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Association of Systemic Medication Use with Glaucoma and Intraocular Pressure

The European Eye Epidemiology Consortium

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Purpose: To investigate the association of commonly used systemic medications with glaucoma and intraocular pressure (IOP) in the European population.

Design: Meta-analysis of 11 population-based cohort studies of the European Eye Epidemiology Consortium.

Participants: The glaucoma analyses included 143 240 participants and the IOP analyses included 47 177 participants.

Methods: We examined associations of 4 categories of systemic medications—antihypertensive medications (β-blockers, diuretics, calcium channel blockers [CCBs], α-agonists, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers), lipid-lowering medications, antidepressants, and antidiabetic medications—with glaucoma prevalence and IOP. Glaucoma ascertainment and IOP measurement method were according to individual study protocols. Results of multivariable regression analyses of each study were pooled using random effects meta-analyses. Associations with antidiabetic medications were examined in participants with diabetes only.

Main Outcome Measures: Glaucoma prevalence and IOP.

Results: In the meta-analyses of our maximally adjusted multivariable models, use of CCBs was associated with a higher prevalence of glaucoma (odds ratio [OR], 1.23; 95% confidence interval [CI], 1.08 to 1.39). This association was stronger for monotherapy of CCBs with direct cardiac effects (OR, 1.96; 95% CI, 1.23 to 3.12). No other antihypertensive medications, lipid-lowering medications, antidepressants, or antidiabetic medications were associated with glaucoma. Use of systemic β-blockers was associated with a lower IOP (β coefficient, −0.33 mmHg; 95% CI, −0.57 to −0.08 mmHg). Monotherapy of both selective systemic β-blockers (β coefficient, −0.45 mmHg; 95% CI −0.74 to −0.16 mmHg) and nonselective systemic β-blockers (β coefficient, −0.54 mmHg; 95% CI, −0.94 to −0.15 mmHg) was associated with lower IOP. A suggestive association was found between use of high-ceiling diuretics and lower IOP (β coefficient, −0.30 mmHg; 95% CI, −0.47 to −0.14 mmHg) but not when used as monotherapy. No other antihypertensive medications, lipid-lowering medications, antidepressants, or antidiabetic medications were associated with IOP.

Conclusions: We identified a potentially harmful association between use of CCBs and glaucoma prevalence. Additionally, we observed and quantified the association of lower IOP with systemic β-blocker use. Both findings potentially are important, given that patients with glaucoma frequently use systemic antihypertensive medications. Determining causality of the CCB association should be a research priority.

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Glaucoma is the leading cause of irreversible visual impairment worldwide[1] and the second most common cause in Europe.[2] Elevated intraocular pressure (IOP) is currently the only modifiable risk factor for glaucoma onset and progression. Glaucoma onset is highly associated with older age, whereas older age is also associated with increased frequency of comorbidities (and, therefore, polypharmacy).[3] Patients with glaucoma, thus, often demonstrate chronic systemic comorbidities, such as hypertension and diabetes mellitus (DM),[4−6] which makes it crucial to understand what effect commonly used systemic medications may have on glaucoma risk and IOP regulation.

Several classes of systemic medications are known to or suspected to modulate glaucoma risk by affecting optic nerve head perfusion, retinal ganglion cell survival, and aqueous humor outflow facility.[7] In an exploratory United States health claims data study that analyzed associations with all recorded classes of systemic medications, selective serotonin reuptake inhibitors (SSRIs) and calcium channel blockers (CCBs) were associated with a reduced and increased risk of incident primary open-angle glaucoma, respectively.[8] Other medications that may modulate the risk of open-angle glaucoma include β-blockers, metformin, statins, and bupropion.[7] Systemic β-blockers, and especially non-selective β-blockers, also have been demonstrated to lower IOP.[9,10] In contrast, an association with higher IOP has been observed for angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), statins, and sulfonylureas.[11] For many of the cited associations, findings between studies have been inconsistent, and few studies have accounted for polypharmacy or important confounders. For example, the apparently protective association between statin use and glaucoma risk may be confounded by systemic β-blocker use; recent studies taking this into account have not demonstrated a significant association between statin use and glaucoma risk.[12]

We aimed to examine definitively the association of commonly used systemic medications with glaucoma prevalence and IOP in Europeans. Our analyses aimed to identify consistent associations across 11 independent population cohorts (the European Eye Epidemiology [E3] Consortium), accounting for important confounders and polypharmacy.

Methods

Included Population-Based Studies

Eleven population-based cohort studies participating in the E3 Consortium were included in the present study.[13] All studies contributed data to the glaucoma analyses, and 10 studies were included in the IOP analyses. The E3 Consortium is a collaboration of European population-based and cohort studies that aims to increase understanding of eye disease and vision loss.[13] Participants were recruited between 1991 and 2017 from the following countries: France, Germany, Greece, the Netherlands, Norway, Portugal, Russia, and the United Kingdom. All studies adhered to the tenets of the Declaration of Helsinki and had local ethical committee approval. All participants gave written informed consent before examination.

Methods Used for Ascertainment of Study Variables

A total of 143 240 participants from 11 population-based studies from the E3 Consortium were included in the glaucoma analyses (Table 1). Eight of 11 included studies used visual field testing or optic nerve head examination to ascertain glaucoma diagnosis; 3 studies used nonobjective (e.g., self-reported) glaucoma diagnosis. We a priori elected to include the broadest case definition for glaucoma available within each study, given that we were interested in identifying medications that may alter the risk of any form of glaucoma. A total of 47 177 participants from 10 population-based studies were included in the IOP analyses. Eight of 10 studies used a noncontact tonometer to obtain IOP measurements; 2 studies used Goldmann applanation tonometry. We considered only IOP measurements obtained at the same time as systemic medication use ascertainment, assuming that any IOP-altering effects may be apparent only while the drug is being used. We considered each participant's IOP as the arithmetic mean IOP of both eyes; if IOP was available for only 1 eye, we considered that value as the participant's IOP. Seven studies collected medication data based on medical prescriptions and medication containers; 4 studies used self-reported (questionnaire) data. Systolic blood pressure (SBP) measurements were performed at the research centers and collected in all studies. SBP measurements were not adjusted for antihypertensive treatment. Total cholesterol was measured in blood samples collected at the research center and was available for 8 of 11 studies. Diabetes mellitus diagnosis ascertainment method was variable across studies, and, in most cases, multiple criteria were used: self-reported DM diagnosis, physician-confirmed DM diagnosis, use of antidiabetic medications, and fasting and nonfasting glucose of more than a certain cutoff or hemoglobin A1c level of more than certain cutoff. Ethnicity was determined in 8 of 11 studies. Descriptive data for the contributing studies can be viewed in Table 1. Detailed study methods and protocols are available in the Supplemental Methods (available at www.aaojournal.org).

Systemic Medication Assessments

Systemic medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[14] We analyzed associations with 11 antihypertensive medication subgroups: α-agonists (e.g., reserpine, methyldopa, and clonidine), low-ceiling diuretics (e.g., thiazides such as hydrochlorothiazide and bendroflumethiazide), other low-ceiling diuretics (e.g., chlorthalidone and theobromine), high-ceiling diuretics (e.g., torsemide and furosemide), aldosterone antagonists (e.g., spironolactone), nonselective β-blockers (e.g., propranolol, sotalol, and tertatolol), selective β-blockers (e.g., metoprolol and atenolol), selective CCBs with mainly vascular effects (e.g., amlodipine and felodipine), selective CCBs with direct cardiac effects (e.g., verapamil and diltiazem), ACEIs (e.g., enalapril, lisinopril, and perindopril), and ARBs (e.g., valsartan and losartan). We also analyzed associations with 3 lipid-lowering medication subgroups: statins (e.g., simvastatin and fluvastatin), fibrates (e.g., clofibrate and gemfibrozil), and other lipid-lowering medications (e.g., ezetimibe and lomitapide). Included antidepressants were nonselective monoamine reuptake inhibitors (NSMRIs [e.g., maprotiline and doxepin]), SSRIs (e.g., fluoxetine, citalopram, and sertraline), and other antidepressants (e.g., vortioxetine and bupropion). In participants with diabetes only, we assessed the associations of the following antidiabetic medications: insulin, biguanides (e.g., phenformin, metformin, and buformin), and sulfonylureas (e.g., glibenclamide and chlorpropamide). The Ural Eye and Medical Study did not have medication data available specified per ATC code but did have data on diuretics, systemic β-blockers, CCBs, and renin-angiotensin system (RAS) inhibitors; therefore, we included this study only in those broader analyses. For antihypertensive medications, we additionally determined the use of monotherapy (i.e., use of only 1 antihypertensive medication class).

Statistical Analysis

For the glaucoma analyses, multivariable logistic regression analyses with glaucoma status as the dependent variable and medication use (per ATC code) as a binary explanatory variable were conducted. For antihypertensive medications, additional separate regression analyses were carried out with antihypertensive medications grouped more broadly as diuretics, systemic β-blockers, CCBs, and RAS inhibitors. Each medication (per ATC code) or medication class was analyzed in its own separate model and not together with other medication classes, unless stated otherwise. For IOP analyses, we performed multivariable linear regression models with IOP as the dependent variable. For both glaucoma and IOP analyses, we ran 4 models with increasing adjustment for covariables. Model 1 was adjusted for age and sex. Model 2 was considered the maximally adjusted model, adjusting for age, sex, body mass index, and DM status. For antidiabetic medications, DM was not included as covariate, because the analyses were performed only in participants with DM. We did not adjust the analyses for the duration of DM or serum glucose levels. Model 3 included further adjustment of model 2 with SBP; this helped to identify whether any drug association was mediated by change in SBP, rather than via other effects. Model 4 was performed only for lipid-lowering medications and included additional adjustment of model 2 with total cholesterol. To assess the potential confounding effect of ethnicity, we performed sensitivity analyses, adding ethnicity to our maximally adjusted model (model 2). We performed analyses separately for each individual study. Subsequently, we conducted random-effects meta-analyses, given the heterogeneity of study participants and study designs. For analyses of glaucoma status, we repeated meta-analyses after exclusion of studies with nonobjective glaucoma ascertainment (i.e., self-reported data only). Moreover, we performed sensitivity analyses, including only patients with glaucoma whose disease was defined as open-angle glaucoma (primary or secondary was not defined). For IOP as an outcome, these sensitivity analyses were not performed because we aimed to include the full range of IOPs from the complete population (regardless of glaucoma status). Statistical analyses were performed using SPSS software version 25.0 (SPSS, Inc.) and RStudio version 4.0.0 (R Foundation for Statistical Computing) with the add-on package meta.

Results

The baseline characteristics of participants from the included studies are presented in Table 2. Glaucoma prevalence ranged from 0.9% to 8.7%, with the lowest prevalence in a relatively young population and the highest prevalence in the oldest population. Mean ± standard deviation IOP ranged between 13.8 ± 3.7 mmHg and 16.1 ± 3.7 mmHg. Table S3 (available at www.aaojournal.org) presents the use of systemic medications in each included study. Overall, the most frequently prescribed antihypertensive medications were selective β-blockers and selective CCBs with mainly vascular effects. Participants using lipid-lowering medications most often used statins. Selective serotonin reuptake inhibitors were the most commonly prescribed antidepressants.

Associations with Glaucoma Prevalence

In the meta-analyses of the maximally adjusted multivariable models (Table 4), use of CCBs was associated with a higher glaucoma prevalence (selective CCBs with mainly vascular effects: odds ratio [OR], 1.22; 95% confidence interval [CI], 1.04 to 1.43; Fig 1A; selective CCBs with direct cardiac effects: OR, 1.39; 95% CI, 1.07 to 1.81; Fig 1B). Additional adjustment for SBP (Table S5, model 3, available at www.aaojournal.org) did not change the results meaningfully. These associations persisted in sensitivity analyses including only studies with objectively ascertained patients with glaucoma (Table S6, available at www.aaojournal.org) and in sensitivity analyses including only patients with open-angle glaucoma (Table S7, available at www.aaojournal.org). When additionally adjusting the previous associations for ethnicity (Table S8, available at www.aaojournal.org), the association of glaucoma prevalence with selective CCBs with direct cardiac effects was reduced to some extent (OR, 1.25; 95% CI, 0.93 to 1.67), but the association with selective CCBs with mainly vascular effects (OR, 1.26; 95% CI, 1.07 to 1.47) was not. This association persisted in sensitivity analyses including only studies with objectively ascertained patients with glaucoma. When assessing antihypertensive use as solely monotherapy and not in combination with other antihypertensives (Table S9, available at www.aaojournal.org), the use of selective CCBs with direct cardiac effects was associated with a higher glaucoma prevalence (model 2: OR, 1.96; 95% CI, 1.23 to 3.12). This association was stronger when analyzing only objectively ascertained patients with glaucoma (model 2: OR, 2.15; 95% CI, 1.30 to 3.54). When grouping the CCBs together, use of any CCB was associated with a 23% higher prevalence of glaucoma (OR, 1.23; 95% CI, 1.08 to 1.39; Table S10, model 2, available at www.aaojournal.org). This associations persisted, with significant *P* values, in sensitivity analyses including only studies with objectively ascertained patients with glaucoma.

The association between CCB use and glaucoma did not change after additional adjustment for systemic β-blocker use (which was associated significantly with IOP in the present study; see below), in both the primary meta-analyses including all studies with objective and self-reported patients with glaucoma (all CCBs: OR, 1.25; 95% CI, 1.09−1.42; Table S11, model 2[c], available at www.aaojournal.org) and sensitivity analyses including only studies with objectively ascertained patients with glaucoma. Additional adjustment for simultaneous use of the 2 medications (i.e., modelling an interaction) showed no strong evidence for a significant interaction between systemic β-blocker and CCB use.

We found several associations with a higher prevalence of glaucoma in the primary meta-analyses, including all studies with objective and self-reported patients with glaucoma, that did not retain statistical significance in sensitivity analyses: RAS inhibitors (OR, 1.13; 95% CI, 1.03 to 1.24; Table S10, model 2), statins (OR, 1.10; 95% CI, 1.00 to 1.21; Table 4, model 2), NSMRIs (OR, 1.50; 95% CI, 1.15 to 1.96; Table 4, model 2), and insulin (OR, 1.54; 95% CI, 1.09 to 2.18]; Table 4, model 2). None of the other antihypertensive medications, lipid-lowering medications, antidepressants, or antidiabetic medications were associated with glaucoma prevalence (Table 4).

Table 1. Descriptive Data for the Contributing Studies

Study	Glaucoma Ascertainment	Glaucoma Subtypes Included	IOP Measurements	Medication Data Ascertainment	BP Ascertainment	Total Cholesterol	Diabetes Ascertainment
Alienor Study	Objective: ISGEO glaucoma classification,* visual field test (Octopus 101), optic nerve head examination, slit-lamp examination, gonioscopy	OAG (100%); unknown whether primary or secondary	NCT (KT 800); 1 measurement/eye	ATC codes from medical prescriptions and medication containers	OMRON M4	NA	Fasting blood glucose ≥ 7.0 mmol/l or use of antidiabetic medications
Coimbra Eye Study	Objective: diagnosis by the research center based on optic nerve head examination (color fundus and Spectralis SD OCT)	POAG (100%, but not confirmed)	NCT (Tonoref II); mean ≥ 3 measurements/eye (up to 5 readings obtained if any outliers)	ATC codes from self-reported medication	Unknown	NA	Use of antidiabetic medications or self-reported
EPIC-Norfolk Eye Study	Objective: diagnosis by glaucoma specialist based on the ISGEO glaucoma classification, visual field test (Humphrey 750i), optic nerve head examination (HRT II and TRC-NW6S), gonioscopy	POAG (86.5%), PACG (8.0%), secondary glaucoma (5.5%)	NCT (AT555 or ORA); best signal value of ≥ 3 IOPg measurements/eye	ATC codes from medical prescriptions and medication containers	Accutorr Plus	Blood sample collected at visit	Use of antidiabetic medications, HbA1c ≥ 6.5%, or self-reported
Gutenberg Health Study	Objective: ISGEO glaucoma classification, visual field test (FDT), optic nerve head examination (Visucam PRO NM and Spectralis), slit-lamp examination	OAG (100%); unknown whether primary or secondary	NCT (NT-2000); mean of 3 measurements/eye	ATC codes from medical prescriptions and medication containers	Omron HEM 705-CP II	Blood sample collected at visit	Use of antidiabetic medications, blood glucose ≥ 126 mg/dl after overnight fasting, or blood glucose ≥ 200 mg/dl after 8 hrs of fasting
Leipzig Research Centre for Civilization Diseases (LIFE) Adult Study	Nonobjective: self-reported	Unknown	NA	ATC codes from medical prescriptions and medication containers	Omron 705-IT	Blood sample collected at visit	Fasting blood glucose ≥ 7.0 mmol/l, or HbA1c ≥ 6.5%, taking into account use of antidiabetic medications or self-reported

Table 1. (Continued.)

Study	Glaucoma Ascertainment	Glaucoma Subtypes Included	IOP Measurements	Medication Data Ascertainment	BP Ascertainment	Total Cholesterol	Diabetes Ascertainment
Lifelines	Nonobjective: glaucoma definition algorithm that was based on self-reported incisional surgery for glaucoma, glaucoma treatment, and glaucoma-related symptoms	Unknown	NCT (ORA); mean of 1−2 measurements/eye	ATC codes from medical prescriptions, medication containers, and self-reported medication	DinaMap PRO 100V2	Blood sample collected at visit	Use of antidiabetic medications, fasting blood glucose ≥ 7.0 mmol/l, HbA1c ≥ 6.5%, or self-reported
Montrachet Study	Objective: ISGEO glaucoma classification, visual field test (FDT and Humphrey SITA 24-2), optic nerve head examination (TRC-NW6S and SD OCT), gonioscopy	POAG (95%), PEXG (5%)	NCT (Tonoref II); 1 measurement/eye	ATC codes from self-reported medication	Standard cuff	Blood sample collected at visit	Self-reported
Rotterdam Study	Objective: visual field test (FDT and HFA II 740), optic nerve head examination (Topcon TRV-50VT and SD-OCT), medical history	POAG (100%)	GAT; median of 3 measurements/eye	ATC codes from medical prescriptions via automated pharmacies	Hawksley random-zero sphygmomanometer, Omron M6 comfort, Omron M7	Blood sample collected at visit	Diabetes diagnosis based on GP records or hospital letters, use of antidiabetic medications, or serum glucose measurement (fasting > 7.0 mmol/l or nonfasting > 11.1 mmol/l)
Thessaloniki Eye Study	Objective: visual field test (HFA II), optic nerve head examination (HRT), gonioscopy, slit-lamp examination	POAG (62.8%), PACG (6.4%), PEXG (27.6), secondary glaucoma (3.2%)	GAT; mean of 3 measurements/eye	ATC codes from medical prescriptions and medication containers	Omron 705CP	NA	Self-reported
Tromsø Eye Study	Nonobjective: self-reported	Unknown	NCT (ICare rebound tonometer); mean of 4 measurements/eye	ATC codes from self-reported medication, validated against the Norwegian Prescription Drug Registry	Dinamap Vital Signs Monitor	Blood sample collected at visit	Nonfasting blood glucose ≥ 11.1 mmol/l, HbA1c > 6.5%, or self-reported

(*Continued*)

Table 1. (Continued.)

Study	Glaucoma Ascertainment	Glaucoma Subtypes Included	IOP Measurements	Medication Data Ascertainment	BP Ascertainment	Total Cholesterol	Diabetes Ascertainment
Ural Eye and Medical Study	Objective: ISGEO glaucoma classification, visual field test (PTS 1000 Perimeter), optic nerve head examination (VISUCAM 500 and RS-3000 OCT), anterior segment biometry (Pentacam HR, Typ70900), slit-lamp biomicroscopy	OAG (73.1%), ACG (26.9%); unknown whether primary or secondary	NCT (KT 800); 1 measurement/eye (repeated if IOP > 21 mmHg)	Self-reported medication, not per ATC codes	Omron M2	Blood sample collected at visit	Plasma glucose concentration ≥ 7.0 mmol/l, use of antidiabetic medications, or self-reported

ACG = angle-closure glaucoma; ATC = Anatomical Therapeutic Chemical; BP = blood pressure; FDT = frequency doubling technology; GAT = Goldmann applanation tonometer; HbA1c = hemoglobin A1c; HFA = Humphrey field analyzer; HRT = Heidelberg Retinal Tomography; IOP = intraocular pressure; IOPg = Goldmann-correlated intraocular pressure; ISGEO = International Society for Geographical and Epidemiological Ophthalmology; NA = not available; NCT = noncontact tonometry; OAG = open-angle glaucoma; PACG = primary angle-closure glaucoma; PEXG = pseudoexfoliation glaucoma; POAG = primary open-angle glaucoma; SD = spectral-domain; SITA = Swedish Interactive Threshold Algorithm.

*Classification for glaucoma developed at the biennial congress of the International Society for Geographical and Epidemiological Ophthalmology held in Leeuwenhorst, the Netherlands, June 1998: Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol.* 2002;86(2):238-242.

IOP

In the meta-analyses of the maximally adjusted multivariable models (Table 4), systemic β-blocker use was associated with a lower IOP (nonselective β-blockers: β coefficient, −0.55 mmHg; 95% CI, −0.94 to −0.16 mmHg; Fig 2A; selective β-blockers: β coefficient, −0.39 mmHg; 95% CI, −0.62 to −0.15 mmHg; Fig 2B). Additional adjustment for ethnicity did not change these associations meaningfully (Table S12, available at www.aaojournal.org). When assessing antihypertensive use solely as monotherapy and not in combination with other antihypertensives (Table S13, available at www.aaojournal.org), both nonselective β-blockers (β coefficient, −0.54 mmHg; 95% CI, −0.94 to −0.15 mmHg) and selective β-blockers (β coefficient, −0.45 mmHg; 95% CI, −0.74 to −0.16 mmHg) were associated with a lower IOP. When grouping the systemic β-blockers together, use of any systemic β-blocker was associated with a 0.33-mmHg lower IOP (all systemic β-blockers: β coefficient, −0.33 mmHg; 95% CI, −0.57 to −0.08 mmHg; Table S10, model 2). A suggestive association was observed for high-ceiling diuretics and lower IOP (β coefficient, −0.30 mmHg; 95% CI, −0.47 to −0.14 mmHg; Table 4); although this association retained statistical significance after adjustment for SBP (β coefficient, −0.21 mmHg; 95% CI, −0.37 to −0.04 mmHg; Table S14, model 3, available at www.aaojournal.org) or ethnicity (β coefficient, −0.31 mmHg; 95% CI, −0.51 to −0.11 mmHg; Table S12), it was no longer significant when adjusting additionally for use of β-blockers and CCBs (β coefficient, −0.14 mmHg; 95% CI, −0.31 to 0.02 mmHg; Table S15, model 3, available at www.aaojournal.org). Moreover, monotherapy of high-ceiling diuretics was not associated significantly with lower IOP (β coefficient, −0.32 mmHg; 95% CI, −0.71 to 0.06 mmHg; Table S13, model 2).

Although monotherapy of aldosterone antagonists tended to be associated with a higher IOP (β coefficient, 1.21 mmHg; 95% CI, 0.27 to 2.14 mmHg; Table S13, model 2), none of the other antihypertensive medications (e.g., α-agonists, CCBs, ACEIs, and ARBs) were associated with IOP (Table 4; Table S10). Other lipid-lowering medications, but not statins or fibrates, showed a tendency toward being associated with a lower IOP (β coefficient, −0.39 mmHg; 95% CI, −0.78 to 0.00 mmHg; Table 4), but this association did not retain statistical significance after adjusting for total cholesterol level (β coefficient, −0.40 mmHg; 95% CI, −0.81 to 0.01 mmHg; Table S14, model 4). Use of SSRIs was associated with a lower IOP (β coefficient, −0.23 mmHg; 95% CI, −0.45 to −0.01 mmHg; Table 4); however, this association was no longer significant when additionally adjusting for SBP (β coefficient, −0.15 mmHg; 95% CI, −0.37 to 0.06 mmHg; Table S14, model 3). Use of other antidepressants or antidiabetic medications was not associated with IOP (Table 4). Additional adjustment of aforementioned analyses with SBP (Table S14, model 3) or total cholesterol (Table S14, model 4) did not change the results meaningfully, unless stated otherwise.

Discussion

In this large study examining glaucoma prevalence and IOP in > 140 000 participants from 11 populations across 8 European countries, we identified associations between CCB use and high glaucoma prevalence. Nonselective and selective β-blockers were associated with lower IOP. A suggestive association was observed between use of high-ceiling diuretics and lower IOP. Our findings confirmed the known IOP-lowering effect of systemic β-blockers, quantifying the effect on a population level, and identified other potential systemic medication modifiers of glaucoma risk. Although our novel findings require further studies to determine whether the associations are causal, these findings will be of interest to physicians caring for patients with glaucoma with systemic comorbidities.

Our findings further support an association between CCB use and glaucoma prevalence. A previous analysis of the population-based Rotterdam Study reported a significant association between use of CCBs and incidence of open-angle glaucoma (OR, 1.80; 95% CI, 1.04 to 3.20).[15] At the time, only data from the first cohort of the Rotterdam Study were available, with a maximum follow-up of 6.5 years. In the meta-analysis described in the present study, we were able to include participants from all 3 independent cohorts of the Rotterdam Study with a follow-up of up to 20 years, increasing not only the total number of participants in the study but also the number of patients with glaucoma. Zheng et al[8] analyzed United States health insurance data in a case-control design and showed a strong and highly significant association between CCB use and primary open-angle glaucoma (OR, 1.26; 95% CI, 1.18 to 1.35). The association retained statistical significance after adjustment of other medications, for example, systemic β-blockers (OR, 1.23; 95% CI, 1.14 to 1.33). Similarly, Asefa et al[16] and Langman et al[17] reported an adverse association between use of CCBs and glaucoma prevalence (OR, 1.19 [95% CI, 1.01 to 1.40] and 1.34 [95% CI, 1.24 to 1.44], respectively). Calcium channel blockers may exert direct effects on the retina; previously, use of CCBs was associated with a thinner macular retinal nerve fiber layer and thinner ganglion cell−inner plexiform layer.[18]

Some studies have suggested that CCBs more effectively lower BP when taken at bedtime rather than in the morning.[19−23] Simultaneously, nocturnal systemic hypotension may be associated with increased risk of glaucoma progression.[24−26] Thus, this may explain the association between CCBs and increased glaucoma prevalence if CCBs are taken preferentially at bedtime. In the present study, time of medication use was not known. Therefore, we were not able to provide evidence for this hypothesis.

Long-term higher levels of calcium ions may be responsible for apoptotic and necrotic cell death in many cell lines, including (retinal) neurons. Because the primary effect of a CCB is inhibition of intracellular calcium ion influx,[27,28] previous studies have suggested that CCBs harbor neuroprotective effects. By inducing vasodilation, they can restore impaired blood flow in local ischemic tissues and can directly inhibit calcium ion-related cell death pathways. This potentially could rescue ischemic retinal ganglion cells.[29,30] However, in ischemic tissue, vasodilation already may be maximized and autoregulation of blood flow may be impaired, whereas it is preserved in nonischemic areas. Therefore, CCB-induced vasodilation may result in diversion of blood flow, which could worsen damage in ischemic tissue.[31]

We found that RAS inhibitor use was associated with an increased prevalence of glaucoma but only when grouping ACEIs and ARBs together. This association lost its significance when including only studies with objectively ascertained patients with glaucoma. The literature has reported contradicting findings for both ACEIs and ARBs: protective effects,[32] no effects,[15,16,33] and harmful effects.[8,16,17] None of the other antihypertensive medications were associated with glaucoma in the present study. Contradicting findings have been reported for diuretics: although some studies showed no association,[15,16] a case-control study in the United Kingdom showed an association with increased glaucoma prevalence.[33]

Systemic β-blockers were associated significantly with lower IOP, which is in line with previous findings.[10,11,34,35] Additionally, we found a suggestive association between use of high-ceiling diuretics (often prescribed to patients with heart failure) and lower IOP. However, this association was not apparent when adjusting for use of systemic β-blockers, CCBs, and SBP. Thus, it is possible that the association between use of high-ceiling diuretics and lower IOP is explained partly by residual confounding. None of the other antihypertensive medications were associated with IOP in the present study. This is in line with other studies reporting no associations between IOP and diuretics,[10,34] CCBs,[10,34] α-agonists,[10,34] ACEIs,[10,34] and ARBs.[10,34] Although use of systemic β-blockers was associated significantly with lower IOP, we did not find a significant association with glaucoma prevalence. Previous research has suggested that the IOP-lowering effect of systemic β-blockers would translate to a reduced risk of incident glaucoma.[34] In line with this theory, a protective effect of systemic β-blockers on glaucoma risk was reported by Zheng et al[8] (OR, 0.77; 95% CI, 0.72 to 0.83) and Langman et al[17] (OR, 0.77; 95% CI, 0.73 to 0.83). Similarly, Owen et al[33] reported lower prevalence of oral β-blocker use in the 5 years before diagnosis in patients with glaucoma than in control participants (adjusted OR, 0.87; 95% CI, 0.80 to 0.94). After stratification, this effect was present for selective β-blockers (adjusted OR, 0.81; 95% CI, 0.74 to 0.88), but not for nonselective β-blockers (adjusted OR, 1.08; 95% CI, 0.94 to 1.24). However, it is possible that systemic β-blockers do not reduce the risk of glaucoma per se but, rather, limit the detection of glaucoma, given that elevated IOP often is a trigger for diagnosing glaucoma. Moreover, BP, IOP, and optic nerve head perfusion are correlated complexly and can influence glaucoma development and progression in different ways. High BP may cause an increased production (because of elevated ciliary blood flow and capillary pressure) and decreased outflow (because of increased episcleral venous pressure) of aqueous humor, causing an increase in IOP. However, having a low BP, whether spontaneous or secondary to antihypertensive treatment, may reduce perfusion of the optic nerve, leading to ischemic damage. The BP-lowering effect of systemic β-blockers thus may balance out the IOP-lowering effect on glaucoma risk, explaining the null association between use of systemic β-blockers and glaucoma prevalence in the present study.

We did not find clear associations between the use of antidepressants and glaucoma prevalence or IOP regulation.

Table 2. Baseline Characteristics of Participants Included in the Glaucoma or IOP Analyses, or Both

Study	Glaucoma	IOP (mmHg)	Age (yrs)	Female Sex	Body Mass Index (kg/m^2)	DM	SBP (mmHg)	Cholesterol (mmol/l)	European*	Visit Year
Alienor Study (n = 961)	45 (4.7)	13.9 ± 2.4	80.2 ± 4.4	594 (61.8)	25.9 ± 4.1	109 (11.3)	144.1 ± 21.4	NA	NA	2006–2008
Coimbra Eye Study (n = 948)	56 (5.9)	14.2 ± 3.1	72.3 ± 6.8	552 (58.2)	28.0 ± 4.5	173 (18.2)	139.6 ± 19.9	NA	942 (99.4)	2015–2017
EPIC-Norfolk Eye Study (n = 8623)	363 (4.2)	16.1 ± 3.7	68.7 ± 8.1	4762 (55.2)	26.8 ± 4.3	262 (3.0)	136.2 ± 16.6	5.4 ± 1.1	8572 (99.4)	2006–2011
Gutenberg Health Study (n = 14 479)	128 (0.9)	14.3 ± 2.8	55.1 ± 11.1	7187 (49.6)	27.4 ± 5.0	1361 (9.4)	131.3 ± 17.4	5.7 ± 1.1	11 829 (99.1)	2007–2012
Leipzig Research Centre for Civilization Diseases (LIFE) Adult Study (n = 8963)	384 (4.3)	NA	57.4 ± 12.4	4658 (52.0)	27.4 ± 4.9	1255 (14.0)	128.2 ± 16.7	5.6 ± 1.1	8801 (98.2)	2011–2014
Lifelines (n = 86 841)	3838 (4.4)	15.3 ± 3.8	50.3 ± 5.1	35 459 (40.8)	25.4 ± 5.0†	2911 (3.4)	124 ± 20.0†	5.1 ± 1.1	78 028 (98.3)	2006–2017
Montrachet Study (n = 1153)	100 (8.7)	14.8 ± 3.0	82.3 ± 3.8	723 (62.7)	26.1 ± 3.9	93 (8.1)	141.5 ± 18.9	6.9 ± 10.4	NA	2009–2013
Rotterdam Study (n = 8679)	360 (4.1)	14.2 ± 3.0	62.6 ± 7.8	4950 (57.0)	26.9 ± 4.0	1433 (16.5)	136.1 ± 20.5	6.4 ± 4.9	7655 (97.8)	1991–2008
Thessaloniki Eye Study (n = 2554)	156 (6.1)	15.2 ± 3.4	71.6 ± 6.3	1202 (47.1)	28.3 ± 4.4	417 (16.3)	146.1 ± 23.2	NA	2554 (100.0)	1998–2005
Tromsø Eye Study (n = 8012)	234 (3.0)	13.9 ± 3.5	61.1 ± 10.5	3649 (45.5)	NA‡	462 (6.0)	133.4 ± 20.2	5.5 ± 1.1	NA	2015–2016
Ural Eye and Medical Study (n = 5885)	256 (4.4)	13.8 ± 3.7	59.0 ± 10.7	3315 (56.3)	27.9 ± 5.0	682 (11.6)	133.6 ± 20.5	5.8 ± 1.7	1181 (21.9)§	2015–2017

DM = diabetes mellitus; IOP = intraocular pressure; NA = not available; SBP = systolic blood pressure.
Data are presented as no. (%) or mean ± standard deviation, unless otherwise indicated.
*Ethnicity was not available for all participants; percentage is based on number of participants for whom ethnicity data were available.
†Data presented as median (interquartile range).
‡Data were available only on categorical level: body mass index, 0–25 kg/m^2(n = 2507 [31.4%]), 25–30 kg/m^2(n = 3592 [45.0%]), > 30 kg/m^2(n = 1889 [23.6%]).
§Represents the number of participants with Russian ethnicity.

Table 4. Meta-analyzed Associations of Commonly Used Systemic Medications with Glaucoma Prevalence (Objectively and Non-objectively Ascertained Patients with Glaucoma) and IOP (Model 2)

Medication (ATC Code)	Glaucoma			IOP (mmHg)		
	No.	OR (95% CI)	P Value	No.	β Coefficient (95% CI)	P Value
Antihypertensive medications						
α-agonists (C02A)	127 762	1.36 (0.75 to 2.47)	0.31	35 600	0.02 (−0.36 to 0.41)	0.90
Low-ceiling diuretics						
Thiazides (C03A)	134 548	1.05 (0.88 to 1.25)	0.62	40 089	0.06 (−0.09 to 0.22)	0.42
Others (C03B)	120 703	1.28 (0.87 to 1.88)	0.21	36 010	−0.05 (−0.33 to 0.23)	0.73
High-ceiling diuretics (C03C)	137 214	1.06 (0.82 to 1.37)	0.67	41 016	−0.30 (−0.47 to −0.14)	< 0.001*
Aldosterone antagonists (C03C)	116 388	1.01 (0.62 to 1.65)	0.97	41 015	−0.20 (−0.49 to 0.08)	0.17
Nonselective β-blockers (C07AA)	136 286	1.19 (0.90 to 1.57)	0.21	41 018	−0.55 (−0.94 to −0.16)	0.006*
Selective β-blockers (C07AB)	137 214	1.04 (0.95 to 1.15)	0.38	41 016	−0.39 (−0.62 to −0.15)	0.001*
Selective CCBs						
Vascular effects (C08CA)	137 219	1.22 (1.04 to 1.43)	0.01*	41 021	0.03 (−0.08 to 0.14)	0.60
Direct cardiac effects (C08D)	127 681	1.39 (1.07 to 1.81)	0.01*	41 016	0.03 (−0.31 to 0.37)	0.86
Angiotensin-converting enzyme inhibitors (C09A)	137 214	1.13 (0.99 to 1.29)	0.06	41 016	0.04 (−0.10 to 0.19)	0.57
ARBs (C09C)	137 214	1.08 (0.95 to 1.23)	0.24	41 016	0.09 (−0.13 to 0.32)	0.42
Lipid-lowering medications						
Statins (C10AA)	137 260	1.10 (1.00 to 1.21)	0.04*	41 059	−0.07 (−0.19 to 0.05)	0.26
Fibrates (C10AB)	112 482	1.11 (0.64 to 1.95)	0.71	27 842	−0.18 (−0.52 to 0.16)	0.31
Other lipid-lowering medications (C10AX)	112 233	1.20 (0.79 to 1.82)	0.40	41 059	−0.39 (−0.78 to 0.00)	0.05
Antidepressants						
NSMRIs (N06AA)	135 854	1.50 (1.15 to 1.96)	0.003*	41 060	0.14 (−0.17 to 0.45)	0.38
SSRIs (N06AB)	137 655	1.26 (0.87 to 1.84)	0.22	41 060	−0.23 (−0.45 to −0.01)	0.04*
Other antidepressants (N06AX)	130 002	1.50 (1.10 to 2.03)	0.01*	41 060	−0.14 (−0.39 to 0.12)	0.29
Antidiabetic medications†						
Insulin (A10A)	7792	1.54 (1.09 to 2.18)	0.01*	4046	0.14 (−0.19 to 0.47)	0.40
Biguanides (A10BA)	8090	0.84 (0.62 to 1.14)	0.26	4006	0.07 (−0.13 to 0.28)	0.48
Sulfonylureas (A10BB)	8090	0.94 (0.73 to 1.22)	0.66	4006	0.12 (−0.20 to 0.44)	0.45

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ATC = Anatomical Therapeutic Chemical; CCB = calcium channel blocker; CI = confidence interval; IOP = intraocular pressure; NSMRI = nonselective monoamine reuptake inhibitor; OR = odds ratio; SSRI = selective serotonin reuptake inhibitor.

Random-effects meta-analyses of logistic and linear regression analyses assessing the association between systemic medications and glaucoma prevalence (including 10 studies with objectively and nonobjectively ascertained patients with glaucoma, with medication data per ATC code) and IOP, respectively. Each medication was analyzed in its own separate model and not together with other medications. Results from maximally adjusted model 2, adjusted for age, gender, body mass index, and diabetes, are depicted.

*$P < 0.05$.

†Only participants with diabetes mellitus were included in the analyses, and, therefore, these analyses were not adjusted for diabetes diagnosis.

The literature describes NSMRIs as having anticholinergic effects on the eye, including mydriasis and cycloplegia, which in turn may precipitate angle closure.[36] Case studies have reported angle closure and increased IOP with NSMRI use.[37−39] Because most of the objectively ascertained patients with glaucoma in the present study were classified as having open-angle glaucoma, this may explain why we did not find consistent associations between use of NSMRIs and glaucoma prevalence. For SSRIs and SNRIs, for which we did not report any significant association with either glaucoma prevalence or IOP, contradicting findings have been reported in the literature. Chen et al[40] analyzed health insurance data and reported a greater risk of glaucoma incidence in SSRI users. In contrast, Gündüz et al[41] showed that IOP was significantly lower in SSRI users compared with patients not using SSRIs. Protective associations of SSRIs and SNRIs with glaucoma risk also have been reported.[8] Further, Chen et al[42] reported that long-term use of SSRIs did not affect the risk of glaucoma in patients with depression. Similar findings were reported by a recent systemic review and meta-analysis on the risk of glaucoma and serotonergic antidepressants[43]: SSRI use was not associated with glaucoma risk, but lower IOP was found in participants exposed to antidepressants for > 6 months. Another literature review confirmed this meta-analytic finding,[36] as do our results showing no association with SSRI use for both glaucoma and IOP. One factor responsible for the inconsistent results may be the presence of multiple distinct receptor subtypes located at the level of iris−ciliary body complex[44−46] and their different modes of action.[44−47] Moreover, previous research has reported an adverse association between glaucoma severity and depression.[48−51] Thus, differences in glaucoma severity in earlier published reports on the association

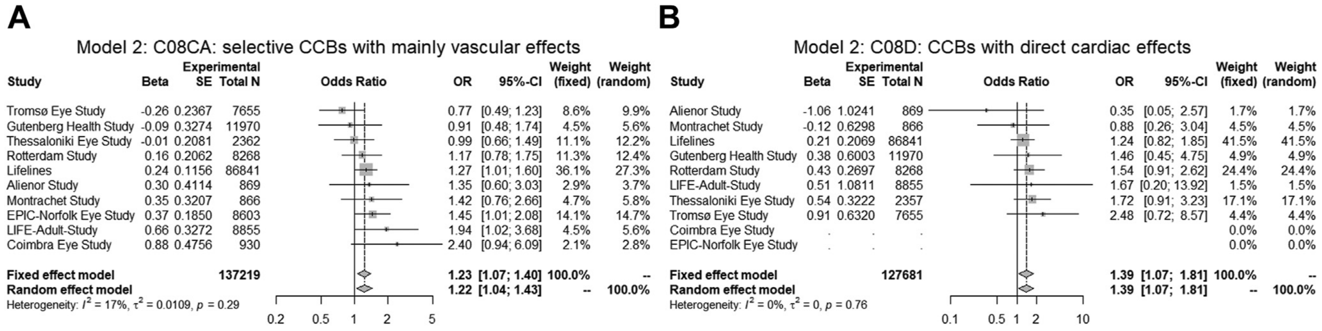

Figure 1. Forest plots showing meta-analyzed associations of calcium channel blockers (CCBs) with glaucoma prevalence, including the 10 studies with objectively and nonobjectively ascertained patients with glaucoma, with data per ATC code: (A) selective CCBs with mainly vascular effects (C08CA) and (B) CCBs with direct cardiac effects (C08D). ATC = Anatomical Therapeutic Chemical; CI = confidence interval; OR = odd ratio; SE = standard error.

between antidepressant use and glaucoma additionally may contribute to the inconsistency of results.

Neither glaucoma prevalence nor IOP were associated with use of lipid-lowering medications or antidiabetic medications. Although we observed an association between statin use and higher glaucoma prevalence in the primary meta-analyses, this association lost its significance when additionally adjusting for cholesterol levels. This means that the harmful association with statins may be spurious; a high cholesterol level potentially was the common cause of both the exposure and outcome (a high level of cholesterol may prompt the use of lipid-lowering medication, and a high level of cholesterol may increase the prevalence of glaucoma[52]). A recently published systematic review and meta-analysis of observational studies evaluated the association of oral statins with the incidence and progression of glaucoma and IOP.[53] Statin use was not associated with glaucoma incidence (OR, 0.94; 95% CI, 0.83 to 1.06) or with IOP. Similarly, other studies investigating the association between use of statins and glaucoma[12,32,54] or IOP[10,12,34] also failed to find significant associations. However, others did find protective effects of statins on the risk of glaucoma.[55–57] Research into the association between antidiabetic medications and glaucoma or IOP are scarce. For metformin specifically, a protective association with glaucoma was reported by Lin et al[58] and Vergroesen et al,[59] whereas George et al[60] did not find any significant association between metformin use and primary open-angle glaucoma incidence. Insulin and sulfonylureas have been associated with higher mean IOP.[11] We were limited by sample size in the analyses for the antidiabetic medications because the prevalence of glaucoma in a population-based study often is only 1% to 8% and the prevalence of DM in such populations is only 3% to 18%. This makes the number of participants with glaucoma and DM even lower, leaving the sample of participants with DM and glaucoma who are treated with, for example, metformin very limited. Moreover, because most of the data in our study was collected > 10 years ago, we were able to examine only frequently used antidiabetic medications at the time (i.e., insulin, biguanides, and sulfonylureas) and not some of the newer classes of antidiabetic medications (e.g., sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists).

Strengths of our study include the use of a large pooled sample size, allowing identification of small effect associations, and good generalizability to European people derived from analyzing associations across 11 populations from 8 European countries. Nevertheless, using a meta-analysis approach also has some limitations. Heterogeneity between studies can limit the validity of statistically combining results. The degree of heterogeneity in the meta-analyses we conducted was variable, with a generally lower heterogeneity in the glaucoma analyses than in the IOP analyses (data not shown). Other limitations of this study include the use of a cross-sectional design. This

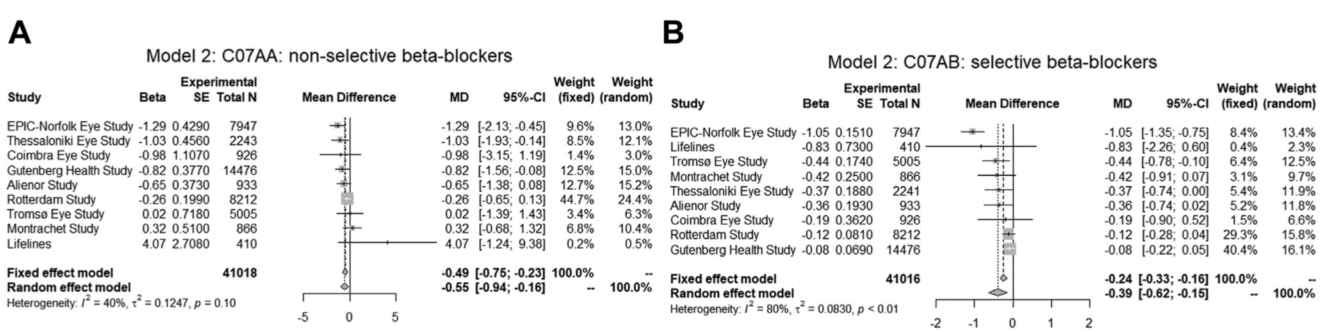

Figure 2. Forest plots showing meta-analyzed associations of systemic β-blockers with IOP: (A) nonselective β-blockers (C07AA) and (B) selective β-blockers (C07AB). CI = confidence interval; IOP = intraocular pressure; MD = mean difference; SE = standard error.

cross-sectional observational study was not able to determine whether the association identified was causal. Longitudinal studies should be performed to confirm the findings from this study. If further studies support a causal relationship, this may have substantial clinical relevance because CCBs frequently are prescribed in the management of arterial hypertension; about 30% to 40% of patients with hypertension are prescribed a CCB.[61] We were unable to assess the potential effect of changes in antihypertensive prescribing patterns following the Systolic Blood Pressure Intervention Trial,[52] given that included participants were recruited between 1991 and 2017. Future studies examining the associations of antihypertensives with glaucoma and IOP, following the move to more aggressive management of hypertension, would be of interest. Another limitation of our study was the different methods used to measure the outcomes (glaucoma and IOP), as well as the exposure and most of the covariables. In the primary meta-analyses, we included both objectively and nonobjectively ascertained patients with glaucoma. For the nonobjectively ascertained patients with glaucoma, it was not determined which glaucoma subtype was present. Therefore, we performed sensitivity analyses excluding nonobjectively ascertained patients with glaucoma; this decreased the sample size and thus limited the statistical power. Also, not all objectively ascertained patients with glaucoma underwent gonioscopy (Table 1). This made it less feasible to discriminate robustly between open-angle or angle-closure disease. It is possible that adding other subtypes of glaucoma may have added noise to our data and may have affected the observed associations. We tried to mitigate this by performing sensitivity analyses including only patients with open-angle glaucoma (Table S7). This did not change the observed associations. In most of the studies, no data on duration or dosage was present. Therefore, we were not able to assess any dose-response relationships. Moreover, although we adjusted for multiple confounders, residual confounding cannot be excluded. It is possible that other confounding factors are at play, but we were not able to adjust for these, distorting the found associations between medication use and glaucoma prevalence or IOP.

In summary, we found significant associations between use of CCBs and increased glaucoma prevalence. Nonselective and selective β-blockers were associated with lower IOP. A potentially harmful association of CCBs for glaucoma is particularly noteworthy, because this is a commonly prescribed class of medication. If further studies confirm a casual nature for this association, this may inform alternative treatment strategies for patients with hypertension who have, or are at risk of having, glaucoma.

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HUMAN SUBJECTS: Human subjects were included in this study. All studies adhered to the tenets of the Declaration of Helsinki and had local ethical committee approval. The Alienor Study was approved by the Ethical Committee of Bordeaux (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III). The Coimbra Eye Study was approved by AIBILI Ethics Committee (ClinicalTrials.gov: NCT01715870). The EPIC-Norfolk Eye Study was approved by the Norwich Local Research Ethics Committee (05/Q0101/191) and East Norfolk & Waveney National Health Service (NHS) Research Governance Committee (2005EC07L). The Medical Ethics Commission of Rhineland-Palatinate and local and Gutenberg-University of Mainz data protection officials approved the Gutenberg Health Study (ethics committee review number 837.020.07(5555). The LIFE-Adult-Study was approved by the institutional ethics board of the Medical Faculty of the University of Leipzig. The Lifelines protocol was approved by the UMCG Medical ethical committee under number 2007/152. The Montrachet Study was approved by the Dijon University Hospital ethics committee and was registered as 2009-A00448-49. The Rotterdam Study was approved by the Medical Ethics Committee of Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license no. 071272-159521-PG). The Thessaloniki Eye Study was approved by the Aristotle University Medical School, Ethics Committee. The Institutional Review Board of the University of California, Los Angeles approved the plans for data analyses. The Tromsø7 Eye Study was approved by the Regional Committee of Medical and Health Research Ethics North (reference 2014/940) and the Norwegian Data Protection Authority (reference 14/01463-4/CGN). The Ethics Committee of the Academic Council of the Ufa Eye Research Institute approved the Ural Eye and Medical Study. All participants gave written informed consent prior to examination.

No animal subjects were included in this study.

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Analysis and interpretation: Vergroesen, Schuster, Stuart, Asefa, Ramdas, Khawaja

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Abbreviations and Acronyms:

ACEI = angiotensin-converting enzyme inhibitor; **ARB** = angiotensin II receptor blocker; **ATC** = Anatomical Therapeutic Chemical; **BP** = blood pressure; **CCB** = calcium channel blocker; **CI** = confidence interval; **DM** = diabetes mellitus; **E3** = European Eye Epidemiology; **IOP** = intraocular pressure; **NSMRI** = nonselective monoamine reuptake inhibitor; **OR** = odds ratio; **RAS** = renin-angiotensin system; **SBP** = systolic blood pressure; **SSRI** = selective serotonin reuptake inhibitor.

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Epidemiology, Glaucoma, Intraocular pressure, Systemic medication.

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