Supplementary Material*

Rouse B, Cipriani A, Shi Q, Coleman AL, Dickersin K, Li T. Network meta-analysis for clinical practice guidelines: A case study on first-line medical therapies for primary open-angle glaucoma. Ann Intern Med. 2016. [Epub ahead of print]. doi:10.7326/M15-2367

*This supplementary material was provided by the authors to give readers further details on their article. It was reviewed but not copyedited.

Supplement 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

Supplement 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.

References

54. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades A. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making. 2013 Jul;33(5):641–56. [PMID: 23804508] doi:10.1177/0272989X12455847

55. White IR. Multivariate random-effects meta-regression: Updates to mvmeta. Stata J. 2011;11(2):255–70.

56. White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods. 2012 Jun 20;3(2):111–25. doi:10.1002/jrsm.1045

Supplement 3. References for Included Studies (the numbering does not represent any reference citations in the text or Supplement).

1. Radius RL. Use of betaxolol in the reduction of elevated intraocular pressure. Arch Ophthalmol. 1983;101(6):898-900.
2. Berry DP, Jr., Van Buskirk EM, Shields MB. Betaxolol and timolol. A comparison of efficacy and side effects. Arch Ophthalmol. 1984;102(1):42-5.
3. Bensinger RE, Keates EU, Gofman JD, Novack GD, Duzman E. Levobunolol. A three-month efficacy study in the treatment of glaucoma and ocular hypertension. Arch Ophthalmol. 1985;103(3):375-8.
4. Berson FG, Cohen HB, Foerster RJ, Lass JH, Novack GD, Duzman E. Levobunolol compared with timolol for the long-term control of elevated intraocular pressure. Arch Ophthalmol. 1985;103(3):379-82.
5. Cinotti A, Cinotti D, Grant W, Jacobs I, Galin M, Silverstone D, et al. Levobunolol vs timolol for open-angle glaucoma and ocular hypertension. Am J Ophthalmol. 1985;99(1):11-7.
6. Ober M, Scharrer A, David R, Biedner BZ, Novack GD, Lue JC, et al. Long-term ocular hypotensive effect of levobunolol: results of a one-year study. Br J Ophthalmol. 1985;69(8):593-9.
7. Stryz JR, Merte HJ. [Pressure lowering effect and side effects of 0.5% and 1.0% levobunolol eyedrops, compared with 0.5% timolol eyedrops in patients with open-angle glaucoma]. Klin Monbl Augenheilkd. 1985;187(6):537-44.
8. Stewart RH, Kimbrough RL, Ward RL. Betaxolol vs timolol. A six-month double-blind comparison. Arch Ophthalmol. 1986;104(1):46-8.
9. Boozman FW, 3rd, Carriker R, Foerster R, Allen RC, Novack GD, Batoosingh AL. Long-term evaluation of 0.25% levobunolol and timolol for therapy for elevated intraocular pressure. Arch Ophthalmol. 1988;106(5):614-8.
10. Feghali JG, Kaufman PL, Radius RL, Mandell AI. A comparison of betaxolol and timolol in open angle glaucoma and ocular hypertension. Acta Ophthalmol (Copenh). 1988;66(2):180-6.
11. Freyler H, Novack GD, Menapace R, Skorpik C, Mordaunt J, Batoosingh AL. [Comparison of the effectiveness and safety of levobunolol and timolol in ocular hypertension and chronic open-angle glaucoma]. Klin Monbl Augenheilkd. 1988;193(3):257-60.
12. Long DA, Johns GE, Mullen RS, Bowe RG, Alexander D, Epstein DL, et al. Levobunolol and betaxolol. A double-masked controlled comparison of efficacy and safety in patients with elevated intraocular pressure. Ophthalmology. 1988;95(6):735-41.
13. Seamone C, LeBlanc R, Saheb N, Novack G. Efficacy of twice-daily levobunolol in the treatment of elevated intraocular pressure. Can J Ophthalmol. 1988;23(4):168-70.
14. Epstein DL, Krug JH, Jr., Hertzmark E, Remis LL, Edelstein DJ. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. Ophthalmology. 1989;96(10):1460-7.
15. Kass MA, Gordon MO, Hoff MR, Parkinson JM, Kolker AE, Hart WM, Jr., et al. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals. A randomized, double-masked, long-term clinical trial. Arch Ophthalmol. 1989;107(11):1590-8.

16. Yoshiaki K, Ikuo A, Makoto A. Clinical evaluation of betaxolol hydrochloride in the treatment of primary open angle glaucoma and ocular hypertension. Multi-center double-masked study in comparison with timolol. Rinsho Hyoka (Clinical Evaluation). 1989;17(2):243-74.
17. Schulzer M, Drance SM, Douglas GR. A comparison of treated and untreated glaucoma suspects. Ophthalmology. 1991;98(3):301-7.
18. Silverstone D, Zimmerman T, Choplin N, Mundorf T, Rose A, Stoecker J, et al. Evaluation of once-daily levobunolol 0.25% and timolol 0.25% therapy for increased intraocular pressure. Am J Ophthalmol. 1991;112(1):56-60.
19. Beehler CC, Stewart WC, Macdonald DK, Croyle TA, Ostrov CS, Rosanelli EG, et al. A comparison of the ocular hypotensive efficacy of twice-daily 0.25% levobunolol to 0.5% timolol in patients previously treated with 0.5% timolol. J Glaucoma. 1992;1(4):237-42.
20. Flammer J, Kitazawa Y, Bonomi L, Mills B, Fsadni M, Dorigo MT, et al. Influence of carteolol and timolol on IOP an visual fields in glaucoma: a multi-center, double-masked, prospective study. Eur J Ophthalmol. 1992;2(4):169-74.
21. Azuma I, Masuda K, Kitazawa Y, Takase M, Yamamura H. Double-masked comparative study of UF-021 and timolol ophthalmic solutions in patients with primary open-angle glaucoma or ocular hypertension. Jpn J Ophthalmol. 1993;37(4):514-25.
22. Nagasubramanian S, Hitchings RA, Demailly P, Chuniaud M, Pannarale MR, Pecori-Giraldi J, et al. Comparison of apraclonidine and timolol in chronic open-angle glaucoma. A three-month study. Ophthalmology. 1993;100(9):1318-23.
23. Wilkerson M, Cyrlin M, Lippa EA, Esposito D, Deasy D, Panebianco D, et al. Four-week safety and efficacy study of dorzolamide, a novel, active topical carbonic anhydrase inhibitor. Arch Ophthalmol. 1993;111(10):1343-50.
24. Behrens-Baumann W, Kimmich F, Walt JG, Lue J. A comparison of the ocular hypotensive efficacy and systemic safety of 0.5% levobunolol and 2% carteolol. Ophthalmologica. 1994;208(1):32-6.
25. Kitazawa Y. Phase III comparative study of MK-507 ophthalmic solution in primary open-angle glaucoma and ocular hypertension. Folia Ophthalmol Jpn. 1994;45(9):1023-33.
26. Ravalico G, Salvetat L, Toffoli G, Pastori G, Croce M, Battaglia P. Ocular hypertension: A follow-up study in treated and untreated patients. NEW TRENDS OPHTHALMOL. 1994;9(2):97-101.
27. Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Scandinavian Latanoprost Study Group. Ophthalmology. 1995;102(12):1743-52.
28. Schwartz B, Lavin P, Takamoto T, Araujo DF, Smits G. Decrease of optic disc cupping and pallor of ocular hypertensives with timolol therapy. Acta Ophthalmol Scand Suppl. 1995(215):5-21.
29. Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group. Arch Ophthalmol. 1995;113(8):1009-16.
30. Fristrom B. A 6-month, randomized, double-masked comparison of latanoprost with timolol in patients with open angle glaucoma or ocular hypertension. Acta Ophthalmol Scand. 1996;74(2):140-4.

31. Mishima HK, Masuda K, Kitazawa Y, Azuma I, Araie M. A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. A 12-week study. Arch Ophthalmol. 1996;114(8):929-32.
32. Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. Surv Ophthalmol. 1996;41 Suppl 1:S27-37.
33. Serle JB. A comparison of the safety and efficacy of twice daily brimonidine 0.2% versus betaxolol 0.25% in subjects with elevated intraocular pressure. The Brimonidine Study Group III. Surv Ophthalmol. 1996;41 Suppl 1:S39-47.
34. Stewart WC, Laibovitz R, Horwitz B, Stewart RH, Ritch R, Kottler M. A 90-day study of the efficacy and side effects of 0.25% and 0.5% apraclonidine vs 0.5% timolol. Apraclonidine Primary Therapy Study Group. Arch Ophthalmol. 1996;114(8):938-42.
35. Watson P, Stjernschantz J. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. The Latanoprost Study Group. Ophthalmology. 1996;103(1):126-37.
36. Yamamoto T, Kitazawa Y, Noma A, Maeda S, Kato A, Ando Y, et al. The effects of the beta-adrenergic-blocking agents, timolol and carteolol, on plasma lipids and lipoproteins in Japanese glaucoma patients. J Glaucoma. 1996;5(4):252-7.
37. Kitazawa Y, Azuma I, Shirato S, Tsukahara S, Mishima H, Mizogami K, et al. Phase III Clinical Study of AG-901 Ophthalmic Solution on Primary Open-Angle Glaucoma and Ocular Hypertension: A Multicenter, Double-Blind Comparison with 0.5% Timolol Maleate. Journal of Clinical Therapeutics and Medicines. 1997;13(11):2975-91.
38. Stewart WC, Cohen JS, Netland PA, Weiss H, Nussbaum LL. Efficacy of carteolol hydrochloride 1% vs timolol maleate 0.5% in patients with increased intraocular pressure. Nocturnal Investigation of Glaucoma Hemodynamics Trial Study Group. Am J Ophthalmol. 1997;124(4):498-505.
39. Boyle JE, Ghosh K, Gieser DK, Adamsons IA. A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol and dorzolamide. Dorzolamide-Timolol Study Group. Ophthalmology. 1998;105(10):1945-51.
40. Clineschmidt CM, Williams RD, Snyder E, Adamsons IA. A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. Dorzolamide-Timolol Combination Study Group. Ophthalmology. 1998;105(10):1952-9.
41. Diestelhorst M, Almegard B. Comparison of two fixed combinations of latanoprost and timolol in open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 1998;236(8):577-81.
42. LeBlanc RP. Twelve-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in patients with glaucoma or ocular hypertension. Brimonidine Study Group 2. Ophthalmology. 1998;105(10):1960-7.
43. Rusk C, Sharpe E, Laurence J, Polis A, Adamsons I. Comparison of the efficacy and safety of 2% dorzolamide and 0.5% betaxolol in the treatment of elevated intraocular pressure. Dorzolamide Comparison Study Group. Clin Ther. 1998;20(3):454-66.
44. Silver LH. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. Brinzolamide Primary Therapy Study Group. Am J Ophthalmol. 1998;126(3):400-8.

45. Bojic L, Bagatin J, Ivanisevic M, Hozo I, Racic G, Karelovic D. Influence of betaxolol and timolol on the venous tone in glaucoma patients. Int Ophthalmol. 1999;23(3):149-53.
46. Stewart WC, Dubiner HB, Mundorf TK, Laibovitz RA, Sall KN, Katz LJ, et al. Effects of carteolol and timolol on plasma lipid profiles in older women with ocular hypertension or primary open-angle glaucoma. Am J Ophthalmol. 1999;127(2):142-7.
47. Toris CB, Camras CB, Yablonski ME. Acute versus chronic effects of brimonidine on aqueous humor dynamics in ocular hypertensive patients. Am J Ophthalmol. 1999;128(1):8-14.
48. Alm A, Widengard I. Latanoprost: experience of 2-year treatment in Scandinavia. Acta Ophthalmol Scand. 2000;78(1):71-6.
49. O'Donoghue EP. A comparison of latanoprost and dorzolamide in patients with glaucoma and ocular hypertension: a 3 month, randomised study. Ireland Latanoprost Study Group. Br J Ophthalmol. 2000;84(6):579-82.
50. Sall K. The efficacy and safety of brinzolamide 1% ophthalmic suspension (Azopt) as a primary therapy in patients with open-angle glaucoma or ocular hypertension. Brinzolamide Primary Therapy Study Group. Surv Ophthalmol. 2000;44 Suppl 2:S155-62.
51. Bron AM, Denis P, Nordmann JP, Rouland JF, Sellem E, Johansson M. Additive IOP-reducing effect of latanoprost in patients insufficiently controlled on timolol. Acta ophthalmologica Scandinavica. 2001;79(3):289-93.
52. DuBiner HB, Mroz M, Shapiro AM, Dirks MS, Brimonidine vs. Latanoprost Study G. A comparison of the efficacy and tolerability of brimonidine and latanoprost in adults with open-angle glaucoma or ocular hypertension: a three-month, multicenter, randomized, double-masked, parallel-group trial. Clin Ther. 2001;23(12):1969-83.
53. Kobayashi H, Kobayashi K, Okinami S. A comparison of intraocular pressure-lowering effect of prostaglandin F2 -alpha analogues, latanoprost, and unoprostone isopropyl. J Glaucoma. 2001;10(6):487-92.
54. Susanna R, Jr., Giampani J, Jr., Borges AS, Vessani RM, Jordao ML. A double-masked, randomized clinical trial comparing latanoprost with unoprostone in patients with open-angle glaucoma or ocular hypertension. Ophthalmology. 2001;108(2):259-63.
55. Aung T, Chew PT, Oen FT, Chan YH, Thean LH, Yip L, et al. Additive effect of unoprostone and latanoprost in patients with elevated intraocular pressure. Br J Ophthalmol. 2002;86(1):75-9.
56. Bergstrand IC, Heijl A, Harris A. Dorzolamide and ocular blood flow in previously untreated glaucoma patients: a controlled double-masked study. Acta Ophthalmol Scand. 2002;80(2):176-82.
57. Fellman RL, Sullivan EK, Ratliff M, Silver LH, Whitson JT, Turner FD, et al. Comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients with elevated intraocular pressure: a 6-month, masked, multicenter trial. Ophthalmology. 2002;109(5):998-1008.
58. Halpern MT, Covert DW, Robin AL. Projected impact of travoprost versus both timolol and latanoprost on visual field deficit progression and costs among black glaucoma subjects. Trans Am Ophthalmol Soc. 2002;100:109-17
59. Higginbotham EJ, Feldman R, Stiles M, Dubiner H, Fixed Combination Investigative G. Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial. Arch Ophthalmol. 2002;120(7):915-22.

60. Jampel HD, Bacharach J, Sheu WP, Wohl LG, Solish AM, Christie W, et al. Randomized clinical trial of latanoprost and unoprostone in patients with elevated intraocular pressure. Am J Ophthalmol. 2002;134(6):863-71.
61. Kampik A, Arias-Puente A, O'Brart DP, Vuori ML, European Latanoprost Study G. Intraocular pressure-lowering effects of latanoprost and brimonidine therapy in patients with open-angle glaucoma or ocular hypertension: a randomized observer-masked multicenter study. J Glaucoma. 2002;11(2):90-6.
62. Nordmann JP, Mertz B, Yannoulis NC, Schwenninger C, Kapik B, Shams N, et al. A double-masked randomized comparison of the efficacy and safety of unoprostone with timolol and betaxolol in patients with primary open-angle glaucoma including pseudoexfoliation glaucoma or ocular hypertension. 6 month data. Am J Ophthalmol. 2002;133(1):1-10.
63. Pfeiffer N, European Latanoprost Fixed Combination Study G. A comparison of the fixed combination of latanoprost and timolol with its individual components. Graefes Arch Clin Exp Ophthalmol. 2002;240(11):893-9.
64. Simmons ST, Earl ML, Alphagan/Xalatan Study G. Three-month comparison of brimonidine and latanoprost as adjunctive therapy in glaucoma and ocular hypertension patients uncontrolled on beta-blockers: tolerance and peak intraocular pressure lowering. Ophthalmology. 2002;109(2):307-14; discussion 14-5.
65. Sponsel WE, Paris G, Trigo Y, Pena M. Comparative effects of latanoprost (Xalatan) and unoprostone (Rescula) in patients with open-angle glaucoma and suspected glaucoma. Am J Ophthalmol. 2002;134(4):552-9.
66. Tsukamoto H, Mishima HK, Kitazawa Y, Araie M, Abe H, Negi A, et al. A comparative clinical study of latanoprost and isopropyl unoprostone in Japanese patients with primary open-angle glaucoma and ocular hypertension. J Glaucoma. 2002;11(6):497-501.
67. Camras CB, Hedman K, Group USLS. Rate of response to latanoprost or timolol in patients with ocular hypertension or glaucoma. J Glaucoma. 2003;12(6):466-9.
68. Cardascia N, Vetrugno M, Trabucco T, Cantatore F, Sborgia C. Effects of travoprost eye drops on intraocular pressure and pulsatile ocular blood flow: a 180-day, randomized, double-masked comparison with latanoprost eye drops in patients with open-angle glaucoma. Curr Ther Res Clin Exp. 2003;64(7):389-400.
69. Inan UU, Ermis SS, Yucel A, Ozturk F. The effects of latanoprost and brimonidine on blood flow velocity of the retrobulbar vessels: a 3-month clinical trial. Acta Ophthalmol Scand. 2003;81(2):155-60.
70. Kamal D, Garway-Heath D, Ruben S, O'Sullivan F, Bunce C, Viswanathan A, et al. Results of the betaxolol versus placebo treatment trial in ocular hypertension. Graefes Arch Clin Exp Ophthalmol. 2003;241(3):196-203.
71. Parrish RK, Palmberg P, Sheu WP, Group XLTS. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol. 2003;135(5):688-703.
72. Erkin EF, Tarhan S, Kayikcioglu OR, Deveci H, Guler C, Goktan C. Effects of betaxolol and latanoprost on ocular blood flow and visual fields in patients with primary open-angle glaucoma. Eur J Ophthalmol. 2004;14(3):211-9.

73. Kobayashi H, Iwakiri R, Kobayashi K, Okinami S. Hypotensive effect of unoprostone as adjunct to latanoprost during multiple drug therapy for glaucoma. Japanese Journal of Clinical Ophthalmology. 2004;58(2):193-7.
74. Vetrugno M, Cardascia N, Cantatore F, Sborgia C. Comparison of the effects of bimatoprost and timolol on intraocular pressure and pulsatile ocular blood flow in patients with primary open-angle glaucoma: A prospective, open-label, randomized, two-arm, parallel-group study. Curr Ther Res Clin Exp. 2004;65(6):444-54.
75. Walters TR, DuBiner HB, Carpenter SP, Khan B, VanDenburgh AM, Bimatoprost Circadian IOPSG. 24-Hour IOP control with once-daily bimatoprost, timolol gel-forming solution, or latanoprost: a 1-month, randomized, comparative clinical trial. Surv Ophthalmol. 2004;49 Suppl 1:S26-35.
76. Wang TH, Huang JY, Hung PT, Shieh JW, Chen YF. Ocular hypotensive effect and safety of brinzolamide ophthalmic solution in open angle glaucoma patients. J Formos Med Assoc. 2004;103(5):369-73.
77. Barnebey HS, Orengo-Nania S, Flowers BE, Samples J, Mallick S, Landry TA, et al. The safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution. Am J Ophthalmol. 2005;140(1):1-7.
78. Camras CB, Sheu WP, United States Latanoprost-Brimonidine Study G. Latanoprost or brimonidine as treatment for elevated intraocular pressure: multicenter trial in the United States. J Glaucoma. 2005;14(2):161-7.
79. Miglior S, Zeyen T, Pfeiffer N, Cunha-Vaz J, Torri V, Adamsons I, et al. Results of the European Glaucoma Prevention Study. Ophthalmology. 2005;112(3):366-75.
80. Erkin EF, Celik P, Kayikcioglu O, Deveci HM, Sakar A. Effects of latanoprost and betaxolol on cardiovascular and respiratory status of newly diagnosed glaucoma patients. Ophthalmologica. 2006;220(5):332-7.
81. Koz OG, Ozsoy A, Yarangumeli A, Kose SK, Kural G. Comparison of the effects of travoprost, latanoprost and bimatoprost on ocular circulation: a 6-month clinical trial. Acta Ophthalmol Scand. 2007;85(8):838-43.
82. Martin E, Martinez-de-la-Casa JM, Garcia-Feijoo J, Troyano J, Larrosa JM, Garcia-Sanchez J. A 6-month assessment of bimatoprost 0.03% vs timolol maleate 0.5%: hypotensive efficacy, macular thickness and flare in ocular-hypertensive and glaucoma patients. Eye (Lond). 2007;21(2):164-8.
83. Alagoz G, Gurel K, Bayer A, Serin D, Celebi S, Kukner S. A comparative study of bimatoprost and travoprost: effect on intraocular pressure and ocular circulation in newly diagnosed glaucoma patients. Ophthalmologica. 2008;222(2):88-95.
84. Brandt JD, Cantor LB, Katz LJ, Batoosingh AL, Chou C, Bossowska I, et al. Bimatoprost/timolol fixed combination: a 3-month double-masked, randomized parallel comparison to its individual components in patients with glaucoma or ocular hypertension. J Glaucoma. 2008;17(3):211-6.
85. Kaback M, Scoper SV, Arzeno G, James JE, Hua SY, Salem C, et al. Intraocular pressure-lowering efficacy of brinzolamide 1%/timolol 0.5% fixed combination compared with brinzolamide 1% and timolol 0.5%. Ophthalmology. 2008;115(10):1728-34, 34 e1-2.

86. Williams RD, Cohen JS, Gross RL, Liu CC, Safyan E, Batoosingh AL, et al. Long-term efficacy and safety of bimatoprost for intraocular pressure lowering in glaucoma and ocular hypertension: year 4. Br J Ophthalmol. 2008;92(10):1387-92.
87. Yildirim N, Sahin A, Gultekin S. The effect of latanoprost, bimatoprost, and travoprost on circadian variation of intraocular pressure in patients with open-angle glaucoma. J Glaucoma. 2008;17(1):36-9.
88. Casson RJ, Liu L, Graham SL, Morgan WH, Grigg JR, Galanopoulos A, et al. Efficacy and safety of bimatoprost as replacement for latanoprost in patients with glaucoma or ocular hypertension: a uniocular switch study. Journal of glaucoma. 2009;18(8):582-8.
89. Prata TS, Piassi MV, Melo LA, Jr. Changes in visual function after intraocular pressure reduction using antiglaucoma medications. Eye (Lond). 2009;23(5):1081-5.
90. Sharma R, Kohli K, Kapoor B, Mengi RK, Sadhotra P. The cardio-vascular effects of topical timolol, levobunolol and betaxolol in patients of chronic simple glaucoma. Journal of Clinical and Diagnostic Research. 2009;3(4):1615-20.
91. Zhao WJ. [Comparison of travoprost and timolol in patients with primary open angle glaucoma and ocular hypertension]. International Journal of Ophthalmology. 2009;9(9):1753-4.
92. Birt CM, Buys YM, Ahmed, II, Trope GE. Prostaglandin efficacy and safety study undertaken by race (the PRESSURE study). Journal of glaucoma. 2010;19(7):460-7.
93. Craven ER, Liu CC, Batoosingh A, Schiffman RM, Whitcup SM. A randomized, controlled comparison of macroscopic conjunctival hyperemia in patients treated with bimatoprost 0.01% or vehicle who were previously controlled on latanoprost. Clin. Ophthalmol. 2010;4:1433-40.
94. Higginbotham EJ, Olander KW, Kim EE, Grunden JW, Kwok KK, Tressler CS. Fixed combination of latanoprost and timolol vs individual components for primary open-angle glaucoma or ocular hypertension: a randomized, double-masked study. Archives of ophthalmology. 2010;128(2):165-72.
95. Kammer JA, Katzman B, Ackerman SL, Hollander DA. Efficacy and tolerability of bimatoprost versus travoprost in patients previously on latanoprost: a 3-month, randomised, masked-evaluator, multicentre study. The British journal of ophthalmology. 2010;94(1):74-9.
96. Macky TA. Bimatoprost versus travoprost in an Egyptian population: a hospital-based prospective, randomized study. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics. 2010;26(6):605-10.
97. Traverso CE, Ropo A, Papadia M, Uusitalo H. A phase II study on the duration and stability of the intraocular pressure-lowering effect and tolerability of Tafluprost compared with latanoprost. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics. 2010;26(1):97-104.
98. Nie X, Yang XH, Qin XF, Quan CJ, Yang SS. Correlation between the development of high myopia and intraocular pressure. International Journal of Ophthalmology. 2011;11(6):1092-4.

99. Zhao L, Wang YL, Meng ZY, Hong H. Efficacy and safety of domestic Latanoprost in treating with open angle glaucoma and ocular hypertension. [Chinese]. International Journal of Ophthalmology. 2011;11(11):1973-5.
100. Araie M, Yamazaki Y, Sugiyama K, Kuwayama Y, Tanihara H. [Phase III clinical trial of brimonidine in patients with primary open-angle glaucoma and ocular hypertension--comparison of the effects of brimonidine monotherapy versus timolol monotherapy, or combination brimonidine/prostaglandins therapy versus combination placebo/prostaglandins therapy]. Nippon Ganka Gakkai Zasshi - Acta Societatis Ophthalmologicae Japonicae. 2012;116(10):955-66.
101. Chabi A, Varma R, Tsai JC, Lupinacci R, Pigeon J, Baranak C, et al. Randomized clinical trial of the efficacy and safety of preservative-free tafluprost and timolol in patients with open-angle glaucoma or ocular hypertension. American journal of ophthalmology. 2012;153(6):1187-96.
102. Crichton AC, Vold S, Williams JM, Hollander DA. Ocular surface tolerability of prostaglandin analogs and prostamides in patients with glaucoma or ocular hypertension. Advances in Therapy. 2013;30(3):260-70.
103. Delval L, Baudouin C, Gabisson P, Alliot E, Vincent B. Safety and efficacy of unpreserved timolol 0.1% gel in patients controlled by preserved latanoprost with signs of ocular intolerance. Journal français d'ophtalmologie. 2013;36(4):316-23.
104. Katz G, Dubiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. JAMA Ophthalmology. 2013;131(6):724-30.
105. Nguyen QH, McMenemy MG, Realini T, Whitson JT, Goode SM. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. Journal of Ocular Pharmacology and Therapeutics. 2013;29(3):290-7.

Legends for Supplement Figures

Figure 1. Selection of studies. POAG = primary open-angle glaucoma; RCT = randomized, controlled trial.

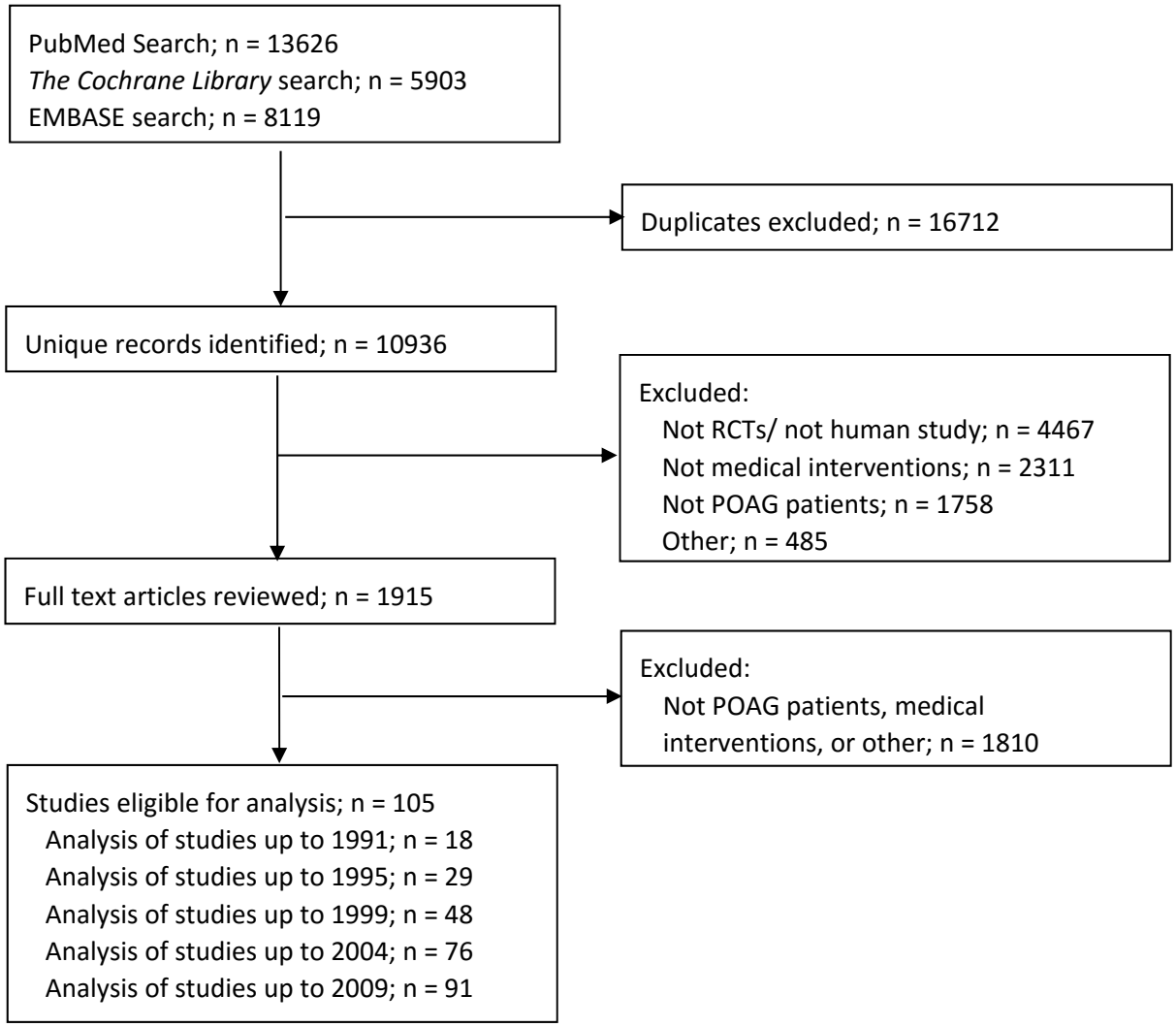
Figure 2. Network graphs. **A.** 1991. **B.** 1995. **C.** 1999. **D.** 2004. **E.** 2009. Each node represents 1 drug or class, color-coded by class. The size of the node is proportional to the number of participants randomly assigned to that drug/class. The edges represent direct comparisons (that is, when a line connects 2 drugs, the 2 drugs have been compared directly to each other). The width of the edge is proportional to the number of trials.

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

Figure 4. Summary estimates for intraocular pressure at 3 months derived from network meta-analysis. Drugs: **A.** 1991. **B.** 1995. **C.** 1999. **D.** 2004. **E.** 2009. Classes: **F.** 1991. **H.** 1999. **I.** 2004. **J.** 2009.

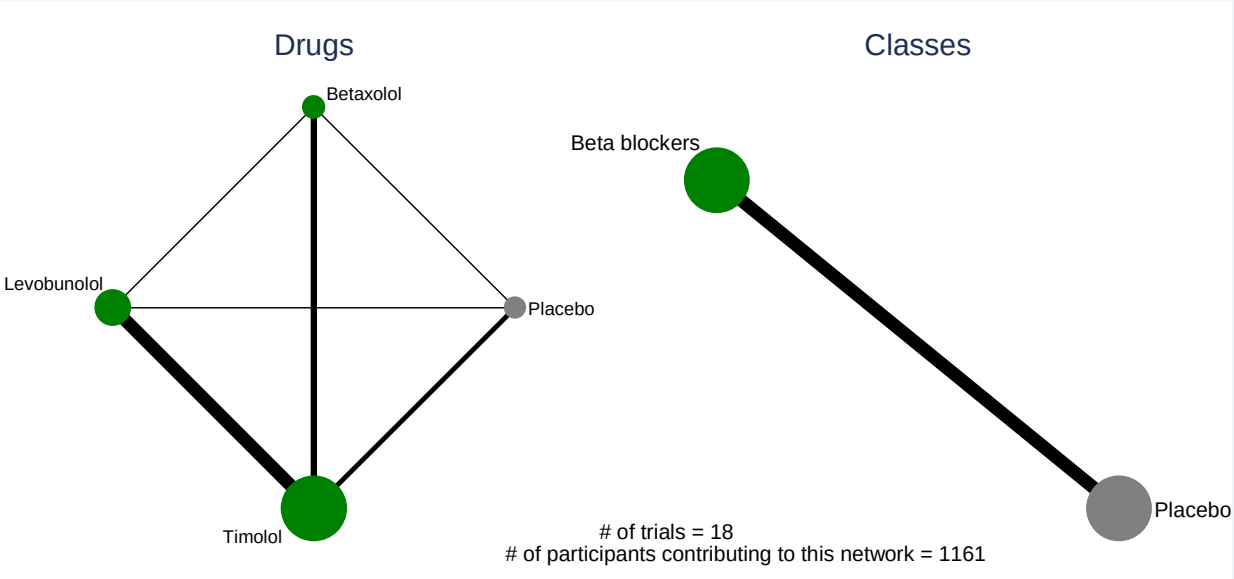
Figure 5. Cumulative ranking probabilities.

Supplement Figure 1. Summary of evidence search and selection.

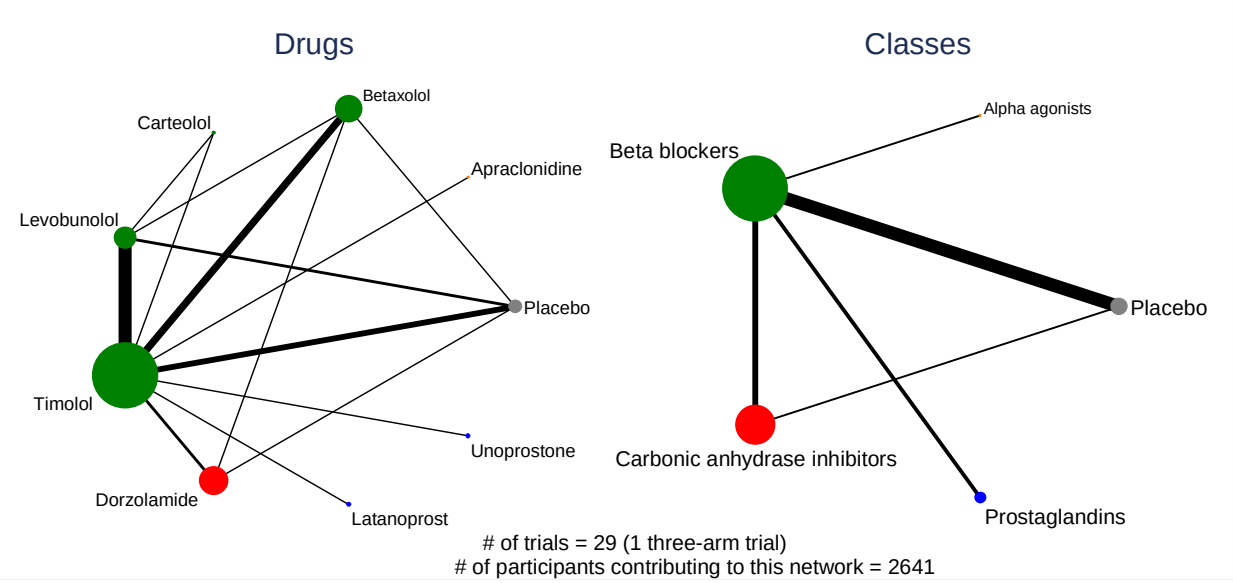


Supplement Figure 2. Network graphs

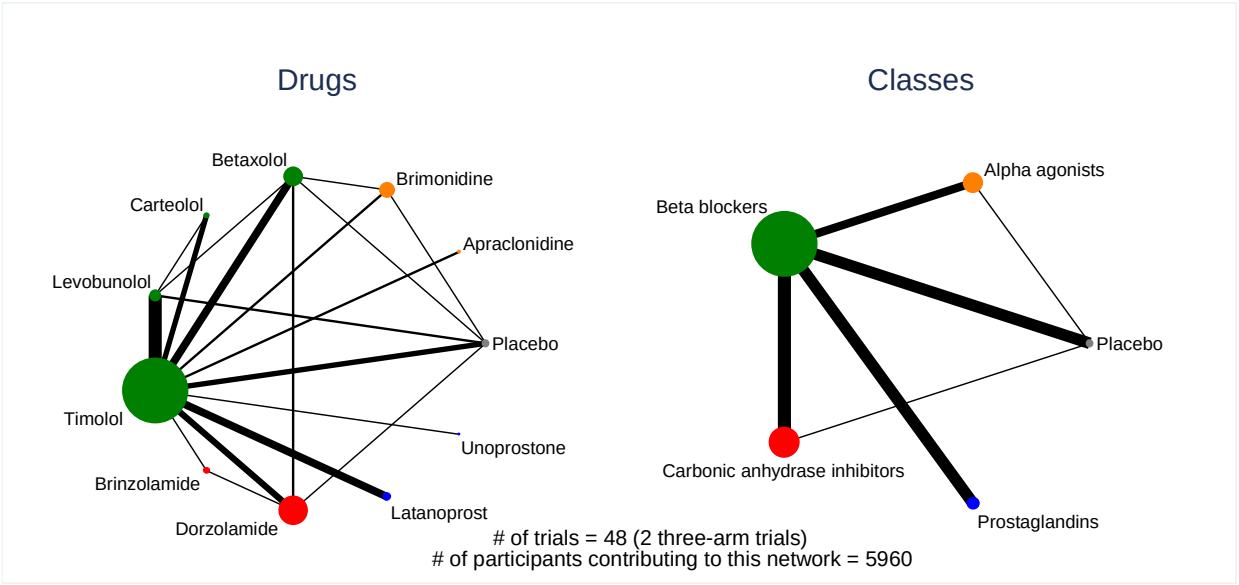
a. 1991 Network graphs



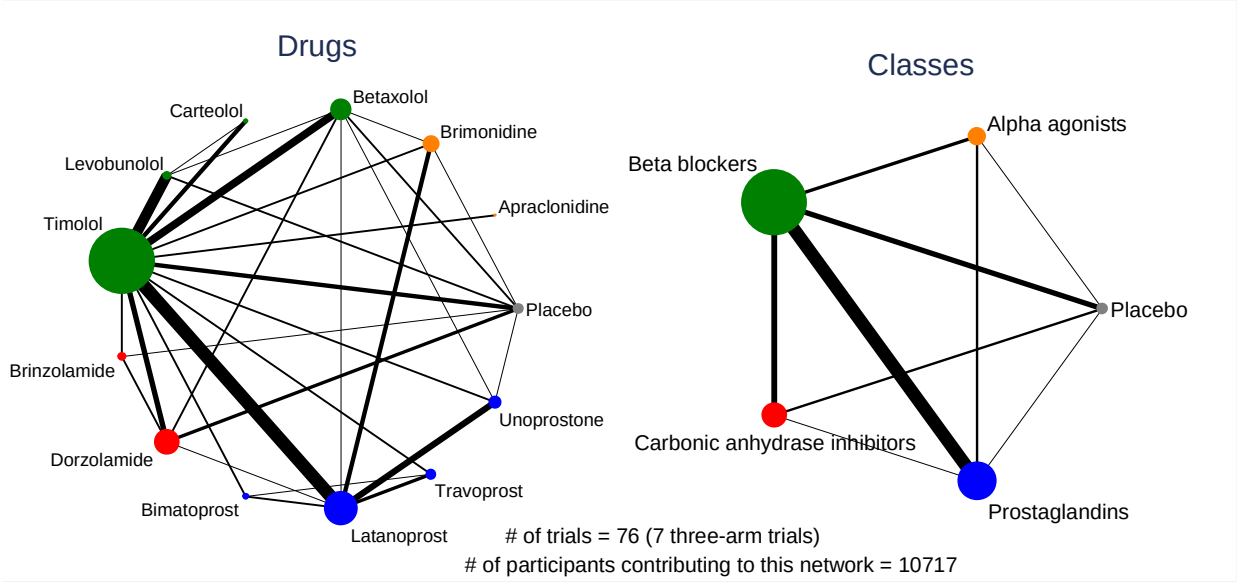
b. 1995 Network graphs



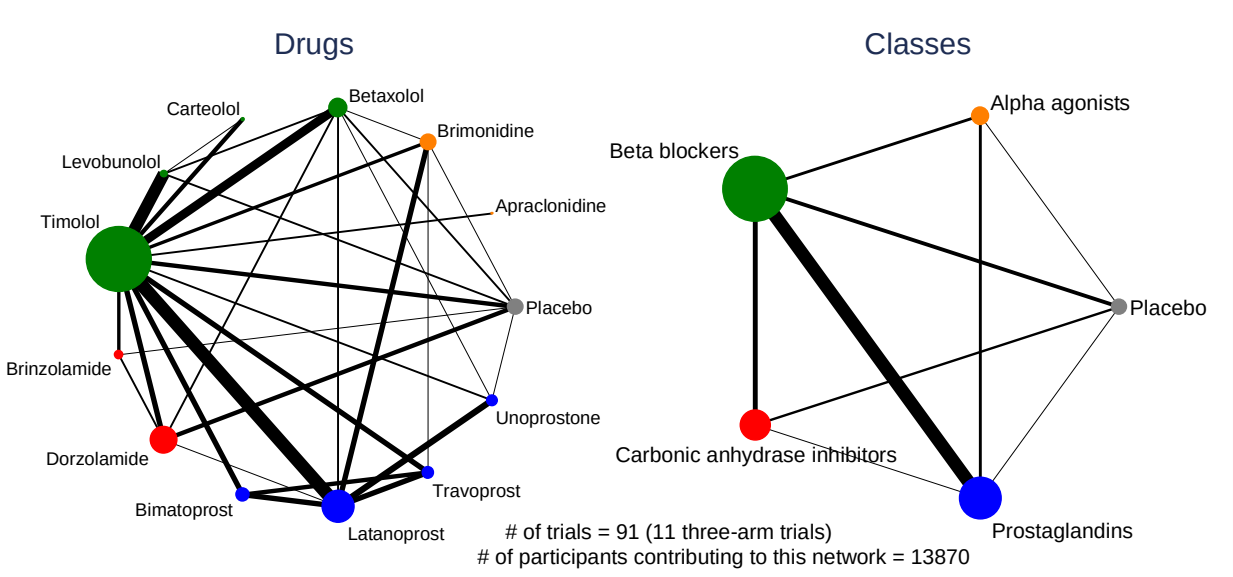
c. 1999 Network graphs



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.

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

Supplement 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					
		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	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**					
		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	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					
		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	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					
		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	-2.30	-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 calcuated using the intraocular pressure of the drug in column 2 - column 1.

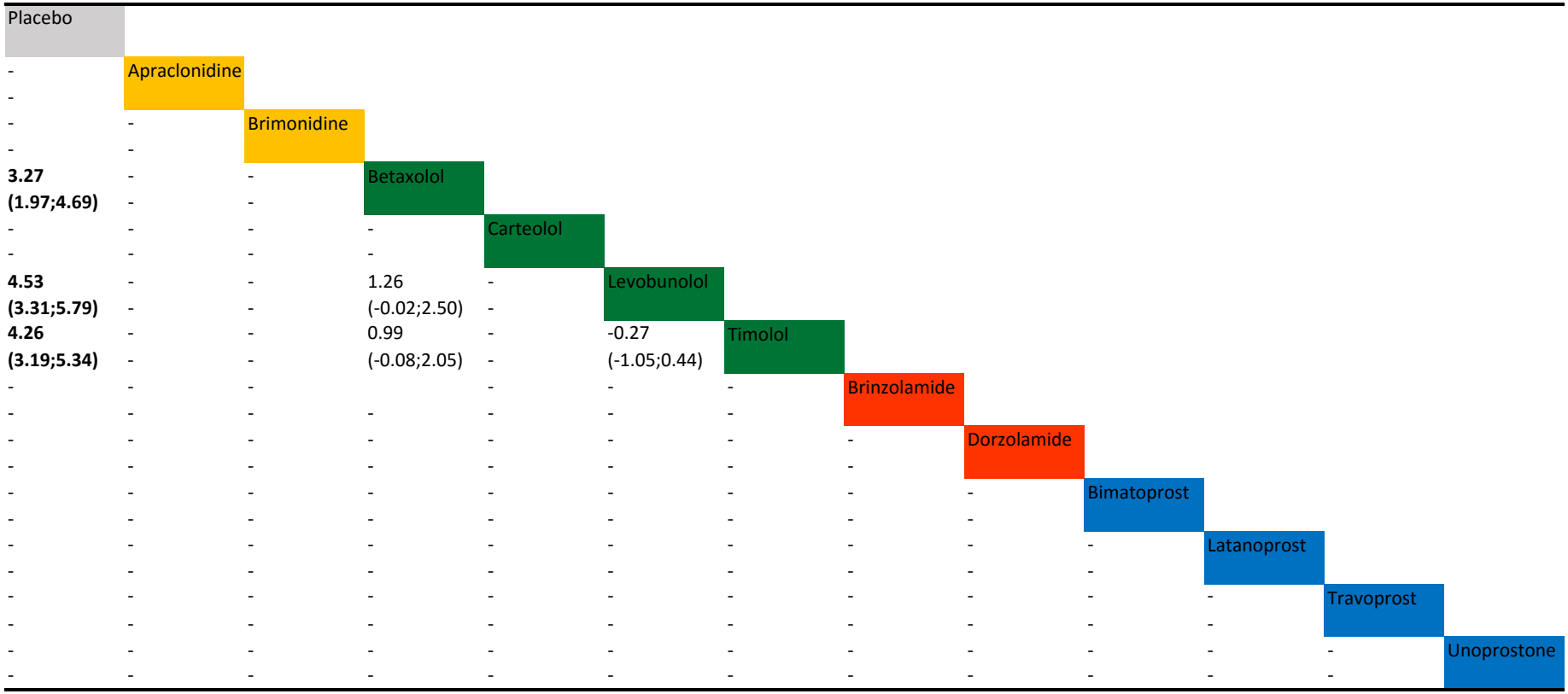
Glaucoma drugs are expected to lower intraocular pressure, therefore, mean difference > 0 favors the drug in column 1; mean difference < 0 favors the drug in column 2.

Color coding

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

Supplement Figure 4. Summary estimates for intraocular pressure at 3 months derived from network meta-analysis

a. 1991 Network - Drugs



b. 1995 Network - Drugs

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

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

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

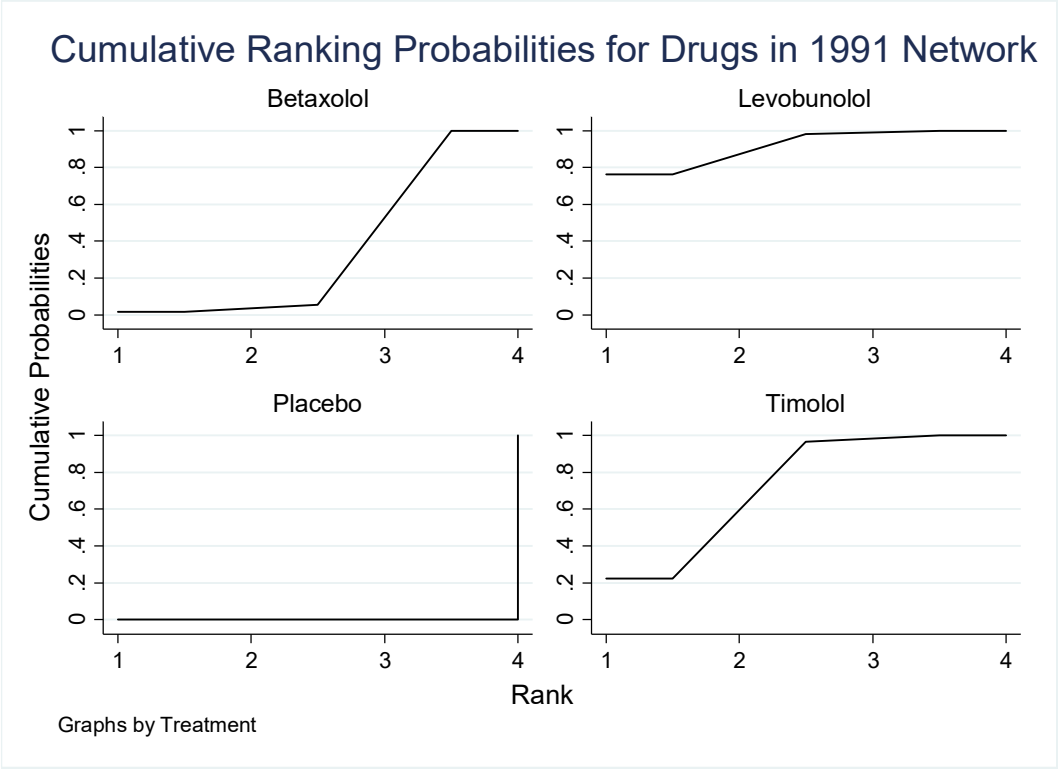
Placebo				
3.36 (0.99;5.7)	Alpha agonists			
3.60 (1.98;5.23)	0.24 (-2.48;2.99)	Beta blockers		
2.58 (0.34;4.80)	-0.78 (-3.89;2.38)	-1.02 (-3.67;1.65)	Carbonic anhydrase inhibitors	
4.58 (2.94;6.24)	1.23 (-1.46;3.98)	0.99 (-1.15;3.14)	2.00 (-0.65;4.67)	Prostaglandins

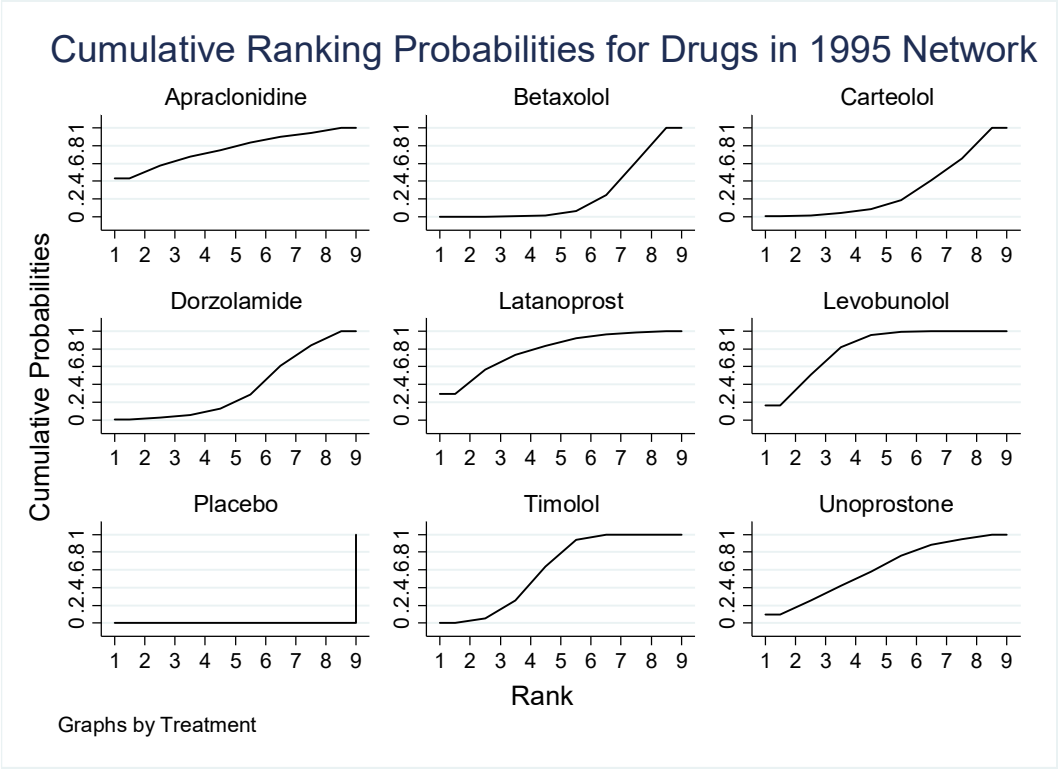
-: Not available because drugs were not yet studied in trials included in the network
Reported posterior means and 95% Bayesian credible intervals
Positive numbers favor the drug in the row
Negative numbers favor the drug in the column
Reported numbers are calculated by column - row under the Lu and Ades homogeneous andom-effects model assuming consistency
Bolded font indicates difference is statistically significant

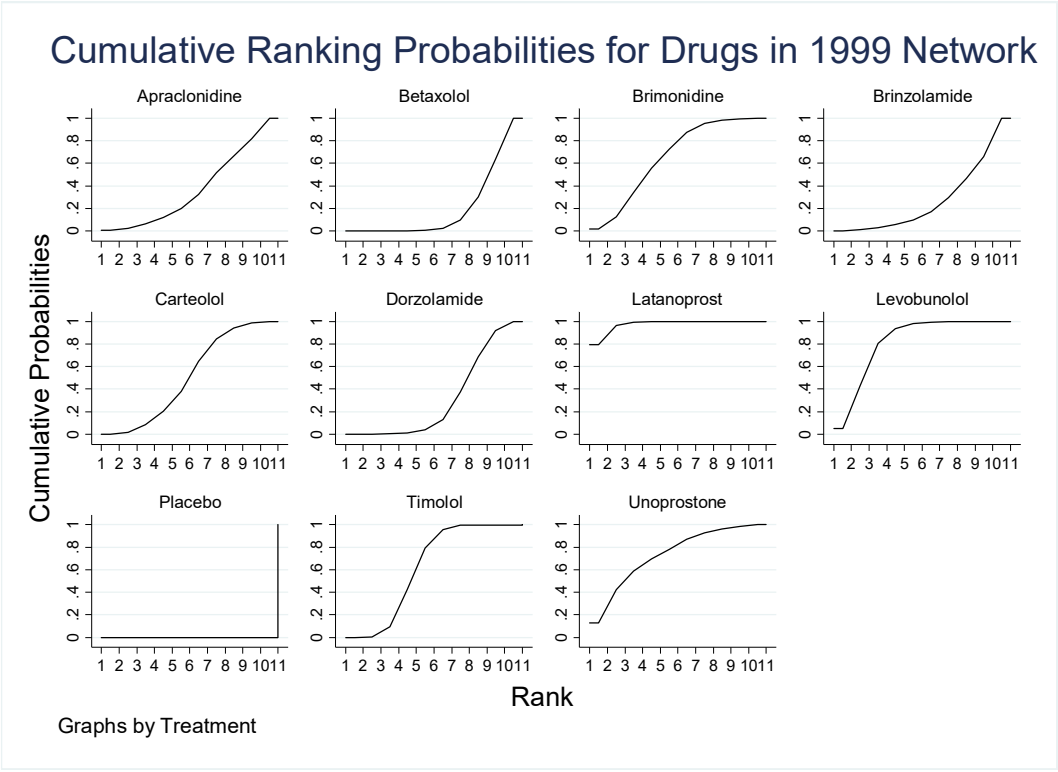
Color coding

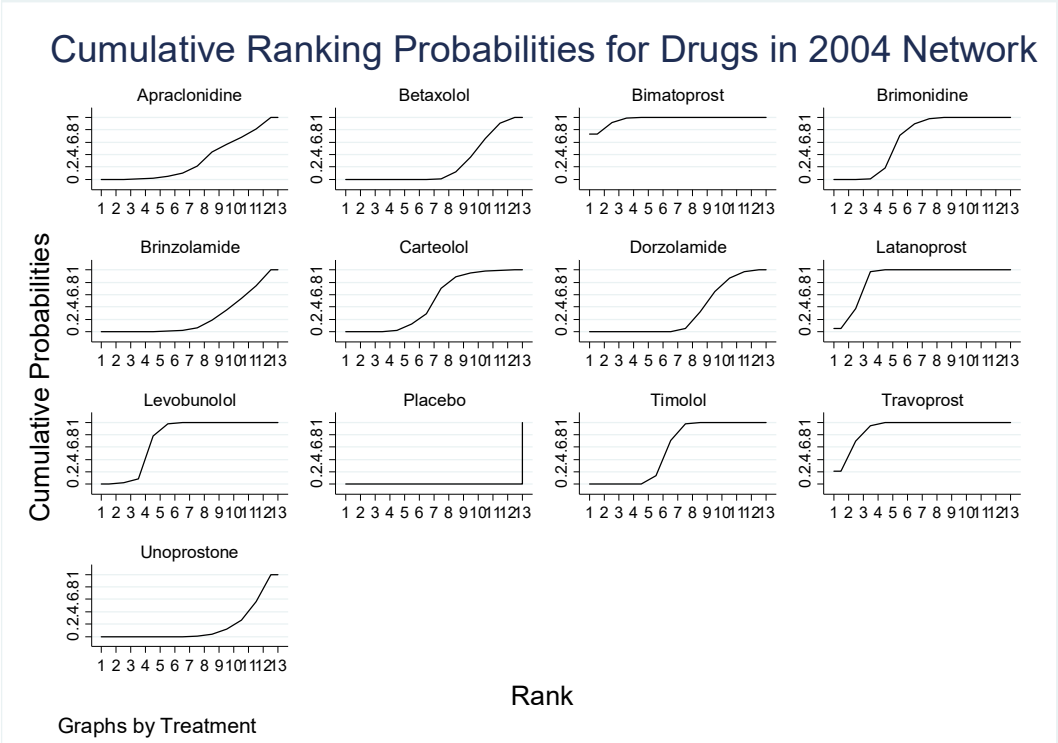
Gray	Placebo/vehicle/no treatment
Orange	Alpha-2 adrenergic agonist
Green	Beta-blocker
Red	Carbonic anhydrase inhibitor
Blue	Prostaglandin analog

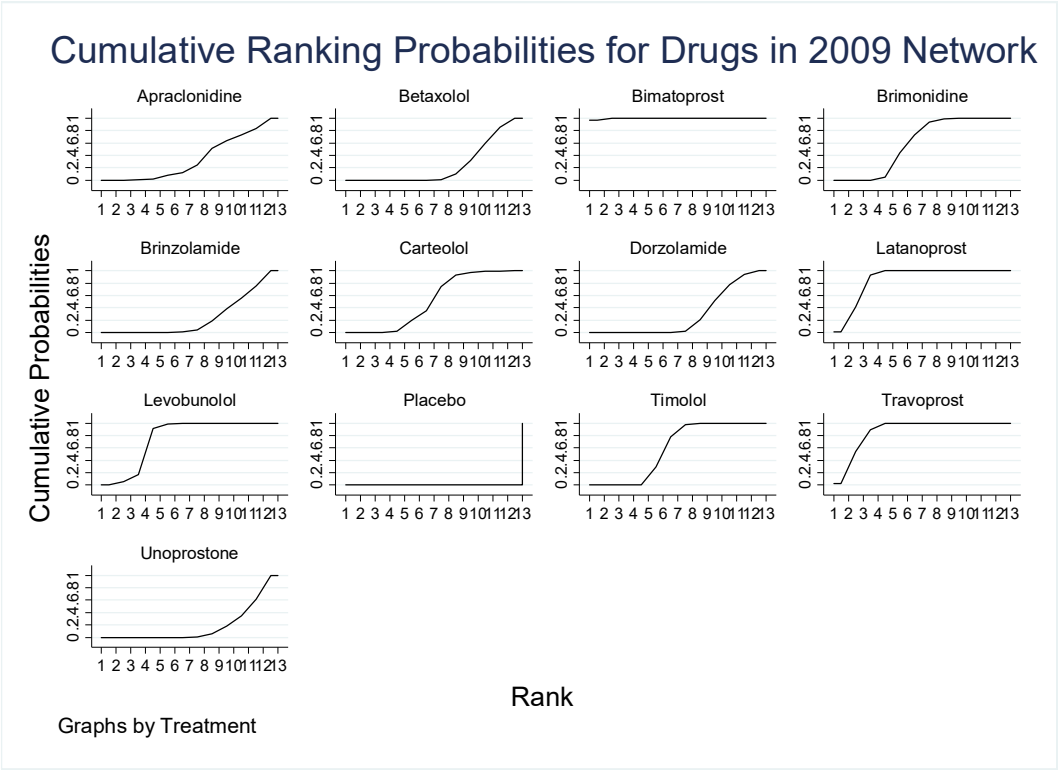
Supplement Figure 5. Cumulative ranking probabilities

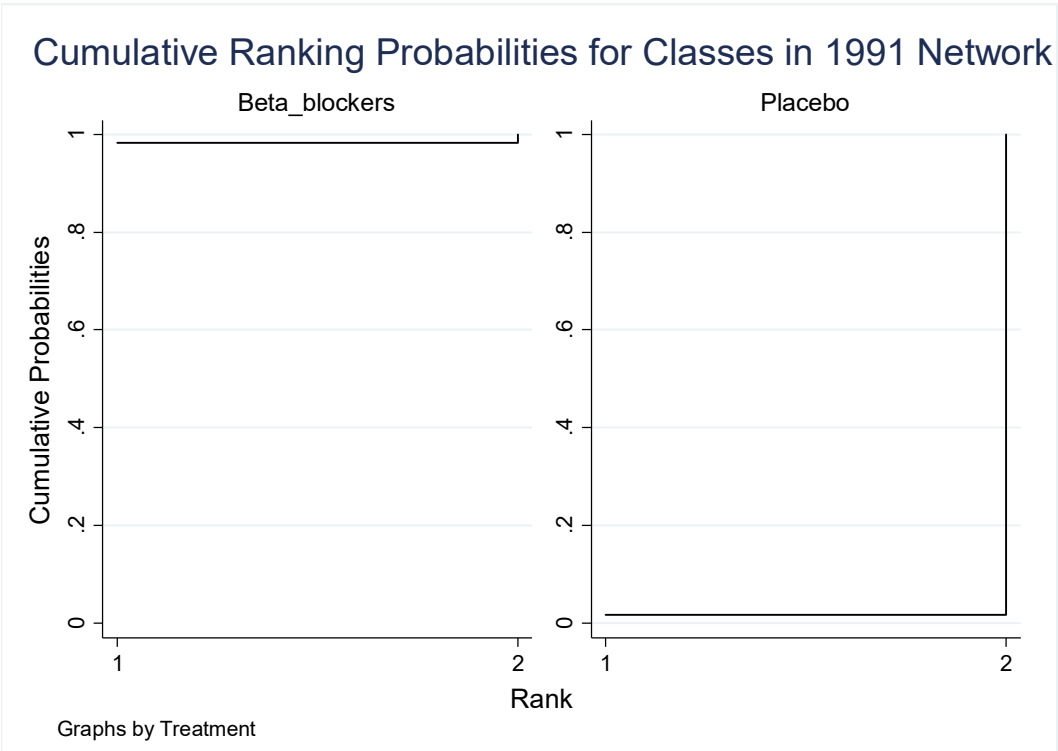


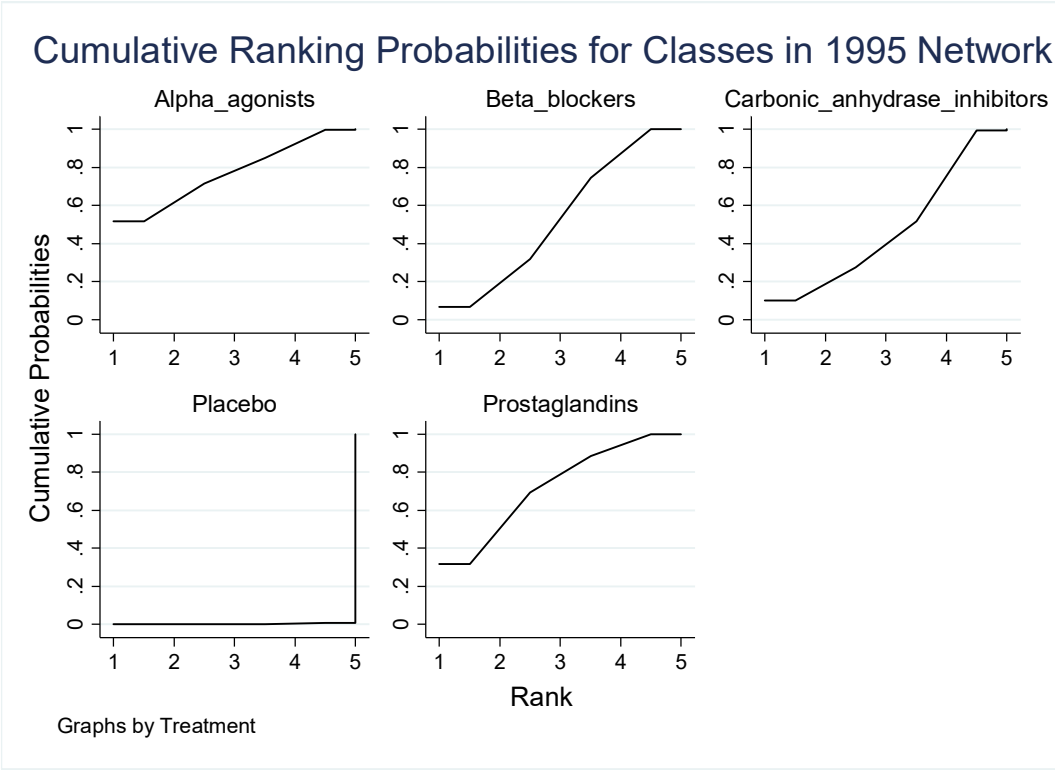


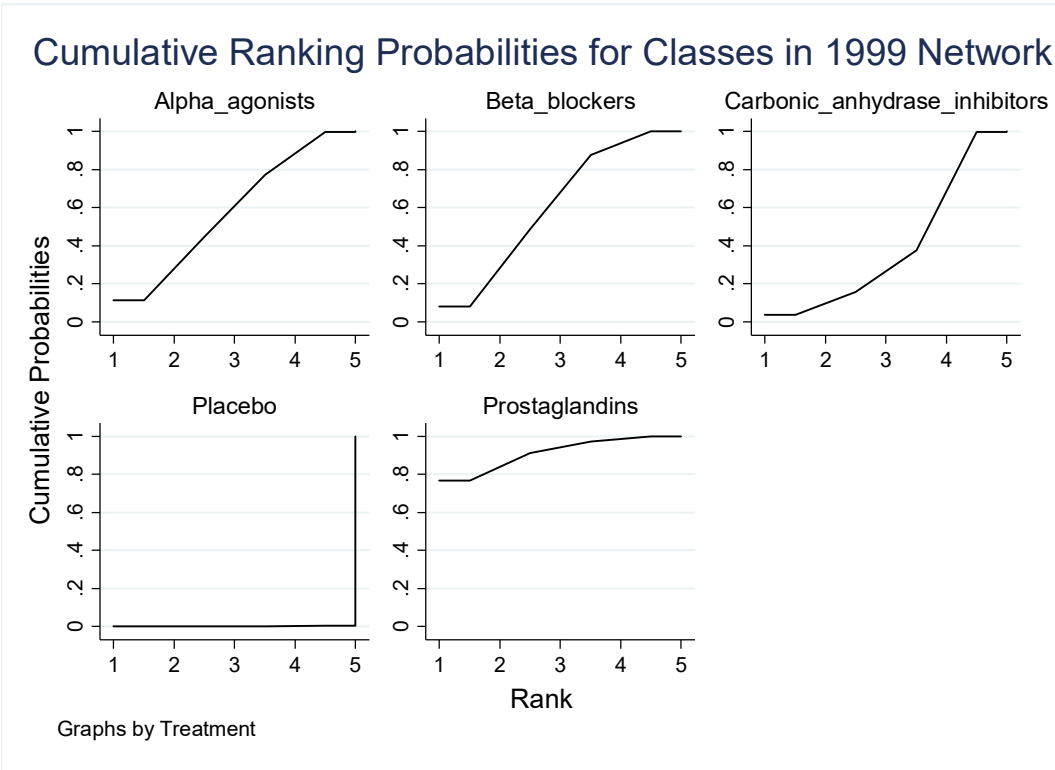


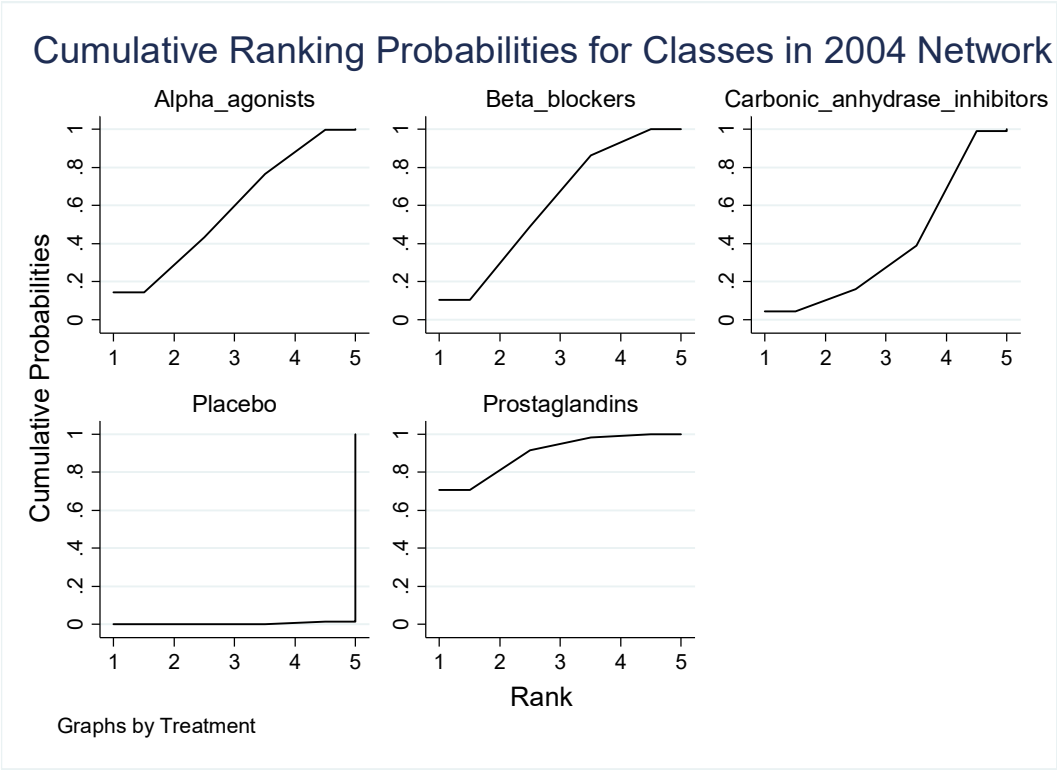












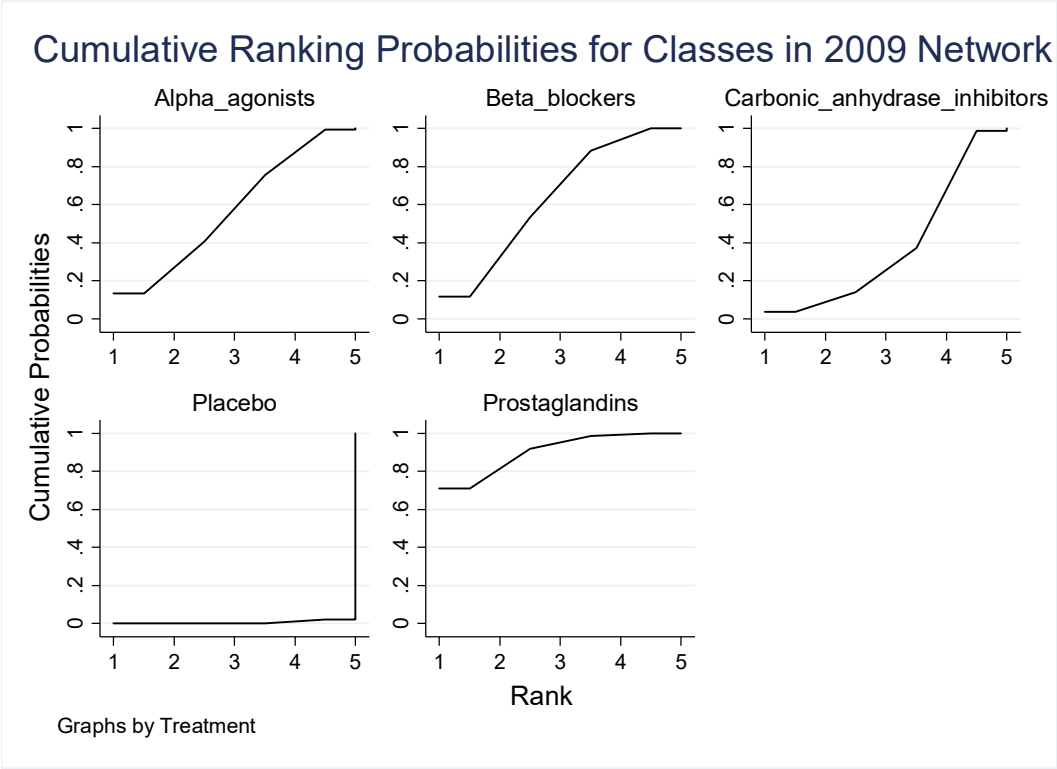


Table 1. Recommendations from the American Academy of Ophthalmology Preferred Practice Pattern Guidelines for Primary Open-Angle

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 lOP and ordinary background fluctuations of lOP."	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 lOP and ordinary background fluctuations of lOP."	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 lOP and ordinary background fluctuations of lOP."	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, Kruft B. Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines.

Table 2. Characteristics and risk of bias of networks

		Analysis year				
Characteristics of the Trial Network		**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

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