Table 1. Summary of Systemic Medications that May Increase or Decrease the Risk of Glaucoma

OPEN ANGLE GLAUCOMA			
Medications Known to Increase the Risk of OAG	Medications Known to Decrease the Risk of OAG	Medications that May Decrease the Risk of OAG	Medications with Mixed Findings
Corticosteroids	Beta blockers	Metformin Statins Bupropion (TNF-alpha antagonists) SSRIs Post-menopausal hormones Cannabinoids	Calcium channel blockers

ANGLE CLOSURE GLAUCOMA
Medications Known to Increase the Risk of AACC
Anticholinergics Adrenergics Cholinergics Sulfonamides Anticoagulants

OAG = open-angle glaucoma; AACC = acute angle-closure crisis; TNF = tumor necrosis factor; SSRIs = selective serotonin reuptake inhibitors

Table 2. Summary of Studies Reporting Association Between Statin Use and Glaucoma

Study title	Design, participants, and follow-up	Key findings
Marcus MW, et al. Cholesterol-lowering drugs and incident open-angle glaucoma: a population-based cohort study. PLoS One. 2012.[51]	3,939 participants in a prospective population-based cohort study, mean follow-up of 9.8 years with baseline exam from 1991 to 1993 and follow-up exams 1997 to 1999 and 2002 to 2006.	108 (2.7%) participants developed OAG. Hazard ratio for statin use was 0.54 (95% CI 0.31-0.96; P = 0.034) and for non-statin cholesterol-lowering drugs 2.07 (0.81-5.33; P = 0.13). Effect of statins was more pronounced with prolonged use (HR 0.89 [0.41-1.94; P = 0.77] for use two years or less; 0.46 [0.23-0.94; P = 0.033] for use more than two years; P-value for trend 0.10). Adjusted for age and gender, baseline IOP and IOP-lowering treatment, the family history of glaucoma, and myopia. There was no effect of statins on IOP.
McGwin G Jr, et al. Statins and other cholesterol-lowering medications and the presence of glaucoma. Arch Ophthalmol. 2004.[44]	667 cases selected from administrative clinical databases at the Veterans Affairs Medical Center, Birmingham, Alabama to include in a matched case-control study from January 1, 1997 through December 31, 2001.	Longer duration of statin use was associated with a lower risk of OAG (P for trend =.04) primarily among those with 24 months or more of use (OR, 0.60; 95% CI, 0.39-0.92). A protective association was also observed among those who used non-statin cholesterol-lowering agents (OR, 0.59; 95% CI, 0.37-0.97).
Stein JD, et al. The relationship between statin use and open-angle glaucoma. Ophthalmology. 2012.[50]	524,109 individuals aged ⩾60 years with hyperlipidemia enrolled in a national United States managed care network between 2001 and 2009; retrospective, longitudinal cohort analysis.	The hazard of developing OAG decreased 0.3% (adjusted HR, 0.997; 95% CI 0.994-0.999) for every additional month of statin consumption. The hazard of progressing from a diagnosis of glaucoma suspect to OAG decreased 0.4% (adjusted HR, 0.996; 95% CI, 0.993-0.999) for every additional month of statin exposure. The hazard of requiring medical treatment for OAG decreased 0.4% (adjusted HR, 0.996; 95% CI, 0.993-0.998) for every additional month of statin exposure. No differences in need for glaucoma surgery were found among those with OAG who were and were not taking statins (adjusted HR, 1.002; 95% CI, 0.994-1.010).
Talwar N, et al. Association of Daily Dosage and Type of Statin Agent With Risk of Open-Angle Glaucoma. JAMA Ophthalmol. 2017.[49]	25,420 patients from claims data from January 2001 to December 2009 with no preexisting glaucoma	After accounting for baseline low-density lipoprotein levels, persons who filled prescriptions for statins continuously for 2 years had a 21% reduced risk of OAG compared with nonusers (adjusted HR, 0.79; 95% CI, 0.66-0.96; P = .02). There was no additional protective effect associated with taking the highest dosage of statins (80 mg) compared with a lower dosage (40 mg) (HR, 1.03; 95% CI, 0.59-1.80; P = .91). The protective effect of the following statins on OAG risk did not differ between types of statins.
Kang JH, et al. Association of Statin Use and High Serum Cholesterol Levels With Risk of Primary Open-Angle Glaucoma. JAMA Ophthalmol. 2019.[52]	136,782 participants in 3 population-based cohorts aged 40 years or older who were free of glaucoma and had eye examinations (Nurses' Health Study, Nurses' Health Study 2, Health Professionals Follow-up Study), 1999-2015	886 incident cases of POAG were identified. A history of any statin use was associated with a 15% lower risk of POAG (RR, 0.85 [95% CI, 0.73-0.99]). Use of statins for 5 or more years vs never use of statins was associated with a 21% lower risk of POAG (RR, 0.79 [95% CI, 0.65-0.97]; P = .02). The association between use of statins for 5 or more years vs never use and risk of POAG was more inverse in those who were older (⩾65 years: RR, 0.70 [95% CI, 0.56-0.87] vs <65 years: RR, 1.05 [95% CI, 0.68-1.63]; P = .01 for interaction).
Whigham B, et al. The influence of oral statin medications on progression of glaucomatous visual field loss: A propensity score analysis. Ophthalmic Epidemiol. 2018.[53]	847 Veterans seen between 1/1/2005 and 1/1/2011 at the Durham Veterans Administration Medical Center eye clinic. Visual field progression was judged by an ophthalmologist masked to statin use history.	Visual field progression rates were 35% for statin users compared to 56% for nonusers in the matched cohort (McNemar's p<0.001).
Leung DY, et al. Simvastatin and disease stabilization in normal tension glaucoma: a cohort study. Ophthalmology. 2010.[54]	256 eyes from 256 Chinese subjects with NTG, prospective cohort study, recruited in 2004 and 2005, followed up at 4-month intervals for 36 months	121 patients (47.3%) showed evidence of VF progression during 36-month follow-up. Simvastatin use was present among 8 of 121 patients (6.6%) who progressed compared with 23 of 135 patients (17.0%) who did not progress (P = 0.011). Simvastatin use conferred a protective effect (RR 0.36; 95% CI, 0.14-0.91; P = 0.030) against VF progression.
De Castro DK, et al. Effect of statin drugs and aspirin on progression in open-angle glaucoma suspects using confocal scanning laser ophthalmoscopy. Clin Exp Ophthalmol. 2007.[55]	149 eyes from 76 patients OAG suspects who had undergone at least two CSLO tests at the Beckman Vision Center at UCSF from January 2001 to June 2006, retrospective chart review	Statins were associated with slowed progression of multiple CSLO parameters per year, including rim volume (-13.7% controls, +26.7% statin only; P = 0.0156), retinal nerve fiber layer cross-sectional area (-12.2% controls, +24.3% statin only; P = 0.0051), and mean global retinal nerve fiber layer thickness (-10.3% controls, +26.6% statin only; P = 0.0114), with adjustment for age, gender, race, IOP, central corneal thickness, refractive error and multiple systemic comorbidities.
Ho H, et al. Association of Systemic Medication Use With Intraocular Pressure in a Multiethnic Asian Population: The Singapore Epidemiology of Eye Diseases Study. JAMA Ophthalmol. 2017.[57]	8,063 participants from the Singapore Epidemiology of Eye Diseases study, recruited 2004-2011	Systemic β-blocker use was independently associated with an IOP of 0.45 mm Hg lower (95% CI, -0.65 to -0.25 mm Hg; P < .001). Conversely, higher mean IOP was associated with use of ACEIs (0.33 mm Hg higher; 95% CI, 0.08 to 0.57 mm Hg; P = .008), ARBs (0.40 mm Hg higher; 95% CI, 0.40-0.75 mm Hg; P = .02), statins (0.21 mm Hg higher; 95% CI, 0.02-0.4 mm Hg; P = .03), and sulfonylureas (0.34 mm Hg higher; 95% CI, 0.05-0.63 mm Hg; P = .02).
Chen HY, et al. Association Between Statin Use and Open-angle Glaucoma in Hyperlipidemia Patients: A Taiwanese Population-based Case-control Study. Medicine (Baltimore). 2015.[56]	1,276 patients with newly diagnosed OAG identified from 2004 to 2011 from the research database of the Taiwan National Health Insurance program	The adjusted odds ratio of OAG in the group with statin use was 1.02 (95% confidence interval 0.90-1.15) when compared with the group without statin use. Sub-analyses showed that high dose statin use (⩾120 DDD/y) resulted in a 1.24-fold increased risk of OAG (OR 1.24, 95% CI 1.03-1.49). The incidence of OAG increased with increased statin dose (P for trend = 0.0458). Controlled for: comorbidities, frequency of eye care visits, and the use of non-statin cholesterol-lowering drugs.
Iskedjian M. Effect of selected antihypertensives, antidiabetics,	8,548 patients with pharmaceutical records from the Québec prescription	For the 5614 patients taking systemic medications, significantly fewer (p < 0.001) required an additional IOP lowering medication if taking a systemic

statins and diuretics on adjunctive medical treatment of glaucoma: a population based study. Curr Med Res Opin. 2009.[58]	database between July 28, 1997 and February 28, 2006.	antihypertensive medication. The use of a statin or a diabetic medication, alone or in combination, in addition to a PGA, made no significant difference in the need for adjunct glaucoma therapy.
Khawaja AP, et al. Systemic medication and intraocular pressure in a British population: the EPIC-Norfolk Eye Study. Ophthalmology. 2014.[32]	7,093 participants from the European Prospective Investigation into Cancer-Norfolk Eye Study receiving ophthalmic exams between 2004 and 2011.	Use of systemic β-blockers (-0.92 mmHg; 95% CI, -1.19, -0.65; P<0.001) and nitrates (-0.63 mmHg; 95% CI, -1.12, -0.14; P = 0.011) were independently associated with lower IOP. The associations between statin or aspirin use with IOP were no longer significant after adjustment for β-blocker use.

OAG = open-angle glaucoma; POAG = primary open-angle glaucoma; NTG = normal tension glaucoma; IOP = intraocular pressure; CI = confidence interval; HR = hazard ratio; RR = relative risk; VF = visual field; CSLO = confocal scanning laser ophthalmoscopy; ACEI = angiotensin-converting-enzyme inhibitor; DDD = defined daily dose; ARB = angiotensin II receptor blocker; PGA = prostaglandin analogue

Table 3a. Studies Reporting Relationships Between Postmenopausal Hormone Use and Intraocular Pressure

	Study design	Number of treated/ control patients	IOP associated with no PMH use (Mean ± SD) mm Hg	IOP associated with PMH use (Mean ± SD) mm Hg	Change in IOP (mm Hg)	Months on PMH therapy	Type of PMH
Vajaranant TS, et al. Effects of Hormone Therapy on Intraocular Pressure: The Women's Health Initiative-Sight Exam Study. Am J Ophthalmol. 2016[73]	Post hoc analysis of data from randomized controlled trial	E: 808/860 E+P: 1,397/1,282	E: 15.8 ± 3.3 OD 15.9 ± 3.2 OS E+P: 15.7 ± 3.1 OD 15.7 ± 3.0 OS	E: 15.4 ± 3.2 OD 15.3 ± 3.1 OS E+P: 15.6 ± 3.0 OD 15.7 ± 3.0 OS	E: −0.5 OD −0.6 OS E+P: −0.13 OD −0.09 OS	E: 60 (average) E+P: 60 (average)	E or E+P
Lee AJ, et al; Blue Mountains Eye Study. Female reproductive factors and open angle glaucoma: the Blue Mountains Eye Study. Br J Ophthalmol. 2003[67]	Population based survey	324/1748	16.5 ± 0.1	16.1 ± 0.2	-0.4		E or E+P
Affinito P, et al. Effects of hormone replacement therapy on ocular function in postmenopause. Menopause. 2003[76]	Prospective controlled randomized study	25/25	16.1 ± 2.3	14.1 ± 2.0	−2	3	E+P
Altintaş O, et al. The effects of menopause and hormone replacement therapy on quality and quantity of tear, intraocular pressure and ocular blood flow. Ophthalmologica. 2004[77]	Prospective study with age matched controls	20/24	16.2± 2.3	12.3±1.8	−3.8	2	E or E+P
Coksuer H, et al. Effects of estradiol-drospirenone on ocular and nasal functions in postmenopausal women. Climacteric. 2011[78]	Prospective	34/0	14.1±2.8	13.4±2.7	−0.7	6	E+P
Sator MO, et al. Hormone replacement therapy and intraocular pressure. Maturitas. 1997[79]	Prospective study	25/0	16.2 ± 2.4 OS 15.3 ± 2.3 OD	14.0 ± 2.0 OS 13.8 ± 1.9 OD	−2.2 OS −1.5 OD	3	E+P
Tint NL, et al. Hormone therapy and intraocular pressure in nonglaucomatous eyes. Menopause. 2010[71]	Prospective cross sectional study	91/172	13.3 ± 2.9	11.85 ± 2.65	−1.7		E or E+P
Treister G, Mannor S. Intraocular pressure and outflow facility. Effect of estrogen and combined estrogen-progestin treatment in normal human eyes. Arch Ophthalmol. 1970[80]	Prospective	15/15	-	-	−2.0 -1.8	6	E E+P
Uncu G, et al. The effects of different hormone replacement therapy regimens on tear function, intraocular pressure and lens. opacity Gynecol Endocrinol. 2006[72]	Prospective study	30/0	14.6 ± 0.8	12.6 ± 0.68	−2.0	12	E or E+P
Abramov Y, et al. Does postmenopausal hormone replacement therapy affect intraocular pressure? J Glaucoma. 2005[81]	Prospective controlled cross sectional study	107/107	15	16	−1	≥12	E or E+P
Guaschino S, et al. Visual function in menopause: the role of hormone replacement therapy. Menopause. 2003[82]	Prospective controlled randomized study	40/40	14.8±3.2	14.9 ±4.3	−0.1	12	E+P
Toker E, et al. Influence of serum levels of sex hormones on intraocular pressure in menopausal women. J Glaucoma. 2003[83]	Retrospective cohort study	30/32	13.3 ± 2.3	13.6 ±2.5	−0.3	48 (average)	E+P

E = Estrogen; E + P = Estrogen + progestin; IOP = intraocular pressure; PMH = postmenopausal hormone; SD = standard deviation; OD = right eye; OS = left eye

Table 3b. Studies Reporting Relationships Between Postmenopausal Hormone Use and Glaucoma

Study title	Study population and design	Key findings
Lee AJ, et al; Blue Mountains Eye Study. Female reproductive factors and open angle glaucoma: the Blue Mountains Eye Study. Br J Ophthalmol. 2003[67]	2,072 women aged 49-97 years in a population-based survey (1992-1994)	Use of PMH was reported by 557 women (26.9%); 324 were current and 233 past users. The mean age of current users (60 years) was younger than both past (64.4 years) and never users (68.7 years). Lower OAG odds were found in women reporting past use of PMH (multivariate adjusted OR = 0.3; CI: 0. to −1.1), but was not statistically significant.
Hulsman CA, et al. Is open-angle glaucoma associated with early menopause? The Rotterdam Study. Am J Epidemiol. 2001[68]	3,078 women aged ≥55 years of age in a population-based survey (1990--1993)	Among women with natural menopause or menopause after irradiation therapy or bilateral oophorectomy (n = 2,678), 188 women had PMH use for some duration. Mean duration of use was 2.5 years (maximum = 24 years). Of women who used PMH, 3 had definite or probable OAG. The risk of OAG was lower in women who had used PMH than in women who never had, but not significant (OR = 0.54 (95 percent CI: 0.17, 1.74), adjusted for age and age at menopause)
Newman-Casey PA, et al. The potential association between postmenopausal hormone use and primary open-angle glaucoma. JAMA Ophthalmol. 2014[69]	152,163 women ≥ 50 years of age in a retrospective longitudinal cohort analysis of claims data (2001-2009)	2925 (1.9%) developed POAG. After adjustment for confounding factors, each additional month of use of PMH containing estrogen only was associated with a 0.4% reduced risk for POAG (HR, 0.996 [95% CI, 0.993-0.999]; P = .02). The risk for POAG did not differ with each additional month of use of estrogen + progesterone (HR, 0.994 [95% CI, 0.987-1.001]; P = .08) or estrogen + androgen (HR, 0.999 [95% CI, 0.988-1.011]; P = .89).
Vajaranant TS, et al. Racial Differences in the Effects of Hormone Therapy on Incident Open-Angle Glaucoma in a Randomized Trial. Am J Ophthalmol. 2018[70]	8,102 women (mean age = 68.5 ± 4.8 years) in the Women's Health Initiative in a secondary analysis of a randomized, placebo-controlled trial (enrollment 1993-1998). Women without a uterus were randomized to receive either oral conjugated equine estrogens (CEE 0.625 mg/day) or placebo, and women with a uterus received oral CEE and medroxyprogesterone acetate (CEE 0.625 mg/day + MPA 2.5 mg/day) or placebo.	No overall benefit of HT in reducing incident OAG (HR = 1.01, 95% CI = 0.79-1.29 in the CEE trial, and HR = 1.05, 95% CI = 0.85-1.29 in the CEE + MPA trial). However, race modified the relationship between CEE use and OAG risk (P interaction = .01), and risk was reduced in African-American women treated with CEE (HR = 0.49, 95% CI = 0.27-0.88), compared to placebo. Race did not modify the relation between CEE + MPA use and OAG risk (P interaction = .68).
Pasquale LR, Kang JH. Female reproductive factors and primary open-angle glaucoma in the Nurses' Health Study. Eye (Lond). 2011[74]	79,440 women ≥40 years of age in the Nurses' Health Study in a prospective study from 1980 to 2006	Ever using OCs was not associated with POAG risk (MVRR=1.14; 95% CI, 0.98, 1.34), ⩾5 years of OC use was associated with 25% increased risk of POAG (MVRR=1.25; 95% CI, 1.02, 1.53; P for linear trend=0.04). Among past OC users, a shorter time since stopping OC use was associated with an increased risk of POAG (P for linear trend=0.02).
Pasquale LR, et al. Attributes of female reproductive aging and their relation to primary open-angle glaucoma: a prospective study. J Glaucoma. 2007[75]	66,417 women ≥40 years old in the Nurses' Health Study in a prospective study from 1980 to 2002	Compared with never use of PMH, past PMH use [MVRR=0.84 (0.61 to 1.18)], and current PMH use [MVRR=0.89 (0.70 to 1.13)] was not significantly associated with POAG. In secondary analysis, compared with never use of PMH, current use of estrogen with progestin [MVRR=0.58 (0.36 to 0.94)] was associated with a reduced risk of POAG characterized by IOP >21 mm Hg before visual field loss; current use estrogen alone [MVRR=0.93 (0.63 to 1.35)] was not significantly associated.
Doshi V, et al. Los Angeles Latino Eye Study Group. Sociodemographic, family history, and lifestyle risk factors for open-angle glaucoma and ocular hypertension. The Los Angeles Latino Eye Study. Ophthalmology. 2008[170]	6142 Latinos ≥ 40 years of age from 6 census tracts in La Puente, California in a population-based cohort study (February 2000 to May 2003).	Older age, male sex, unmarried marital status, and being a first-degree relative were independent risk factors for OAG; PMH use was not associated with OAG (OR = 0.81 [95% CI 0.47-1.40]).
Kang JH, et al. Endothelial nitric oxide synthase gene variants and primary open-angle glaucoma: interactions with sex and postmenopausal hormone use. Invest Ophthalmol Vis Sci. 2010[171]	2070 participants ≥ 40 years of age and of Caucasian race in a nested case-control study from the Nurses' Health Study (1980-2002) and the Health Professionals' Follow-up Study (1986-2002)	Four of the five nitric oxide synthase gene (NOS3) single-nucleotide polymorphisms (SNPs) showed significant interactions with PMH use in relation to HTPOAG: for example, among the women with the TT genotype in T -786C, PMH use was inversely associated (RR = 0.41; 95% CI, 0.22-0.76), but among carriers of the minor allele, use of PMH was not associated.

PMH postmenopausal hormone; RR = relative risk; HTPOAG = high tension primary open-angle glaucoma; OAG = open-angle glaucoma; OR = odds ratio; HR = hazard ratio; CI = confidence interval; POAG = primary open-angle glaucoma; CEE = conjugated equine estrogens; OC = oral contraceptives; MPA = medroxyprogesterone acetate; HT = hormone therapy; MVRR = multivariable rate ratio