	2004	2009
Trials, n	18	29	48	76	91
Total participants, n	1,161	2,641	5,960	10,717	13,870
Trial sample size, median (IQR)	69 (28 to 85)	72 (42 to 137)	76 (41 to 159)	91 (43 to 195)	90 (47 to 213)
Reported as multicenter, n (%)	7 (39)	16 (55)	33 (69)	49 (64)	56 (62)
Trial length, median months (IQR)	6 (3 to 15)	6 (3 to 12)	3 (3 to 12)	3 (3 to 6)	3 (3 to 6)
Reported region of recruitment					
Yes, n (%)	8 (44)	14 (48)	30 (63)	51 (67)	62 (68)
North America, n (%)*,†	5 (63)	8 (57)	17 (57)	27 (53)	32 (52)
Latin America, n (%)*,†	0 (0)	1 (7)	1 (3)	2 (4)	3 (5)
Europe, n (%)*,†	0 (0)	2 (14)	7 (23)	14 (27)	15 (24)
Africa, n (%)*,†	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asia, n (%)*,†	1 (13)	4 (29)	7 (23)	11 (22)	14 (23)
Oceania, n (%)*,†	0 (0)	1 (7)	1 (3)	1 (2)	2 (3)
No, n (%)	10 (56)	15 (52)	18 (38)	25 (33)	29 (32)
Risk of Bias					
Random sequence generation					
Low, n (%)	2 (11)	6 (21)	14 (29)	28 (37)	37 (41)
Unclear, n (%)	16 (89)	23 (79)	34 (71)	48 (63)	54 (59)
High, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Allocation concealment					
Low, n (%)	3 (17)	5 (17)	8 (17)	17 (22)	24 (26)
Unclear, n (%)	15 (83)	24 (83)	40 (83)	59 (78)	67 (74)
High, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Masking of participants					
Low, n (%)	6 (33)	12 (41)	20 (42)	30 (39)	36 (40)
Unclear, n (%)	10 (56)	14 (48)	24 (50)	31 (41)	39 (43)

	High, n (%)	2 (11)	3 (10)	4 (8)	15 (20)	16 (18)
Masking of outcome assessor for IOP						
Low, n (%)		3 (17)	4 (14)	6 (13)	14 (18)	19 (21)
Unclear, n (%)		15 (83)	25 (86)	42 (88)	57 (75)	65 (71)
High, n (%)		0 (0)	0 (0)	0 (0)	5 (7)	7 (8)
Reported funding source						
Yes, n (%)		6 (33)	11 (38)	21 (44)	42 (55)	50 (55)
Industry funding, n (%)*,‡		6 (100)	11 (100)	21 (100)	41 (98)	48 (96)
Government funding, n (%)*,‡		2 (33)	3 (27)	3 (27)	5 (12)	6 (12)
No, n (%)		12 (67)	18 (62)	27 (56)	34 (45)	41 (45)
Reported author financial conflicts of interest						
Yes, n (%)		6 (33)	12 (41)	22 (56)	33 (44)	38 (42)
Conflict of interest for at least one author, n (%)*		6 (100)	12 (100)	18 (82)	24 (73)	28 (74)
No conflicts of interest, n (%)*		0 (0)	0 (0)	4 (18)	9 (27)	10 (26)
No, n (%)		12 (67)	17 (59)	26 (54)	43 (56)	53 (58)

IQR: Interquartile range

* % denominator is n for "Yes"

† Trials could report more than one region of recruitment

‡ Trials could report more than one funding source

Appendix Table 3. Characteristics of comparisons identified in published pairwise systematic reviews

Pairwise systematic review	Literature search year	Participants	Intervention	Comparison	Outcome	Time point	Narrative findings	Mean difference mmHg (95% confidence interval)	Number of studies used in comparison (number of participants)
Li et al., 2006	2005	Patients with OHT or POAG	Travoprost	Timolol	IOP value	Pooled over treatment visits (value at last visit if pooled data not available)	Travoprost is more effective than timolol in lowering IOP	-0.81 (-1.16 to -0.45)	4 (1354)
Li et al., 2006	2005	Patients with OHT or POAG	Travoprost	Bimatoprost	IOP value	Pooled over treatment visits (value at last visit if pooled data not available)	Travoprost seems equivalent to bimatoprost in lowering IOP	-0.08 (-0.62 to 0.79)	5 (402)
Li et al., 2006	2005	Patients with OHT or POAG	Travoprost	Latanoprost	IOP value	Pooled over treatment visits (value at last visit if pooled data not available)	Travoprost seems equivalent to latanoprost in lowering IOP	-0.57 (-1.18 to 0.04)	6 (912)

Fung et al., 2007	2006	Patients with OHT, POAG, or NTG	Latanoprost	Brimonidine	IOP reduction	Trial endpoint	Latanoprost is more effective than brimonidine in lowering IOP	-1.10 (-1.63 to -0.57)	14 (1725)
Aptel et al., 2008	2006	Patients with OHT or POAG	Bimatoprost	Latanoprost	IOP reduction	3 months (or between 1 and 6 months if not available) (Morning IOP)	Bimatoprost is more effective than latanoprost in lowering IOP	-0.50 (-0.99 to -0.01)	5 (893)
Aptel et al., 2008	2006	Patients with OHT or POAG	Bimatoprost	Travoprost	IOP reduction	3 months (or between 1 and 6 months if not available) (Morning IOP)	Bimatoprost is more effective than travoprost in lowering IOP	-1.02 (-1.72 to -0.32)	3 (458)
Aptel et al., 2008	2006	Patients with OHT or POAG	Latanoprost	Travoprost	IOP reduction	3 months (or between 1 and 6 months if not available) (Morning IOP)	Latanoprost seems equivalent to travoprost in lowering IOP	-0.40 (-1.29 to 0.40)	3 (458)

Hodge et al., 2007	2006	Patients with OHT or glaucoma	Latanoprost	Brimonidine	IOP reduction	3 months	Latanoprost seems equivalent to brimonidine in lowering IOP	-1.04 (-3.01 to 0.91)	3 (451)
Hodge et al., 2007	2006	Patients with OHT or glaucoma	Latanoprost	Dorzolamide	IOP reduction	3 months	Latanoprost is more effective than dorzolamide in lowering IOP	-2.64 (-3.25 to -2.04)	3 (328)

POAG: Primary open-angle glaucoma

OHT: Ocular hypertension

IOP: Intraocular pressure

■ 1991 ● 1995 ◆ 1999 ▲ 2004 ■ 2009

Brinzolamide

Dorzolamide

Apraclonidine

Brimonidine

Betaxolol

Carteolol

Timolol

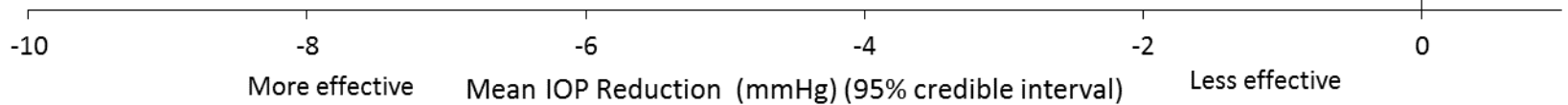
Levobunolol

Unoprostone

Latanoprost

Travoprost

Bimatoprost



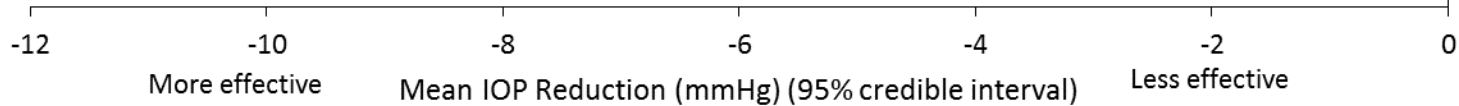
■ 1991 ● 1995 ◆ 1999 ▲ 2004 ■ 2009

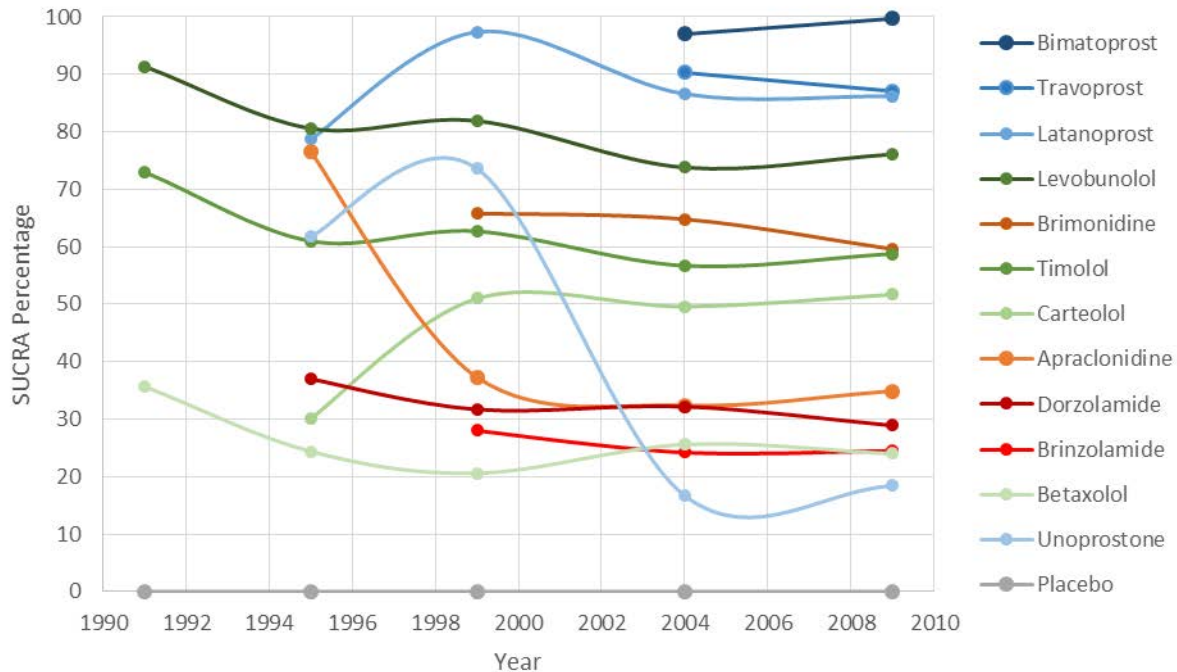
Carbonic anhydrase
inhibitors

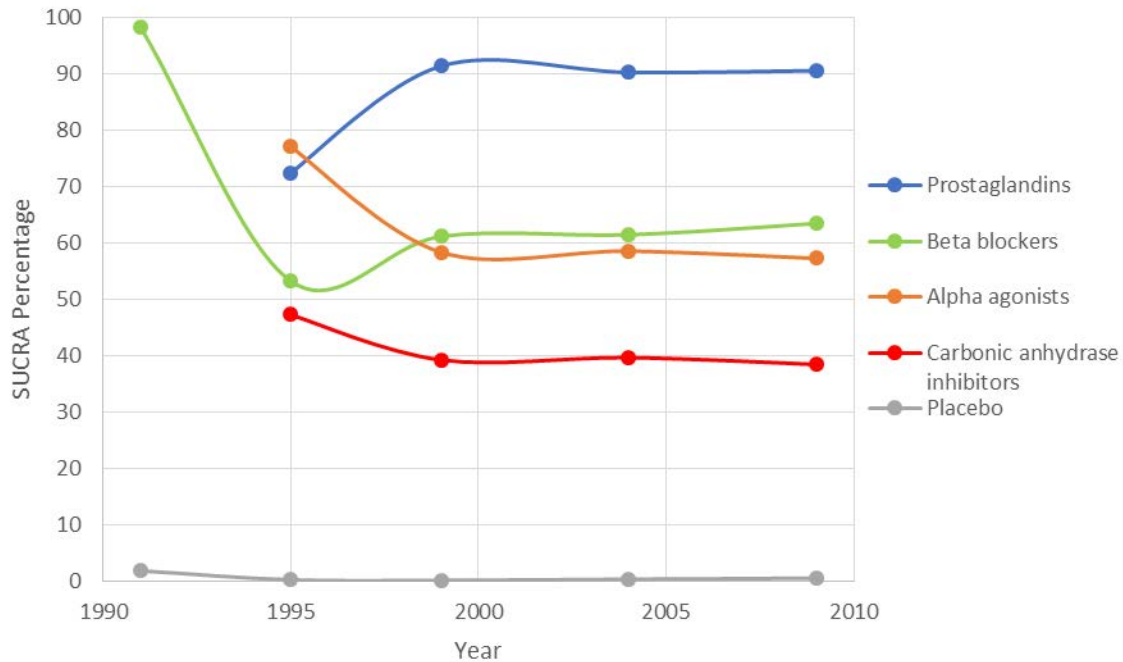
Alpha agonists

Beta blockers

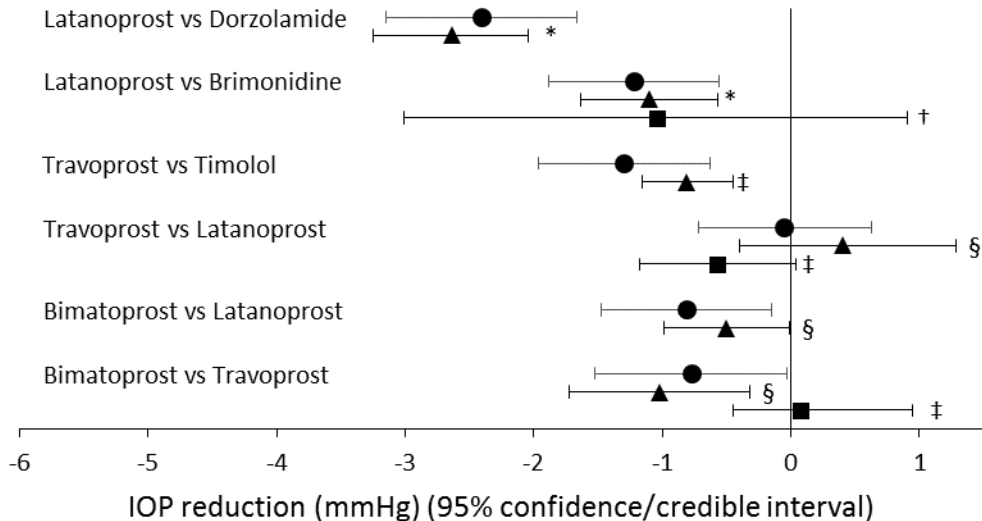
Prostaglandins







● Our results ▲ Published meta-analysis results ■ Published meta-analysis results (II)



Appendix 1. Search Strategies

Cochrane Library

- #1 MeSH descriptor: [Glaucoma, Open-Angle] explode all trees
- #2 MeSH descriptor: [Ocular Hypertension] explode all trees
- #3 (open near/2 angle near/2 glaucoma*)
- #4 (POAG or OHT)
- #5 (((increas* or elevat* or high*) near/3 (ocular or intra-ocular)) and pressure)
- #6 {or #1-#5}
- #7 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
- #8 MeSH descriptor: [Timolol] explode all trees
- #9 Timolol*
- #10 MeSH descriptor: [Metipranolol] explode all trees
- #11 Metipranolol*
- #12 MeSH descriptor: [Carteolol] explode all trees
- #13 Carteolol*
- #14 MeSH descriptor: [Levobunolol] explode all trees
- #15 Levobunolol*
- #16 MeSH descriptor: [Betaxolol] explode all trees
- #17 Betaxolol*
- #18 MeSH descriptor: [Carbonic Anhydrase Inhibitors] explode all trees
- #19 (Carbonic near/2 Anhydrase near/2 Inhibitor*)
- #20 MeSH descriptor: [Acetazolamide] explode all trees
- #21 Acetazolam*
- #22 Brinzolamide*
- #23 Dorzolamide*
- #24 MeSH descriptor: [Prostaglandins, Synthetic] explode all trees
- #25 latanoprost*
- #26 travoprost*
- #27 bimatoprost*
- #28 unoprostone*
- #29 tafluprost*
- #30 MeSH descriptor: [Antihypertensive Agents] explode all trees
- #31 MeSH descriptor: [Pilocarpine] explode all trees
- #32 Pilocarpin*
- #33 MeSH descriptor: [Epinephrine] explode all trees
- #34 epinephrine*
- #35 dipivefrin*
- #36 MeSH descriptor: [Adrenergic alpha-2 Receptor Agonists] explode all trees
- #37 (adrenergic near/2 alpha* near/3 agonist*)
- #38 apraclonidin*
- #39 brimonidine*
- #40 (drug* or medic* or pharmacologic*) near/3 (treat* or therap* or intervent*)
- #41 {or #7-#40}
- #42 #6 and #41

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. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma open angle/
14. exp ocular hypertension/
15. (open adj2 angle adj2 glaucoma\$.tw.
16. (POAG or OHT).tw.
17. (((increas\$ or elevat\$ or high\$) adj3 (ocular or intra-ocular)) and pressure).tw.
18. or/13-17
19. exp adrenergic beta antagonists/
20. exp timolol/
21. timolol\$.tw.
22. exp metipranolol/
23. metipranolol\$.tw.
24. exp carteolol/
25. carteolol\$.tw.
26. exp levobunolol/
27. levobunolol\$.tw.
28. exp betaxolol/
29. betaxolol\$.tw.
30. exp carbonic anhydrase inhibitors/
31. (carbonic adj2 anhydrase adj2 inhibitor\$.tw.
32. exp Acetazolamide/
33. acetazolamide\$.tw.
34. brinzolamide\$.tw.
35. dorzolamide\$.tw.
36. exp Prostaglandins, Synthetic/
37. latanoprost\$.tw.
38. travoprost\$.tw.
39. bimatoprost\$.tw.
40. unoprostone\$.tw.
41. brimonidine\$.tw.
42. exp antihypertensive agents/
43. exp pilocarpine/
44. pilocarpin\$.tw.
45. exp epinephrine/
46. epinephrin\$.tw.
47. dipivefrin\$.tw.
48. exp Adrenergic alpha-2 Receptor Agonists/
49. ((adrenergic adj2 alpha\$ adj2 receptor\$) or (adrenergic adj2 alpha\$ adj2 agonist\$)).tw.

50. apraclonidin\$.tw.
51. tafluprost\$.tw.
52. ((drug\$ or medic\$ or pharmacologic\$) adj3 (treat\$ or therap\$ or intervent\$)).tw.
53. or/19-52
54. 18 and 53
55. 12 and 54

Embase.com

- #1 'randomized controlled trial'/exp
- #2 'randomization'/exp
- #3 'double blind procedure'/exp
- #4 'single blind procedure'/exp
- #5 random*:ab,ti
- #6 #1 OR #2 OR #3 OR #4 OR #5
- #7 'animal'/exp OR 'animal experiment'/exp
- #8 'human'/exp
- #9 #7 AND #8
- #10 #7 NOT #9
- #11 #6 NOT #10
- #12 'clinical trial'/exp
- #13 (clin* NEAR/3 trial*):ab,ti
- #14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
- #15 'placebo'/exp
- #16 placebo*:ab,ti
- #17 random*:ab,ti
- #18 'experimental design'/exp
- #19 'crossover procedure'/exp
- #20 'control group'/exp
- #21 'latin square design'/exp
- #22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
- #23 #22 NOT #10
- #24 #23 NOT #11
- #25 'comparative study'/exp
- #26 'evaluation'/exp
- #27 'prospective study'/exp
- #28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
- #29 #25 OR #26 OR #27 OR #28
- #30 #29 NOT #10
- #31 #30 NOT (#11 OR #23)
- #32 #11 OR #24 OR #31
- #33 'open angle glaucoma'/exp
- #34 'intraocular hypertension'/exp
- #35 (open NEAR/2 angle):ab,ti AND (angle NEAR/2 glaucoma*):ab,ti
- #36 poag:ab,ti OR oht:ab,ti
- #37 ((increas* OR elevat* OR high*) NEAR/3 (ocular OR 'intra ocular')):ab,ti AND pressure:ab,ti
- #38 #33 OR #34 OR #35 OR #36 OR #37
- #39 'beta adrenergic receptor blocking agent'/exp
- #40 'timolol'/exp

#41 timolol*:ab,ti
 #42 'metipranolol'/exp
 #43 metipranolol*:ab,ti
 #44 'carteolol'/exp
 #45 carteolol*:ab,ti
 #46 'levobunolol'/exp
 #47 levobunolol*:ab,ti
 #48 'betaxolol'/exp
 #49 betaxolol*:ab,ti
 #50 'carbonate dehydratase inhibitor'/exp
 #51 (carbonic NEAR/2 anhydrase):ab,ti AND (anhydrase NEAR/2 inhibitor*):ab,ti
 #52 'acetazolamide'/exp
 #53 acetazolamide*:ab,ti
 #54 brinzolamide*:ab,ti
 #55 dorzolamide*:ab,ti
 #56 'latanoprost'/exp
 #57 latanoprost*:ab,ti
 #58 'travoprost'/exp
 #59 travoprost*:ab,ti
 #60 'bimatoprost'/exp
 #61 bimatoprost*:ab,ti
 #62 'unoprostone isopropyl ester'/exp
 #63 unoprostone*:ab,ti
 #64 'brimonidine'/exp
 #65 brimonidine*:ab,ti
 #66 'antihypertensive agent'/exp
 #67 'pilocarpine'/exp
 #68 pilocarpin*:ab,ti
 #69 'adrenalin'/exp
 #70 epinephrin*:ab,ti
 #71 dipivefrin*:ab,ti
 #72 'alpha 2 adrenergic receptor stimulating agent'/exp
 #73 (adrenergic NEAR/2 alpha*):ab,ti AND (alpha* NEAR/2 agonist*):ab,ti
 #74 apraclonidin*:ab,ti
 #75 'tafluprost'/exp
 #76 tafluprost*:ab,ti
 #77 ((drug* OR medic* OR pharmacologic*) NEAR/3 (treat* OR therap* OR intervent*)):ab,ti
 #78 #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
 #79 #38 AND #78
 #80 #32 AND #79

PubMed

#1 ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR
 randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR
 (groups[tiab])) NOT (animals[mh] NOT humans[mh])

#2 (open[tw] AND angle[tw] AND glaucoma*[tw]) NOT Medline[sb]
#3 (POAG[tw] OR OHT[tw]) NOT Medline[sb]
#4 (((increase*[tw] OR elevat*[tw] OR high*[tw]) AND (ocular[tw] OR intra-ocular[tw])) AND pressure[tw]) NOT Medline[sb]
#5 #2 OR #3 OR #4
#6 timolol*[tw] NOT Medline[sb]
#7 metipranolol*[tw] NOT Medline[sb]
#8 carteolol*[tw] NOT Medline[sb]
#9 levobunolol*[tw] NOT Medline[sb]
#10 betaxolol*[tw] NOT Medline[sb]
#11 (carbonic[tw] AND anhydrase[tw] AND inhibitor*[tw]) NOT Medline[sb]
#12 acetazolamide*[tw] NOT Medline[sb]
#13 brinzolamide*[tw] NOT Medline[sb]
#14 dorzolamide*[tw] NOT Medline[sb]
#15 latanoprost*[tw] NOT Medline[sb]
#16 travoprost*[tw] NOT Medline[sb]
#17 bimatoprost*[tw] NOT Medline[sb]
#18 unoprostone*[tw] NOT Medline[sb]
#19 brimonidine*[tw] NOT Medline[sb]
#20 pilocarpin*[tw] NOT Medline[sb]
#21 epinephrin*[tw] NOT Medline[sb]
#22 dipivefrin* NOT Medline[sb]
#23 ((adrenergic[tw] AND alpha*[tw] AND receptor*[tw]) OR (adrenergic[tw] AND alpha*[tw] AND agonist*[tw])) NOT Medline[sb]
#24 apraclonidin*[tw] NOT Medline[sb]
#25 tafluprost*[tw] NOT Medline[sb]
#26 ((drug*[tw] OR medic*[tw] OR pharmacologic*[tw]) AND (treat*[tw] OR therap*[tw] OR intervent*[tw])) NOT Medline[sb]
#27 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28 #5 AND #27
#29 #1 AND #28

Appendix 2. Network Meta-Analysis Statistical Methods

For the Bayesian random-effects network meta-analysis models, we applied non-informative, yet proper, priors so that the data dominate the posterior distribution. We drew samples of the parameters of interest from the full posterior distribution using Markov Chain Monte Carlo algorithms. We used 2 chains and obtained 50,000 samples (after a 20,000 sample burn-in period). Our models assumed that variance was homogeneous at both the drug and the class level.

A valid network meta-analysis requires the assumption that there are no systematic differences between included comparisons other than the treatments themselves (5). In other words, in a hypothetical RCT consisting of all the treatments included in the network, participants could be randomized to any of the treatments (5). We examined this assumption based on the distribution of participant characteristics, interventions, and design characteristics among trials. We further considered the statistical disagreement between direct and indirect comparisons, or inconsistency, present among studies. To assess inconsistency, we used the loop-specific approach with inconsistency models. For the loop-specific approach, each independent closed triangular or quadratic loop (set of three or four treatments connected by direct comparisons) in the network is evaluated for inconsistency and incorporated as separate parameters (i.e. inconsistency factors) in the model (30, 54). This analysis was conducted in STATA 13® (30,55,56).

Up to 2009, the loop-specific approach to inconsistency indicated evidence of inconsistency in 5 of 30 triangular loops (17%). We could not find any qualitative reasons to explain inconsistency among studies included in the inconsistent loops.

Appendix 3. References for Included Studies

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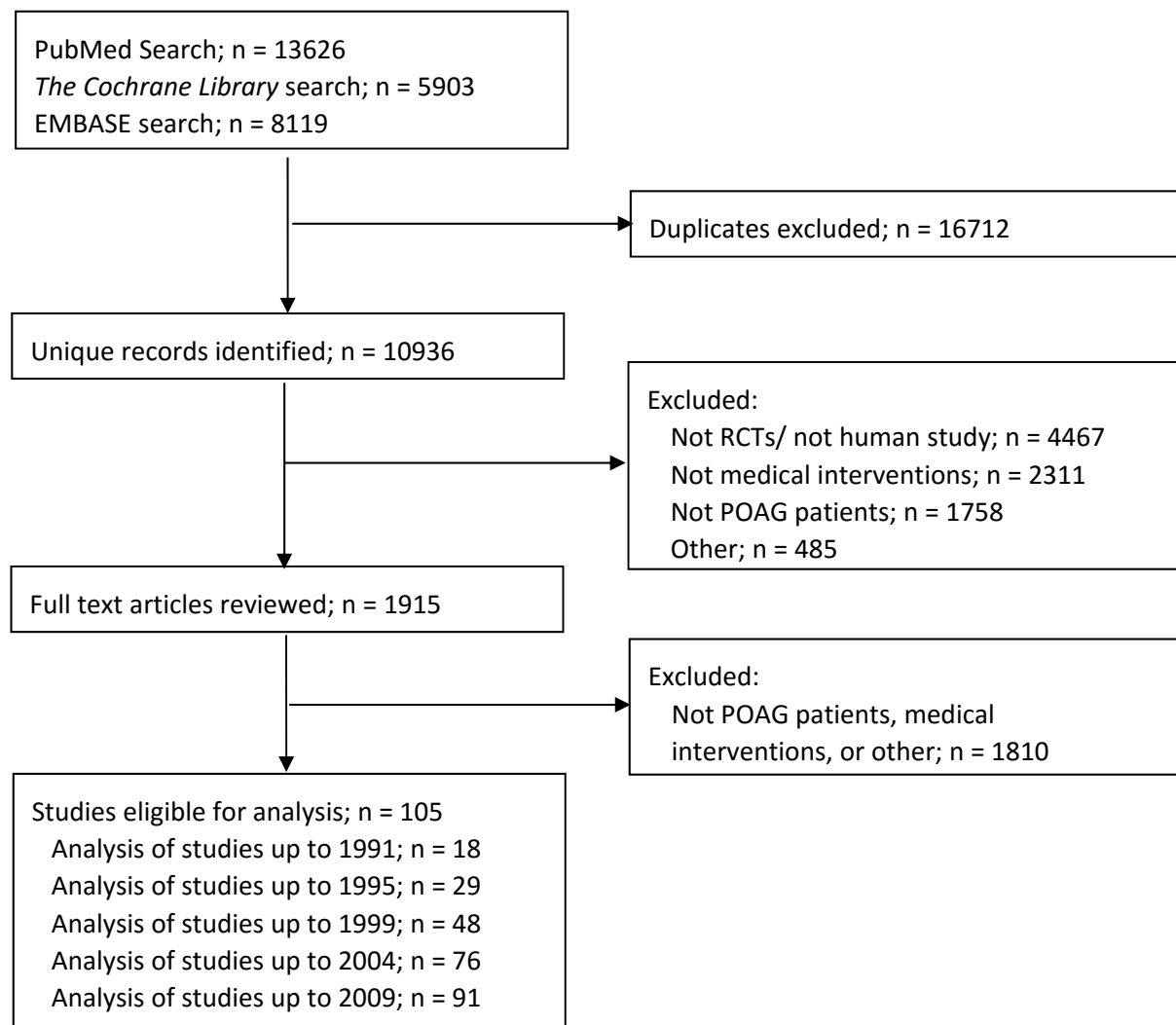
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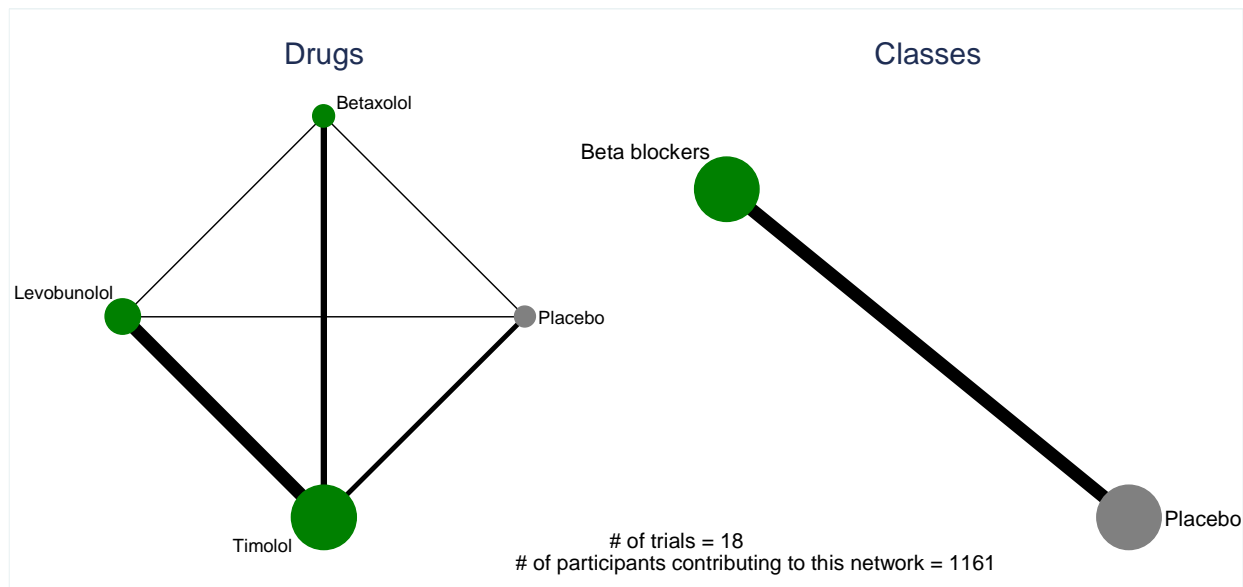
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Appendix Figure 1. Selection of studies

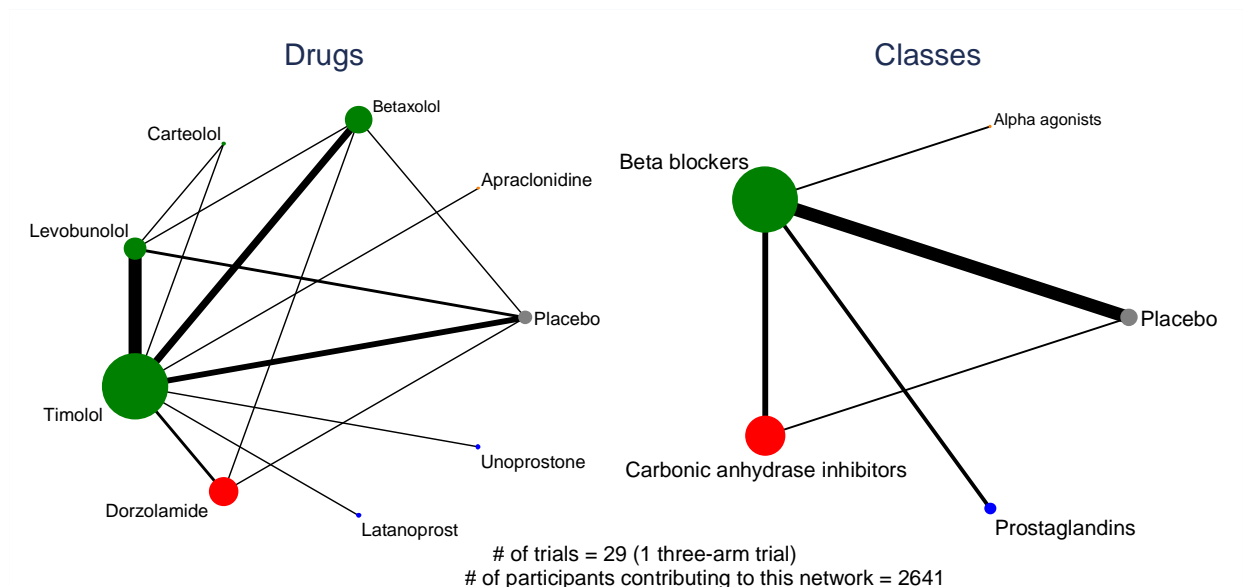


Appendix Figure 2. Network graphs

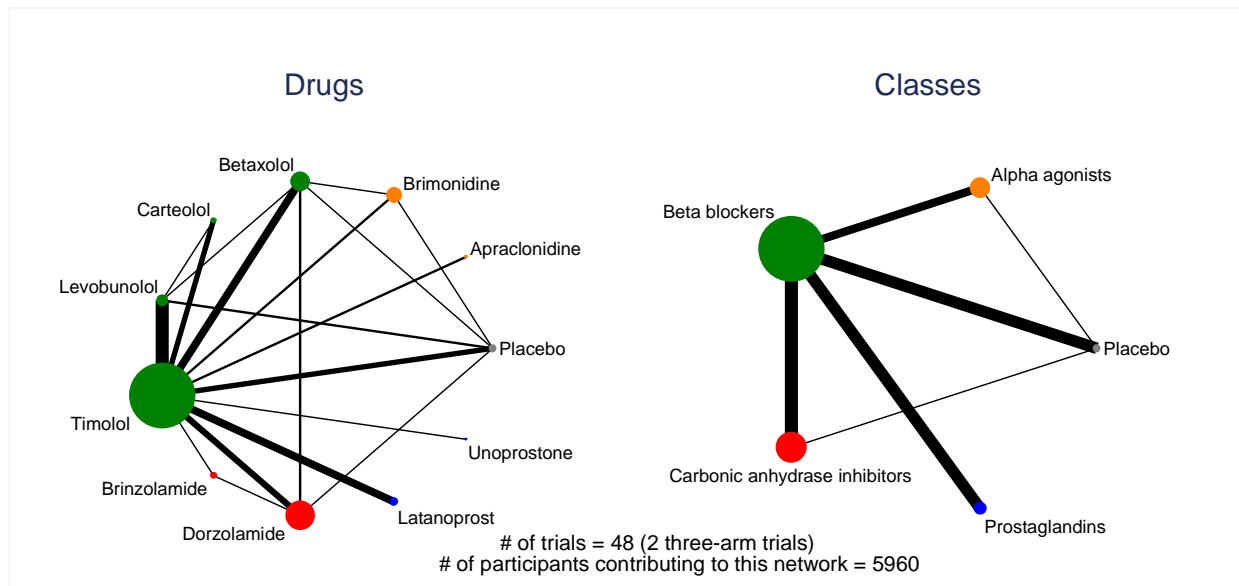
a. 1991 Network graphs



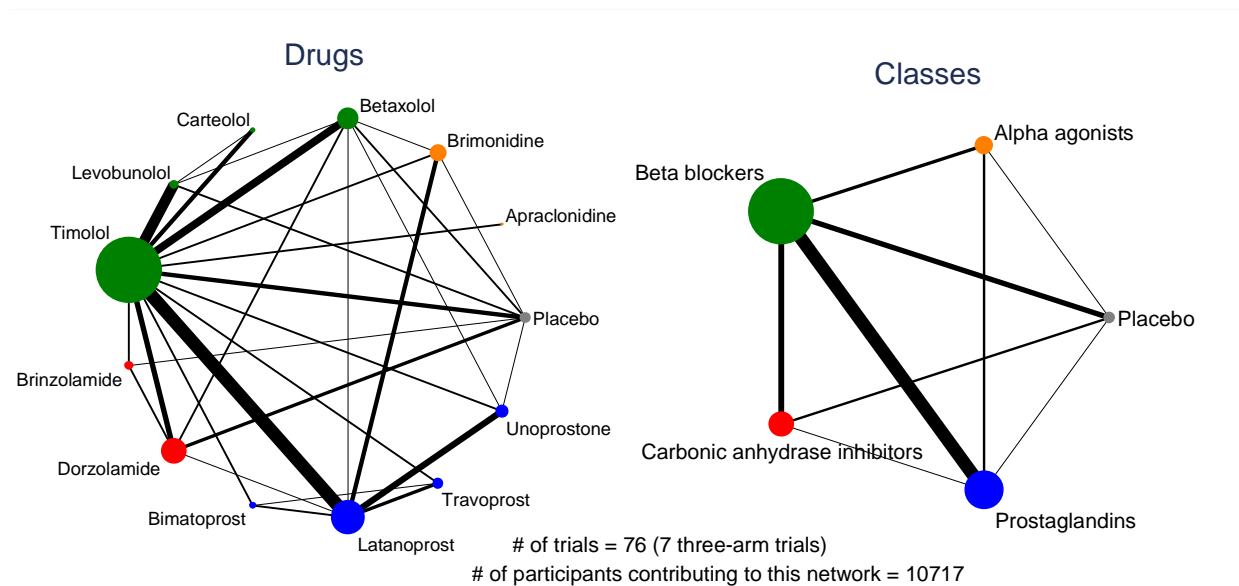
b. 1995 Network graphs



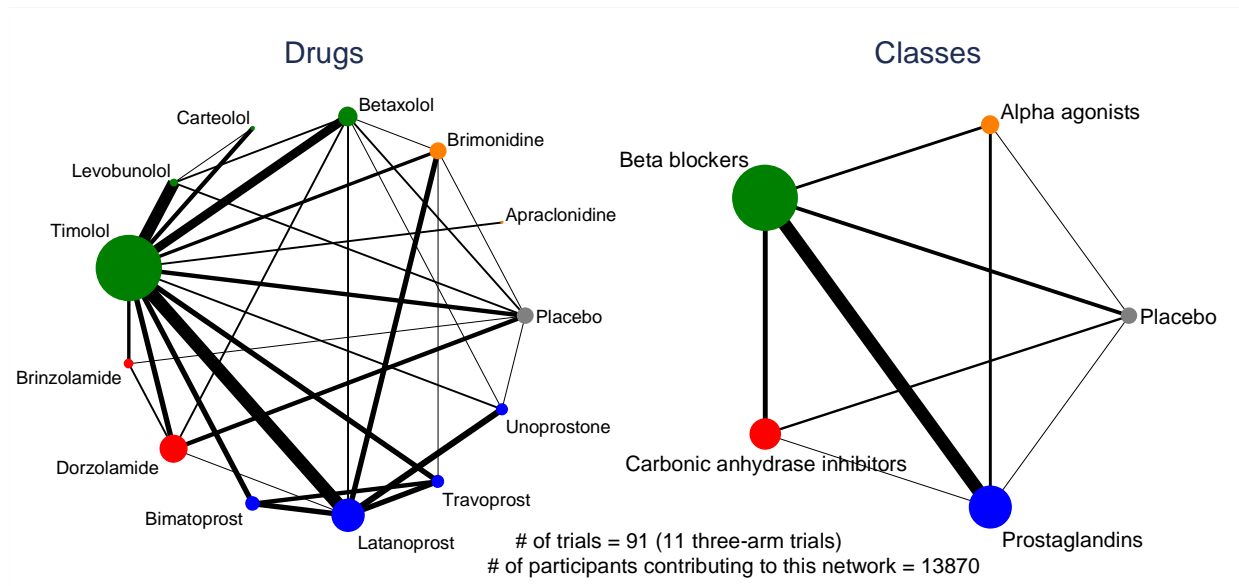
c. 1999 Network graphs



d. 2004 Network graphs



e. 2009 Network graphs



Legend:

Each node represent one drug or class, color-coded by class. The size of the node is proportional to the number of participants randomized to that drug/class.

The edges represent direct comparisons, that is, when there is a line connecting two drugs, the two drugs have been compared directly to each other. The width of the edge is proportional to the number of trials.

Grey	Placebo/vehicle/no treatment
Orange	Alpha-2 adrenergic agonist
Green	Beta-blocker
Red	Carbonic anhydrase inhibitor
Blue	Prostaglandin analog

Appendix Figure 3. Summary estimates for intraocular pressure at 3 months derived from direct comparisons for treatments and classes at each analysis year

a. Drug direct comparisons

Analysis year		1991					
Column 1	Column 2	Comparison-specific heterogeneity					
		Num. of studies	Mean difference*	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Brimonidine	-	-	-	-	-	-
	Betaxolol	1	-3.90	-5.29	-2.52	NA	NA
	Levobunolol	1	-6.98	-9.12	-4.84	NA	NA
	Timolol	3	-3.52	-4.65	-2.39	0.45	45%
	Brinzolamide	-	-	-	-	-	-
	Dorzolamide	-	-	-	-	-	-
	Bimatoprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Apraclonidine vs							
	Timolol	-	-	-	-	-	-
Brimonidine vs							
	Betaxolol	-	-	-	-	-	-
	Timolol	-	-	-	-	-	-
	Brinzolamide	-	-	-	-	-	-
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
Betaxolol vs							
	Levobunolol	1	-2.37	-3.85	-0.90	0.00	0%
	Timolol	4	-1.39	-2.19	-0.58	NA	NA
	Dorzolamide	-	-	-	-	-	-
	Latanoprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Carteolol vs							
	Levobunolol	-	-	-	-	-	-
	Timolol	-	-	-	-	-	-
Levobunolol vs							
	Timolol	8	0.01	-0.70	0.71	0.31	32%
Timolol vs							
	Brinzolamide	-	-	-	-	-	-
	Dorzolamide	-	-	-	-	-	-
	Bimatoprost	-	-	-	-	-	-
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
	Tafluprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Brinzolamide vs							
	Dorzolamide	-	-	-	-	-	-
Dorzolamide vs							
	Latanoprost	-	-	-	-	-	-
Bimatoprost vs							
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
Latanoprost vs							
	Travoprost	-	-	-	-	-	-
	Tafluprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-

Analysis year		1995					
		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference*	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Brimonidine	-	-	-	-	-	-
	Betaxolol	1	-3.90	-5.29	-2.52	NA	NA
	Levobunolol	2	-7.52	-8.53	-6.50	0.00	0%
	Timolol	4	-3.91	-5.12	-2.69	0.85	57%
	Brinzolamide	-	-	-	-	-	-
	Dorzolamide	1	-2.90	-5.23	-0.57	NA	NA
	Bimatoprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Apraclonidine vs							
	Timolol	1	0.80	-1.31	2.91	NA	NA
Brimonidine vs							
	Betaxolol	-	-	-	-	-	-
	Timolol	-	-	-	-	-	-
	Brinzolamide	-	-	-	-	-	-
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
Betaxolol vs							
	Levobunolol	1	-2.37	-3.85	-0.90	NA	NA
	Timolol	5	-1.52	-2.18	-0.86	0.00	0%
	Dorzolamide	1	-0.60	-1.70	0.50	NA	NA
	Latanoprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
Carteolol vs							
	Levobunolol	1	-2.90	-4.59	-1.22	NA	NA
	Timolol	1	-0.70	-2.26	0.86	NA	NA
Levobunolol vs							
	Timolol	9	-0.03	-0.60	0.55	0.16	22%
Timolol vs							
	Brinzolamide	-	-	-	-	-	-
	Dorzolamide	2	0.65	-0.43	1.73	0.41	68%
	Bimatoprost	-	-	-	-	-	-
	Latanoprost	1	-0.90	-1.73	-0.07	NA	NA
	Travoprost	-	-	-	-	-	-
	Tafluprost	-	-	-	-	-	-
	Unoprostone	1	0.20	-0.63	1.03	NA	NA
Brinzolamide vs							
	Dorzolamide	-	-	-	-	-	-
Dorzolamide vs							
	Latanoprost	-	-	-	-	-	-
Bimatoprost vs							
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
Latanoprost vs							
	Travoprost	-	-	-	-	-	-
	Tafluprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-

Analysis year		1999					
		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	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	1	-3.90	-5.29	-2.52	NA	NA
	Levobunolol	2	-7.52	-8.53	-6.50	0.00	0%
	Timolol	4	-3.91	-5.12	-2.69	0.85	57%
	Brinzolamide	1	-2.10	-3.44	-0.76	NA	NA
	Dorzolamide	1	-2.90	-5.23	-0.57	NA	NA
	Bimatoprost	-	-	-	-	-	-
	Unoprostone	-	-	-	-	-	-
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	2	0.69	0.28	1.10	0.00	0%
	Brinzolamide	-	-	-	-	-	-
	Latanoprost	3	-1.04	-2.22	0.14	0.83	77%
	Travoprost	-	-	-	-	-	-
Betaxolol vs							
	Levobunolol	1	-2.37	-3.85	-0.90	NA	NA
	Timolol	6	-1.57	-2.17	-0.98	0.00	0%
	Dorzolamide	2	-0.30	-0.96	0.36	0.00	0%
	Latanoprost	-	-	-	-	-	-
	Unoprostone	1	0.6	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	10	-0.03	-0.48	0.43	0.06	12%
Timolol vs							
	Brinzolamide	1	0.90	-0.17	1.97	NA	NA
	Dorzolamide	5	0.76	0.13	1.39	0.24	47%
	Bimatoprost	-	-	-	-	-	-
	Latanoprost	6	-1.4	-2.17	-0.64	0.43	58%
	Travoprost	2	-2.04	-4.19	0.11	2.14	88%
	Tafluprost	-	-	-	-	-	-
	Unoprostone	1	0.2	-0.63	1.03	NA	NA
Brinzolamide vs							
	Dorzolamide	1	-0.50	-1.23	0.23	NA	NA
Dorzolamide vs							
	Latanoprost	1	-2.90	-3.7	-2.10	NA	NA
Bimatoprost vs							
	Latanoprost	-	-	-	-	-	-
	Travoprost	-	-	-	-	-	-
Latanoprost vs							
	Travoprost	1	-1.40	-2.4	-0.40	NA	NA
	Tafluprost	-	-	-	-	-	-
	Unoprostone	6	3.07	2.51	3.63	0.01	2%

Analysis year		2004					
		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Brimonidine	1	-2.3	-3.99	-0.61	NA	NA
	Betaxolol	2	-2.9	-4.65	-1.15	1.30	81%
	Levobunolol	2	-7.52	-8.53	-6.50	0.00	0%
	Timolol	4	-3.91	-5.12	-2.69	0.85	57%
	Brinzolamide	1	-2.1	-3.44	-0.76	NA	NA
	Dorzolamide	3	-2.59	-3.67	-1.51	0.00	0%
	Bimatoprost	-	-	-	-	-	-
	Unoprostone	1	-0.2	-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	2	0.69	0.28	1.10	0.00	0%
	Brinzolamide	-	-	-	-	-	-
	Latanoprost	4	-1.04	-1.86	-0.22	0.46	67%
	Travoprost	-	-	-	-	-	-
Betaxolol vs							
	Levobunolol	1	-2.37	-3.85	-0.90	NA	NA
	Timolol	7	-1.29	-1.71	-0.87	0.00	0%
	Dorzolamide	2	-0.3	-0.96	0.36	0.00	0%
	Latanoprost	1	-0.2	-2.20	1.80	NA	NA
	Unoprostone	1	0.6	0.09	1.11	NA	NA
Carteolol vs							
	Levobunolol	1	-2.9	-4.59	-1.22	NA	NA
	Timolol	4	0.03	-0.61	0.68	0.11	24%
Levobunolol vs							
	Timolol	10	-0.03	-0.48	0.43	0.06	12%
Timolol vs							
	Brinzolamide	2	0.67	-0.51	1.85	0.12	7%
	Dorzolamide	5	0.76	0.13	1.39	0.24	47%
	Bimatoprost	2	-2.17	-2.89	-1.45	0.00	0%
	Latanoprost	12	-1.4	-1.91	-0.89	0.44	64%
	Travoprost	2	-2.04	-4.19	0.11	2.14	88%
	Tafluprost	-	-	-	-	-	-
	Unoprostone	2	-0.58	-1.15	0.00	0.85	87%
Brinzolamide vs							
	Dorzolamide	2	-0.58	-1.15	0.00	0.00	0%
Dorzolamide vs							
	Latanoprost	1	-2.9	-3.70	-2.10	NA	NA
Bimatoprost vs							
	Latanoprost	2	0.59	-0.36	1.54	0.17	28%
	Travoprost	1	0.6	-0.16	1.36	NA	NA
Latanoprost vs							
	Travoprost	3	-0.35	-1.52	0.83	0.76	73%
	Tafluprost	-	-	-	-	-	-
	Unoprostone	6	3.07	2.51	3.63	0.01	2%

Analysis year		2009					
		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	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	2	-2.90	-4.65	-1.15	1.30	81%
	Levobunolol	2	-7.52	-8.53	-6.50	0.00	0%
	Timolol	4	-3.91	-5.12	-2.69	0.85	57%
	Brinzolamide	1	-2.10	-3.44	-0.76	NA	NA
	Dorzolamide	4	-1.91	-2.92	-0.90	0.51	51%
	Bimatoprost	-	-	-	-	-	-
	Unoprostone	1	3.07	2.51	3.63	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	3	0.66	0.25	1.06	0.00	0%
	Brinzolamide	-	-	-	-	-	-
	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	8	-1.58	-2.29	-0.87	0.43	48%
	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							
	Brinzolamide	3	1.10	0.50	1.70	0.00	0%
	Dorzolamide	5	0.76	0.13	1.39	0.24	47%
	Bimatoprost	5	-2.07	-2.64	-1.49	0.15	35%
	Latanoprost	12	-1.40	-1.91	-0.89	0.44	64%
	Travoprost	5	-1.22	-2.20	-0.24	0.79	67%
	Tafluprost	-	-	-	-	-	-
	Unoprostone	2	0.94	-0.43	2.31	0.85	87%
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	5	0.98	0.02	1.93	0.90	80%
	Travoprost	4	0.62	-0.80	2.05	1.82	87%
Latanoprost vs							
	Travoprost	5	-0.32	-1.01	0.37	0.30	50%
	Tafluprost	-	-	-	-	-	-
	Unoprostone	6	3.07	2.51	3.63	0.01	2%

b. Class direct comparisons

Analysis year		1991					
Column 1	Column 2	Comparison-specific heterogeneity					
		Num. of studies	Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs	Alpha agonists	-	-	-	-	-	-
	Beta blockers	5	4.11	-5.31	-2.91	1.22	67%
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	-	-	-	-	-	-
Alpha agonists vs	Beta blockers	-	-	-	-	-	-
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	-	-	-	-	-	-
Beta Blockers vs	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	-	-	-	-	-	-
Carbonic anhydrase inhibitors vs	Prostaglandins	-	-	-	-	-	-

Analysis year		1995					
		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Alpha agonists	-	-	-	-	-	-
	Beta blockers	7	-4.91	-6.43	-3.38	3.53	86%
	Carbonic anhydrase inhibitors	1	-2.90	-5.23	-0.57	NA	NA
	Prostaglandins	-	-	-	-	-	-
Alpha agonists vs							
	Beta blockers	1	0.80	-1.31	2.91	NA	NA
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	-	-	-	-	-	-
Beta Blockers vs							
	Carbonic anhydrase inhibitors	3	0.27	-0.73	1.28	0.56	71%
	Prostaglandins	2	-0.35	-1.43	0.73	0.43	70%
Carbonic anhydrase inhibitors vs							
	Prostaglandins	-	-	-	-	-	-

Analysis year		1999					
Column 1	Column 2	Comparison-specific heterogeneity					
		Num. of studies	Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs	Alpha agonists	1	-2.3	-3.99	-0.61	NA	NA
	Beta blockers	7	-4.91	-6.43	-3.38	3.53	86%
	Carbonic anhydrase inhibitors	1	-2.9	-5.23	-0.57	NA	NA
	Prostaglandins	-	-	-	-	-	-
Alpha agonists vs	Beta blockers	5	0.39	-0.73	1.51	1.32	87%
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	3	-1.04	-2.22	0.14	0.83	77%
Beta Blockers vs	Carbonic anhydrase inhibitors	8	0.49	-0.04	1.02	0.31	54%
	Prostaglandins	7	-1.14	-1.95	-0.33	0.72	72%
Carbonic anhydrase inhibitors vs	Prostaglandins	1	-2.9	-3.7	-2.10	NA	NA

Analysis year		2004					
		Comparison-specific heterogeneity					
Column 1	Column 2	Num. of studies	Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Alpha agonists	1	-2.3	-3.99	-0.61	NA	NA
	Beta blockers	8	-4.52	-6.11	-2.93	4.66	91%
	Carbonic anhydrase inhibitors	4	-2.4	-3.24	-1.55	0.00	0%
	Prostaglandins	1	-0.2	-1.56	1.16	NA	NA
Alpha agonists vs							
	Beta blockers	5	0.39	-0.73	1.51	1.32	87%
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	4	-1.04	-1.86	-0.22	0.46	67%
Beta Blockers vs							
	Carbonic anhydrase inhibitors	9	0.46	-0.06	0.97	0.29	50%
	Prostaglandins	20	-1.19	-1.84	-0.54	1.78	90%
Carbonic anhydrase inhibitors vs							
	Prostaglandins	1	-2.9	-3.70	-2.10	NA	NA

Analysis year		2009					
Column 1	Column 2	Comparison-specific heterogeneity					
		Num. of studies	Mean difference	95% CI, lower	95% CI, upper	Tau-squared	I-squared
Placebo vs							
	Alpha agonists	1	-2.30	-3.99	-0.61	NA	NA
	Beta blockers	8	-4.52	-6.11	-2.93	4.66	91%
	Carbonic anhydrase inhibitors	5	-1.89	-2.66	-1.12	0.31	43%
	Prostaglandins	1	-0.20	-1.56	1.16	NA	NA
Alpha agonists vs							
	Beta blockers	6	0.29	-0.76	1.34	1.26	84%
	Carbonic anhydrase inhibitors	-	-	-	-	-	-
	Prostaglandins	6	-1.35	-2.14	-0.55	0.65	72%
Beta Blockers vs							
	Carbonic anhydrase inhibitors	10	0.57	0.08	1.06	0.33	55%
	Prostaglandins	27	-1.25	-1.79	-0.72	1.58	88%
Carbonic anhydrase inhibitors vs							
	Prostaglandins	1	-2.90	-3.70	-2.10	NA	NA

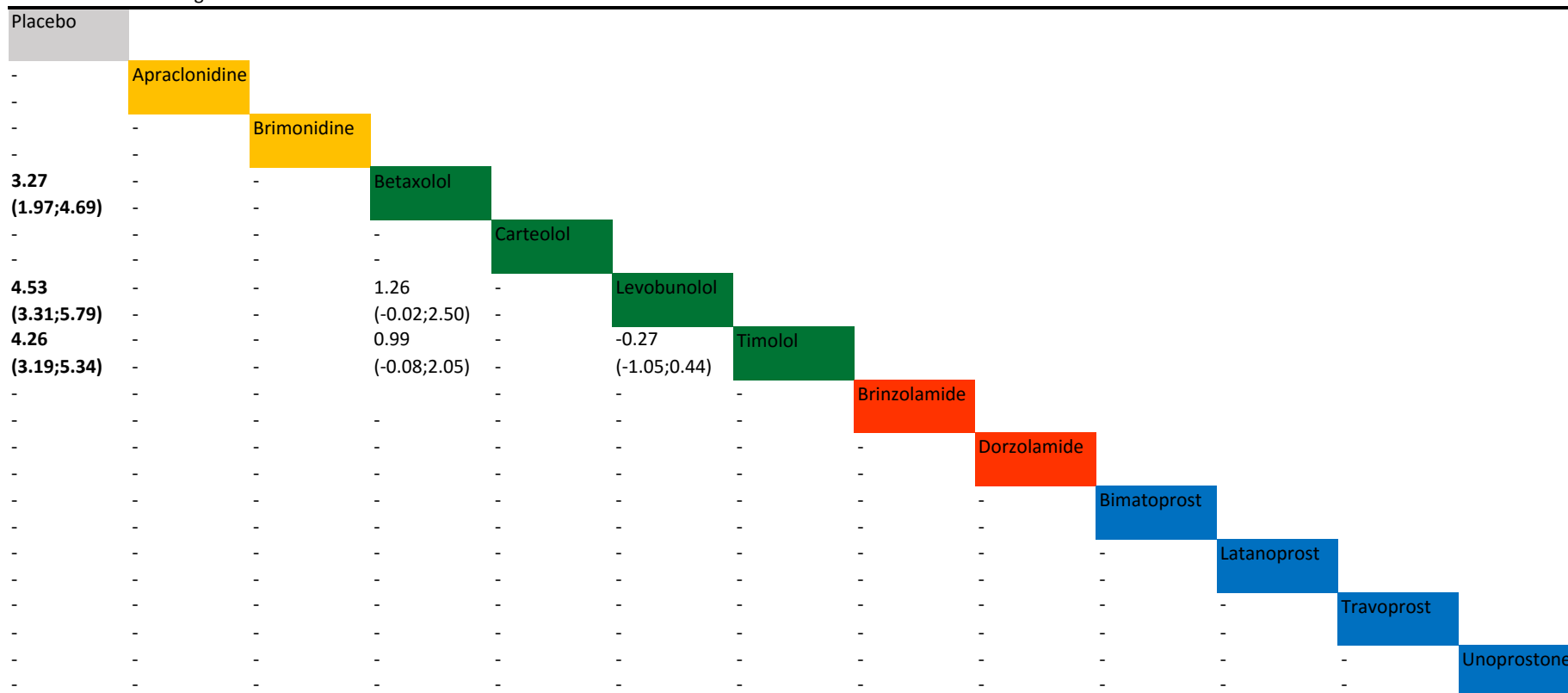
*Mean difference is calculated using the intraocular pressure of the drug in column 2 - column 1.

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

Color coding

Grey	Placebo/vehicle/no treatment
Orange	Alpha-2 adrenergic agonist
Green	Beta-blocker
Red	Carbonic anhydrase inhibitor
Blue	Prostaglandin analog

a. 1991 Network - Drugs



b. 1995 Network - Drugs

Placebo													
5.63 (2.56;8.64)	Apraclonidine												
-	-	Brimonidine											
-	-	-	Betaxolol										
3.61 (2.43;4.82)	-2.02 (-5.02;1.02)	-	-	0.13 (-1.53;1.78)	Carteolol								
3.75 (2.02;5.49)	-1.89 (-5.12;1.4)	-	-	-	-	1.62 (0.08;3.17)	Levobunolol						
5.36 (4.30;6.41)	-0.27 (-3.23;2.70)	-	-	1.75 (0.66;2.81)	1.09 (-0.43;2.60)	-0.53 (-1.24;0.19)	Timolol						
4.83 (3.88;5.78)	-0.80 (-3.67;2.07)	-	-	1.22 (0.28;2.13)	-	-	-	Brinzolamide					
-	-	-	-	-	-	-	-	-	Dorzolamide				
4.03 (2.54;5.5)	-1.60 (-4.76;1.55)	-	-	0.42 (-1.07;1.85)	0.29 (-1.70;2.24)	-1.33 (-2.77;0.11)	-0.80 (-2.12;0.49)	-	-	Bimatoprost			
-	-	-	-	-	-	-	-	-	-	-	Latanoprost		
5.49 (3.40;7.54)	-0.15 (-3.55;3.27)	-	-	1.87 (-0.23;3.93)	1.74 (-0.67;4.13)	0.12 (-1.85;2.09)	0.66 (-1.19;2.50)	-	1.45 (-0.78;3.71)	-	-	Travoprost	
-	-	-	-	-	-	-	-	-	-	-	-	-	
4.88 (2.83;6.97)	-0.75 (-4.12;2.7)	-	-	1.27 (-0.77;3.32)	1.14 (-1.21;3.50)	-0.48 (-2.44;1.53)	0.05 (-1.77;1.92)	-	0.85 (-1.36;3.15)	-	-0.61 (-2.75;1.52)	-	Unoprostone

c. 1999 Network - Drugs

Placebo												
3.84 (2.18;5.44)	Apraclonidine											
4.65 (3.44;5.81)	0.81 (-0.69;2.46)	Brimonidine										
3.39 (2.35;4.47)	-0.45 (-1.97;1.07)	-1.26 (-2.4;-0.04)	Betaxolol									
4.28 (3.09;5.45)	0.44 (-1.21;2.12)	-0.37 (-1.66;0.92)	0.89 (-0.19;2.01)	Carteolol								
5.09 (4.11;6.04)	1.24 (-0.33;2.87)	0.43 (-0.67;1.59)	1.69 (0.65;2.65)	0.81 (-0.17;1.83)	Levobunolol							
4.57 (3.72;5.41)	0.73 (-0.68;2.19)	-0.09 (-1.04;0.91)	1.18 (0.38;1.93)	0.29 (-0.57;1.16)	-0.52 (-1.15;0.11)	Timolol						
3.52 (1.83;5.17)	-0.32 (-2.32;1.72)	-1.13 (-2.89;0.62)	0.13 (-1.42;1.72)	-0.76 (-2.46;0.94)	-1.56 (-3.2;0.01)	-1.04 (-2.54;0.41)	Brinzolamide					
3.73 (2.62;4.82)	-0.12 (-1.72;1.51)	-0.93 (-2.14;0.32)	0.33 (-0.65;1.28)	-0.55 (-1.71;0.61)	-1.36 (-2.37;-0.34)	-0.84 (-1.64;-0.04)	0.20 (-1.15;1.60)	Dorzolamide				
-	-	-	-	-	-	-	-	-	Bimatoprost			
5.89 (4.66;7.14)	2.05 (0.35;3.78)	1.24 (-0.06;2.59)	2.50 (1.28;3.70)	1.61 (0.37;2.87)	0.80 (-0.28;1.90)	1.32 (0.42;2.23)	2.36 (0.67;4.13)	2.16 (0.94;3.39)	-	Latanoprost		
-	-	-	-	-	-	-	-	-	-	-	Travoprost	
4.97 (3.12;6.76)	1.13 (-0.94;3.16)	0.32 (-1.64;2.23)	1.58 (-0.14;3.26)	0.69 (-1.19;2.48)	-0.11 (-1.96;1.63)	0.41 (-1.27;1.98)	1.45 (-0.74;3.57)	1.25 (-0.57;3.02)	-	-0.91 (-2.74;0.65)	-	Unoprostone

d. 2004 Network - Drugs

Placebo												
2.98 (1.43;4.56)	Apraclonidine											
4.20 (3.3;5.09)	1.22 (-0.34;2.78)	Brimonidine										
2.76 (2.02;3.52)	-0.22 (-1.76;1.32)	-1.44 (-2.27;-0.57)	Betaxolol									
3.63 (2.55;4.71)	0.65 (-1.05;2.34)	-0.57 (-1.68;0.54)	0.87 (-0.18;1.91)	Carteolol								
4.59 (3.79;5.40)	1.61 (0.04;3.17)	0.40 (-0.49;1.3)	1.83 (1.04;2.61)	0.96 (-0.03;1.97)	Levobunolol							
3.90 (3.24;4.55)	0.92 (-0.53;2.36)	-0.30 (-0.99;0.41)	1.14 (0.54;1.72)	0.27 (-0.60;1.15)	-0.69 (-1.28;-0.11)	Timolol						
2.69 (1.51;3.89)	-0.29 (-2.11;1.51)	-1.51 (-2.79;-0.21)	-0.07 (-1.27;1.13)	-0.94 (-2.34;0.49)	-1.90 (-3.13;-0.66)	-1.21 (-2.31;-0.09)	Brinzolamide					
2.96 (2.15;3.77)	-0.02 (-1.61;1.55)	-1.24 (-2.15;-0.32)	0.20 (-0.59;0.96)	-0.67 (-1.75;0.42)	-1.64 (-2.49;-0.78)	-0.94 (-1.58;-0.29)	0.27 (-0.8;1.32)	Dorzolamide				
5.87 (4.67;7.06)	2.89 (1.09;4.67)	1.67 (0.49;2.84)	3.10 (1.92;4.26)	2.24 (0.90;3.58)	1.27 (0.11;2.43)	1.97 (0.95;2.97)	3.18 (1.66;4.66)	2.91 (1.71;4.09)	Bimatoprost			
5.24 (4.49;5.99)	2.26 (0.75;3.76)	1.04 (0.36;1.74)	2.48 (1.78;3.16)	1.61 (0.63;2.59)	0.65 (-0.09;1.38)	1.34 (0.89;1.80)	2.55 (1.37;3.72)	2.28 (1.53;3.02)	-0.63 (-1.63;0.39)	Latanoprost		
5.44 (4.34;6.54)	2.46 (0.74;4.16)	1.24 (0.17;2.33)	2.68 (1.61;3.74)	1.81 (0.57;3.07)	0.85 (-0.22;1.91)	1.54 (0.64;2.44)	2.75 (1.32;4.16)	2.48 (1.4;3.57)	-0.42 (-1.57;0.72)	0.20 (-0.68;1.09)	Travoprost	
2.45 (1.55;3.36)	-0.53 (-2.13;1.04)	-1.75 (-2.67;-0.78)	-0.32 (-1.17;0.54)	-1.18 (-2.30;-0.03)	-2.15 (-3.08;-1.20)	-1.45 (-2.18;-0.7)	-0.24 (-1.55;1.05)	-0.51 (-1.44;0.44)	-3.42 (-4.63;-2.18)	-2.79 (-3.49;-2.07)	-2.99 (-4.10;-1.87)	Unoprostone

e. 2009 Network - Drugs

Placebo												
2.88 (1.26;4.52)	Apraclonidine											
3.84 (2.95;4.73)	0.96 (-0.64;2.56)	Brimonidine										
2.51 (1.75;3.27)	-0.38 (-1.97;1.21)	-1.33 (-2.16;-0.49)	Betaxolol									
3.53 (2.42;4.66)	0.65 (-1.10;2.39)	-0.30 (-1.44;0.84)	1.03 (-0.04;2.1)	Carteolol								
4.57 (3.75;5.4)	1.69 (0.08;3.32)	0.74 (-0.16;1.64)	2.07 (1.27;2.87)	1.04 (0.01;2.08)	Levobunolol							
3.80 (3.14;4.47)	0.92 (-0.58;2.41)	-0.04 (-0.71;0.65)	1.29 (0.70;1.89)	0.27 (-0.65;1.18)	-0.77 (-1.39;-0.16)	Timolol						
2.51 (1.42;3.61)	-0.38 (-2.15;1.41)	-1.33 (-2.5;-0.15)	0.00 (-1.09;1.11)	-1.03 (-2.36;0.31)	-2.07 (-3.21;-0.93)	-1.29 (-2.27;-0.31)	Brinzolamide					
2.65 (1.88;3.42)	-0.23 (-1.87;1.39)	-1.19 (-2.08;-0.29)	0.14 (-0.63;0.91)	-0.89 (-2.00;0.23)	-1.92 (-2.79;-1.07)	-1.15 (-1.8;-0.50)	0.14 (-0.85;1.14)	Dorzolamide				
5.87 (4.96;6.77)	2.99 (1.36;4.63)	2.03 (1.16;2.91)	3.36 (2.49;4.22)	2.33 (1.21;3.45)	1.29 (0.41;2.18)	2.07 (1.42;2.72)	3.36 (2.19;4.53)	3.22 (2.32;4.12)	Bimatoprost			
5.05 (4.3;5.81)	2.17 (0.63;3.72)	1.22 (0.56;1.88)	2.55 (1.86;3.22)	1.52 (0.51;2.53)	0.48 (-0.27;1.22)	1.25 (0.81;1.70)	2.55 (1.49;3.60)	2.41 (1.66;3.15)	-0.81 (-1.47;-0.15)	Latanoprost		
5.10 (4.18;6.03)	2.22 (0.59;3.85)	1.26 (0.39;2.15)	2.60 (1.72;3.47)	1.57 (0.44;2.70)	0.53 (-0.37;1.42)	1.30 (0.63;1.96)	2.60 (1.42;3.77)	2.45 (1.54;3.37)	-0.77 (-1.51;-0.02)	0.05 (-0.63;0.72)	Travoprost	
2.31 (1.38;3.25)	-0.57 (-2.23;1.07)	-1.53 (-2.48;-0.56)	-0.20 (-1.07;0.68)	-1.22 (-2.41;-0.04)	-2.26 (-3.24;-1.28)	-1.49 (-2.26;-0.72)	-0.20 (-1.40;1.02)	-0.34 (-1.29;0.63)	-3.56 (-4.51;-2.58)	-2.75 (-3.48;-2.00)	-2.79 (-3.75;-1.83)	Unoprostone

f. 1991 Network - Classes

Placebo				
-	Alpha agonists			
-				
4.01	-	Beta blockers		
(0.48;7.43)	-			
-	-	-	Carbonic anhydrase inhibitors	
-	-	-		
-	-	-	-	Prostaglandins
-	-	-	-	

g. 1995 Network - Classes

Placebo				
5.64	Alpha agonists			
(1.73;9.50)				
4.39	-1.24	Beta blockers		
(2.8;5.96)	(-5.26;2.75)			
4.03	-1.60	-0.36	Carbonic anhydrase inhibitors	
(1.18;6.89)	(-6.26;3.04)	(-3.4;2.69)		
5.18	-0.46	0.79	1.15	Prostaglandins
(2.72;7.65)	(-4.86;3.96)	(-1.83;3.44)	(-2.42;4.76)	

h. 1999 Network - Classes

Placebo				
4.25 (2.30;6.11)	Alpha agonists			
4.33 (2.97;5.7)	0.08 (-1.97;2.23)	Beta blockers		
3.63 (1.67;5.54)	-0.62 (-3.11;1.91)	-0.71 (-2.83;1.38)	Carbonic anhydrase inhibitors	
5.43 (3.38;7.38)	1.18 (-1.35;3.67)	1.10 (-1.12;3.15)	1.80 (-0.77;4.29)	Prostaglandins

i. 2004 Network - Classes

Placebo				
3.59 (1.27;5.90)	Alpha agonists			
3.72 (2.11;5.35)	0.13 (-2.55;2.84)	Beta blockers		
2.83 (0.59;5.09)	-0.76 (-3.88;2.38)	-0.89 (-3.59;1.77)	Carbonic anhydrase inhibitors	
4.75 (3.11;6.44)	1.16 (-1.5;3.9)	1.03 (-1.13;3.23)	1.92 (-0.76;4.64)	Prostaglandins

j. 2009 Network - Classes

Placebo				
3.36 (0.99;5.7)	Alpha agonists			
3.60 (1.98;5.23)	0.24 (-2.48;2.99)	Beta blockers		
2.58 (0.34;4.80)	-0.78 (-3.89;2.38)	-1.02 (-3.67;1.65)	Carbonic anhydrase inhibitors	
4.58 (2.94;6.24)	1.23 (-1.46;3.98)	0.99 (-1.15;3.14)	2.00 (-0.65;4.67)	Prostaglandins

-: Not available because drugs were not yet studied in trials included in the network

Reported posterior means and 95% Bayesian credible intervals

Positive numbers favor the drug in the row

Negative numbers favor the drug in the column

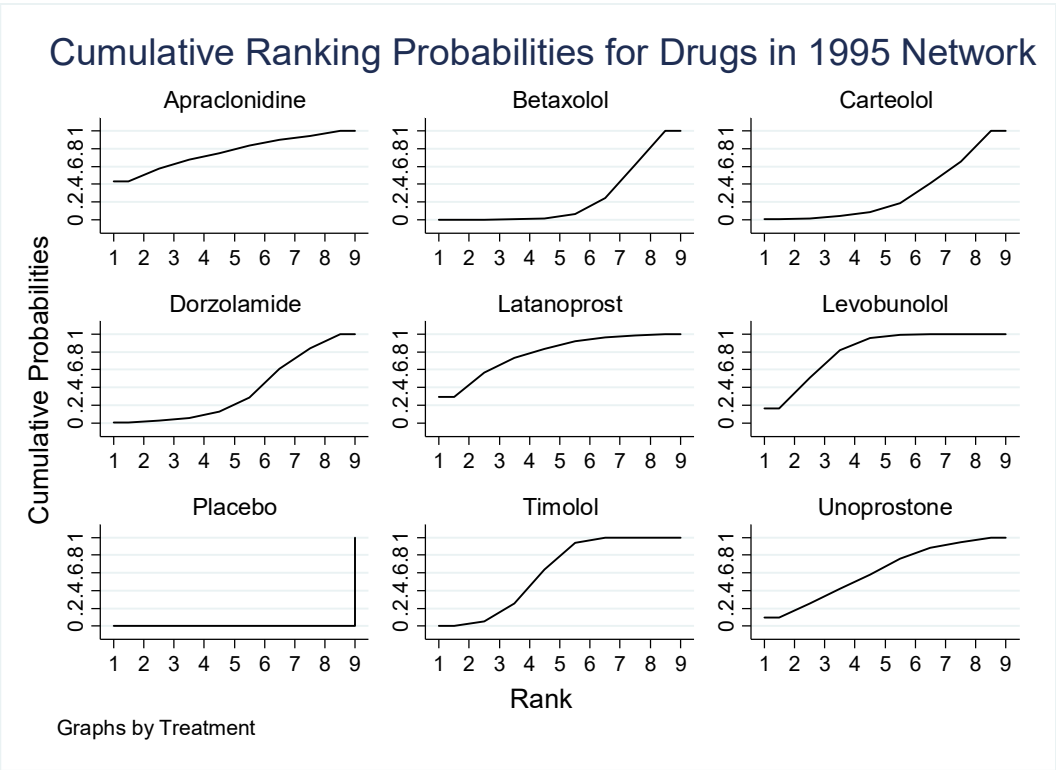
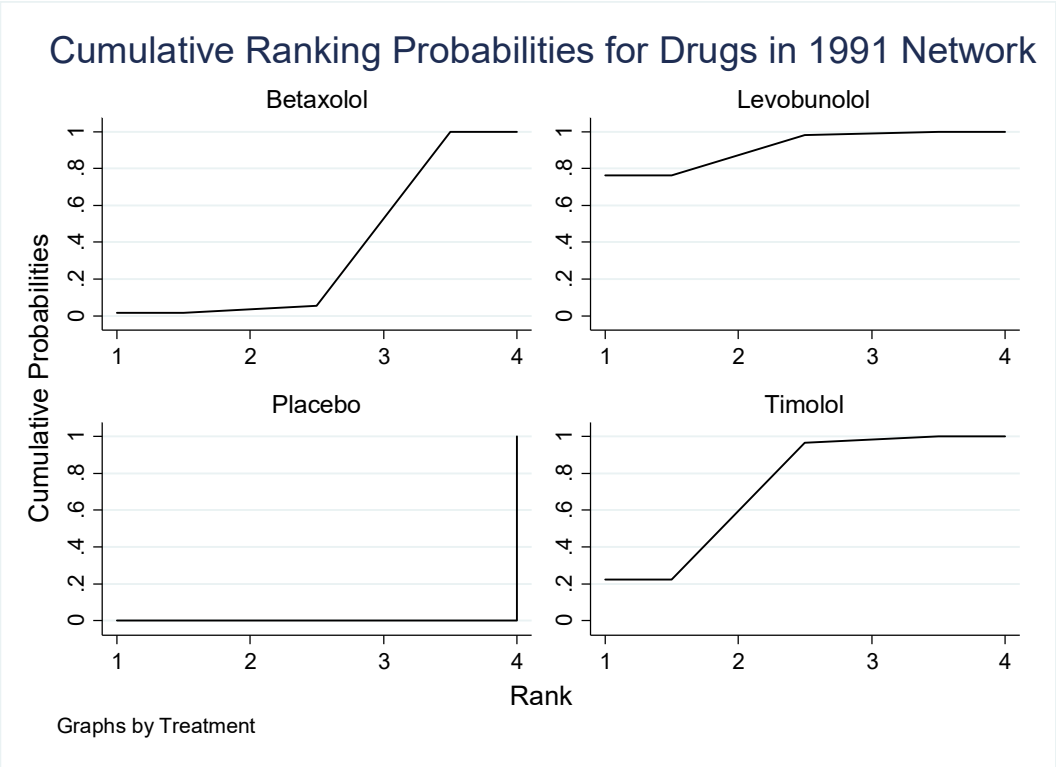
Reported numbers are calculated by column - row under the Lu and Ades homogeneous andom-effects model assuming consistency

Bolded font indicates difference is statistically significant

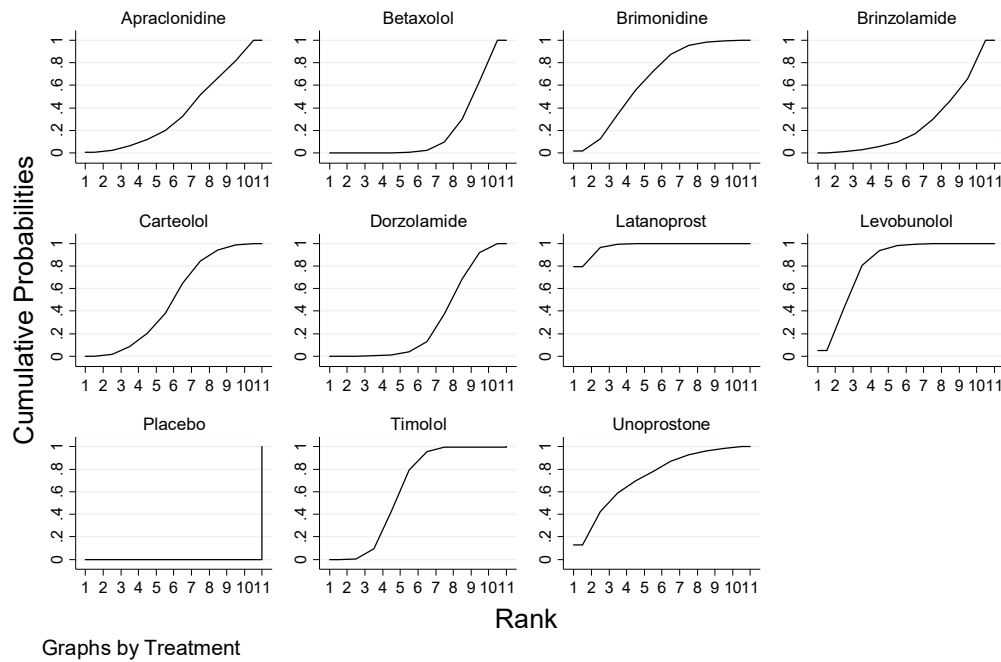
Color coding

Grey	Placebo/vehicle/no treatment
Orange	Alpha-2 adrenergic agonist
Green	Beta-blocker
Red	Carbonic anhydrase inhibitor
Blue	Prostaglandin analog

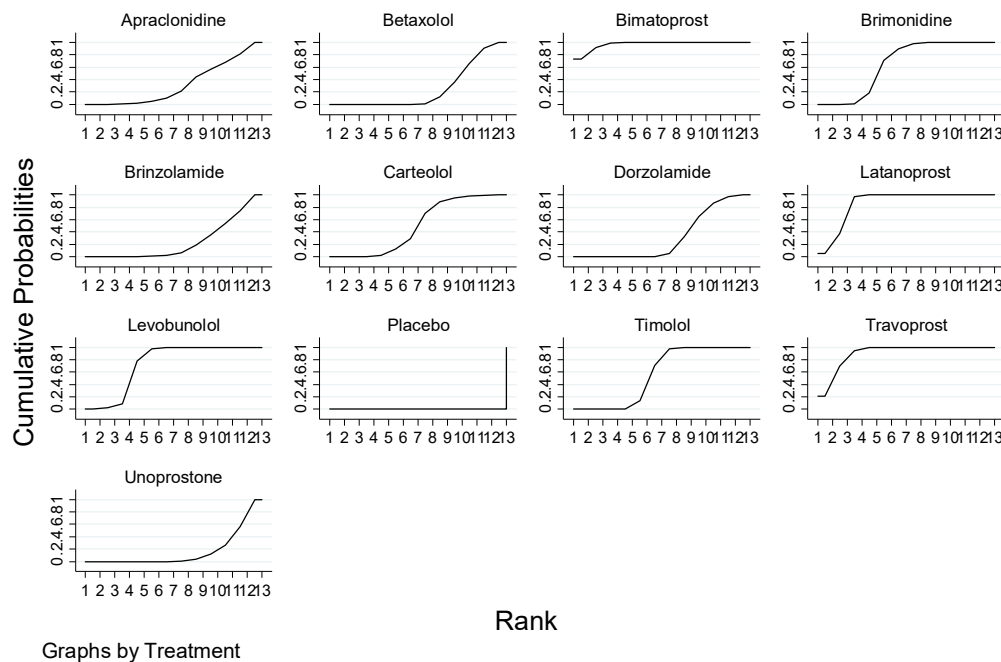
Appendix Figure 5. Cumulative ranking probabilities



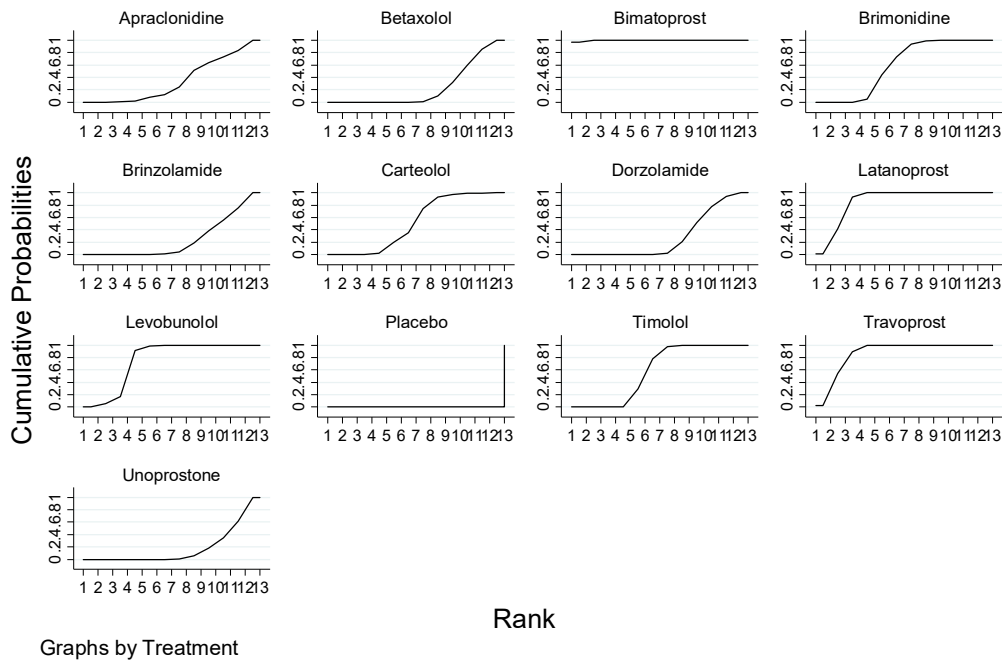
Cumulative Ranking Probabilities for Drugs in 1999 Network



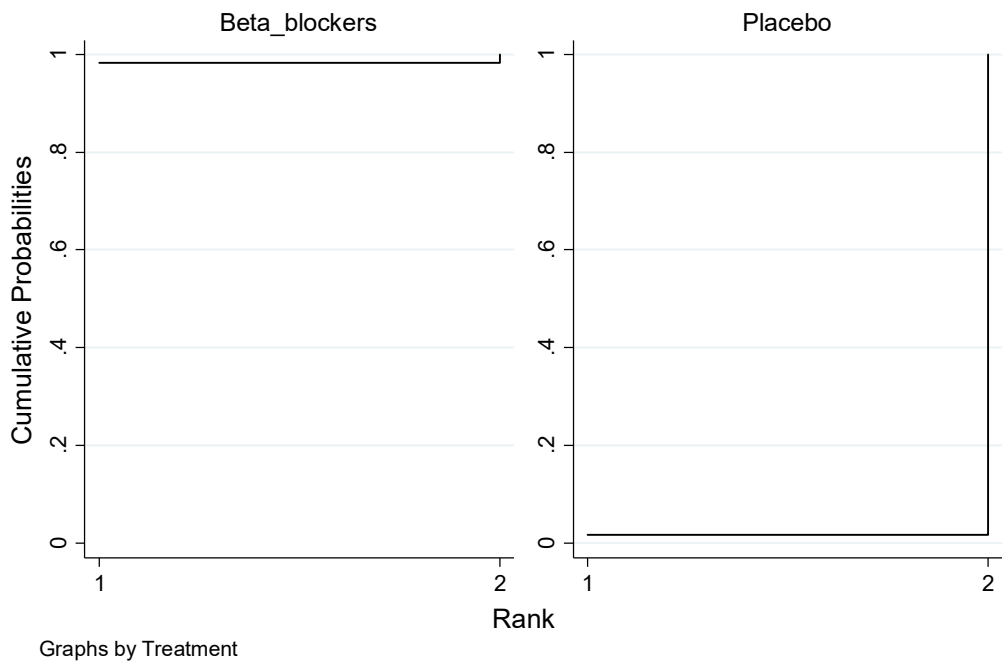
Cumulative Ranking Probabilities for Drugs in 2004 Network



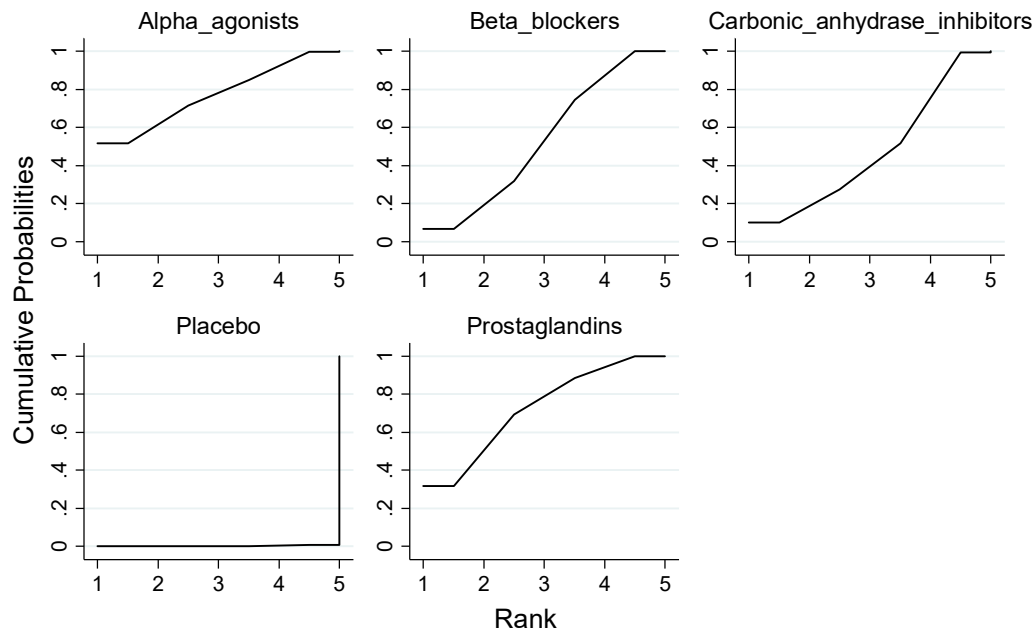
Cumulative Ranking Probabilities for Drugs in 2009 Network



Cumulative Ranking Probabilities for Classes in 1991 Network

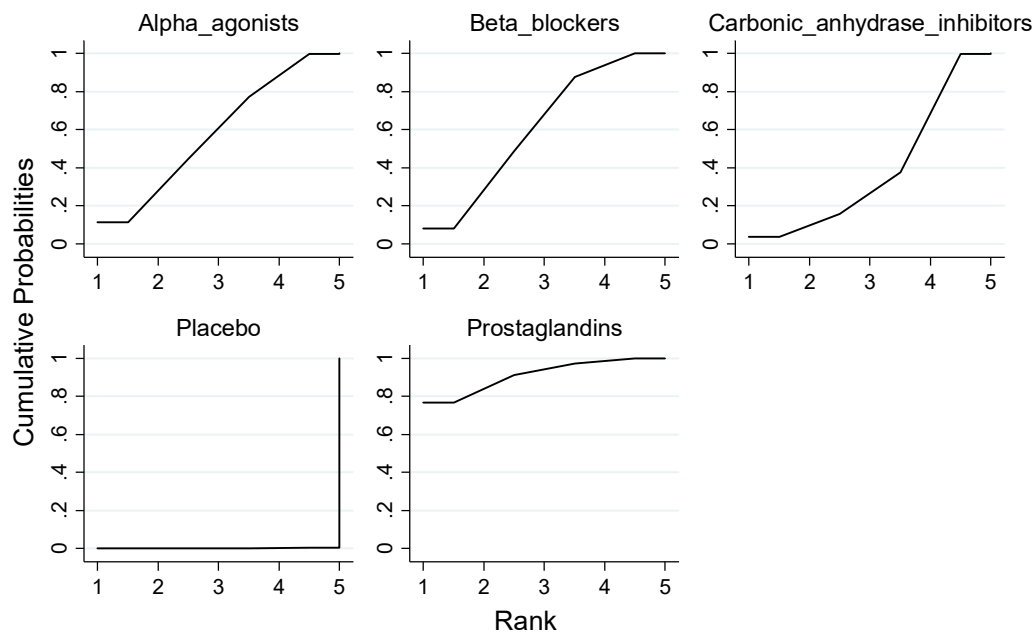


Cumulative Ranking Probabilities for Classes in 1995 Network



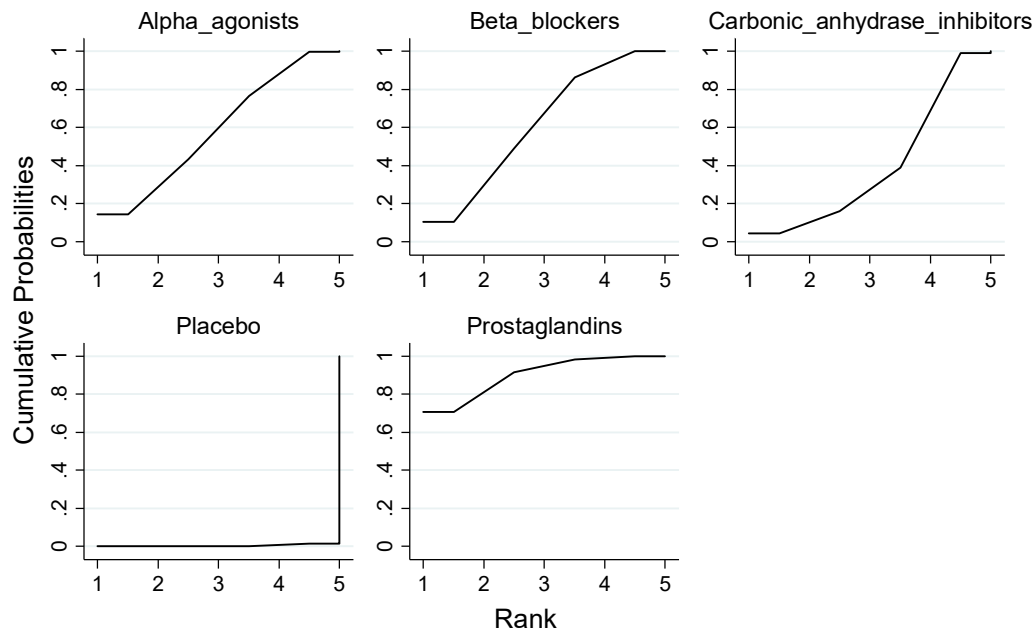
Graphs by Treatment

Cumulative Ranking Probabilities for Classes in 1999 Network



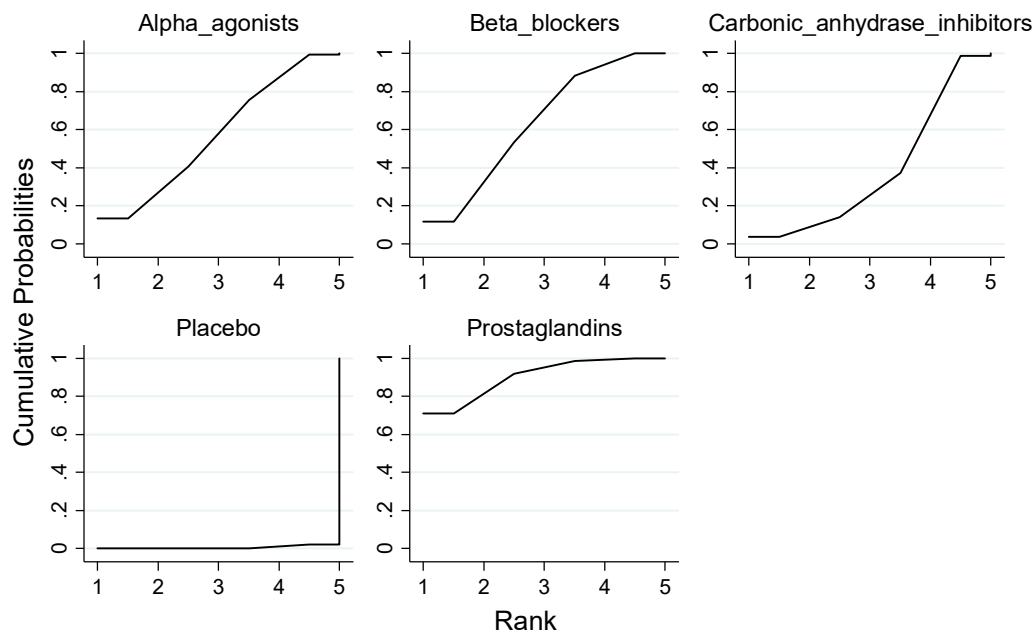
Graphs by Treatment

Cumulative Ranking Probabilities for Classes in 2004 Network



Graphs by Treatment

Cumulative Ranking Probabilities for Classes in 2009 Network



Graphs by Treatment