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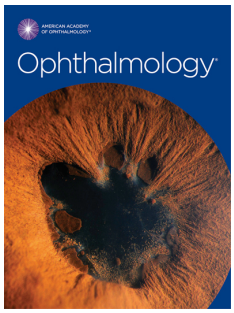

Association of systemic medication use with glaucoma and intraocular pressure: the E3 Consortium

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Association of systemic medication use with glaucoma and intraocular pressure: the E3 Consortium

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Online supplemental materials:

This article contains additional online-only material. The following should appear online-only: Supplementary Methods, Table S3, Table S5, Table S6, Table S7, Table S8, Table S9, Table S10, Table S11, Table S12, Table S13, Table S14, and Table S15.

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Keywords: **systemic medication, glaucoma, intraocular pressure, epidemiology**

ABSTRACT

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

Design: Meta-analysis of eleven population-based cohort studies of the European Eye Epidemiology (E3) consortium.

Participants: A total of 143240 participants were included in the glaucoma analyses and 47177 participants in the IOP analyses.

Methods: We examined associations of four categories of systemic medications (antihypertensive medications: beta-blockers, diuretics, calcium channel blockers [CCBs], alpha-agonists, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers; lipid-lowering medications; antidepressants; antidiabetic medications) with glaucoma prevalence and IOP. Glaucoma ascertainment and IOP measurement method were according to individual study protocols. Multivariable regression analyses were carried out in each study and results were pooled using random effects meta-analyses. Associations with antidiabetic medications were examined in diabetic participants 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] with corresponding 95% confidence interval [95% CI]: 1.23 [1.08 to 1.39]). This association was stronger for monotherapy of CCBs with direct cardiac effects (OR [95% CI]: 1.96 [1.23 to 3.12]). The use of other antihypertensive medications, lipid-lowering medications, antidepressants or antidiabetic medications were not clearly associated with glaucoma. Use of systemic beta-blockers was associated with a lower IOP (Beta [95% CI]: -0.33 [-0.57 to -0.08] mmHg). Monotherapy of both selective (Beta [95% CI]: -0.45 [-0.74 to -0.16] mmHg) and non-selective (Beta [95% CI]: -0.54 [-0.94 to -0.15] mmHg) systemic beta-blockers was associated with lower IOP. There was a suggestive association between use of high-ceiling diuretics and lower IOP (Beta [95% CI]: -0.30 [-0.47; -0.14] mmHg), but not when used as monotherapy. Use of other antihypertensive medications, lipid-lowering medications, antidepressants, or antidiabetic medications were not 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 beta-blocker use. Both findings are potentially important given that glaucoma patients frequently use systemic

antihypertensive medications. Determining whether the CCB association is causal should be a research priority.

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 present with 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 US health claims data study, which 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 (POAG), respectively.[8] Other medications that may modulate the risk of open-angle glaucoma include beta-blockers, metformin, statins, and bupropion.[7] Systemic beta-blockers, and especially non-selective beta-blockers, have also 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, there have been inconsistent findings between studies, 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 beta-blocker use; recent studies taking this into account have not demonstrated a significant association between statin use and glaucoma risk.[12]

We aimed to definitively examine 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 European Eye Epidemiology (E3) consortium were included in the present study.[13] All studies contributed data to the glaucoma analyses and ten studies were included in the IOP analyses. The E3 consortium is a collaboration of European population-based and cohort studies which aims to increase understanding of eye disease and vision loss.[14] 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 prior to examination.

Methods used for ascertainment of study variables

A total of 143240 participants from eleven population-based studies from the E3-consortium were included in the glaucoma analyses (Table 1). Eight of eleven included studies used visual field testing or optic nerve head examination to ascertain glaucoma diagnosis; three studies used non-objective (e.g., self-reported) glaucoma diagnosis. We *a priori* elected to include the broadest case definition for glaucoma available within each study, given we are interested in identifying medications which may alter the risk of any form of glaucoma. A total of 47177 participants from ten population-based studies were included in the IOP analyses. Eight of ten studies used a non-contact tonometer to obtain IOP measurements; two studies used Goldmann applanation tonometry. We only considered IOP measurements taken at the same time as systemic medication use ascertainment, assuming that any IOP-altering effects may only be apparent while the drug is being used. We considered each participant's IOP as the arithmetic mean IOP of both eyes; if IOP was only available for one eye, we considered that value as the participant's IOP. Seven studies collected medication data based on medical prescriptions and medication containers; four 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 eight out of eleven studies. DM 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, fasting and non-fasting glucose above certain cut-off or HbA1c level above certain cut-off. Ethnicity was determined in eight of eleven studies. Descriptive data for the contributing studies can be viewed in

Table 1. Detailed study methods and protocols are available in the Supplementary Methods (available at https://www.aaojournal.org).

Systemic medication assessments

Systemic medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[15] We analyzed associations with eleven antihypertensive medication subgroups: alpha-agonists (C02A, e.g., reserpine, methyldopa, clonidine), low-ceiling diuretics (C03A, e.g., *thiazides such as hydrochlorothiazide, bendroflumethiazide), other low-ceiling diuretics (C03B, e.g., chlorthalidone, theobromine), high-ceiling diuretics (C03C, e.g., torasemide, furosemide), aldosterone antagonists (C03D, e.g., spironolactone), non-selective beta-blockers (C07AA, e.g., propranolol, sotalol, tertatolol), selective beta-blockers (C07AB, e.g. metoprolol, atenolol), selective CCBs with mainly vascular effects (C08CA, e.g., amlodipine, felodipine), selective CCBs with direct cardiac effects (C08D, e.g., verapamil, diltiazem), ACEIs (C09A, e.g., enalapril, lisinopril, perindopril), and ARBs (C09C, e.g., valsartan, losartan). We also analysed associations with three lipid-lowering medication subgroups: statins (C10AA, e.g., simvastatin, fluvastatin), fibrates (C10AB, e.g., clofibrate, gemfibrozil), and other lipid-lowering medications (C10AX, e.g., ezetimibe, lomitapide). Included antidepressants were non-selective monoamine reuptake inhibitors (NSMRIs; N06AA, e.g., maprotiline, doxepin), selective serotonin reuptake inhibitors (SSRIs; N06AB, e.g., fluoxetine, citalopram, sertraline), and other antidepressants (N06AX, e.g., vortioxetine, bupropion). In diabetic participants only, we assessed the associations of the following antidiabetic medications: insulin (A10A), biguanides (A10BA, e.g., phenformin, metformin, buformin), and sulfonylureas (A10BB, e.g., glibenclamide, chlorpropamide). The Ural Eye and Medical Study did not have medication data available specified per ATC-code, but did have data on “diuretics”, “systemic beta-blockers”, “CCBs”, and “renin-angiotensin system (RAS) inhibitors”; we therefore only included this study in those broader analyses. For antihypertensive medications, we additionally determined the use of monotherapy (i.e., use of only one antihypertensive medication class).

Statistical analysis

For the glaucoma analyses, multivariable logistic regression analyses with glaucoma status as 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 beta-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 dependent variable. For both glaucoma and IOP analyses, we ran four 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, BMI, and DM. For antidiabetic medications, DM was not included as covariate, as the analyses were performed in participants with DM only. 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 would help identify whether any drug association was mediated by change in SBP rather than via other effects. Model 4 was only performed 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 following exclusion of studies with non-objective glaucoma ascertainment (i.e., self-reported data only). Moreover, we performed sensitivity analyses, including only glaucoma cases that were defined as open-angle glaucoma (primary or secondary was not defined). For IOP as an outcome, these sensitivity analyses were not performed, since we aimed to include the full range of IOPs from the complete population (regardless of glaucoma status). Statistical analyses were performed using SPSS v25.0 (SPSS Inc., Chicago, IL, USA) and RStudio (version 4.0.0, R Core Team (2020), R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/) 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 and 16.1 ± 3.7 mmHg. Table S3 (available at https://www.aaojournal.org) presents the use of systemic medications in each included study. Overall, the most frequently prescribed antihypertensive medication were selective beta-blockers (C07AB) and selective CCBs with mainly

vascular effects (C08CA). Participants using lipid-lowering medications most often used statins (C10AA). SSRIs (N06AB) were the most commonly prescribed antidepressants.

Associations with glaucoma prevalence

In the meta-analyses of our maximally-adjusted multivariable models (Table 4), use of CCBs was associated with a higher glaucoma prevalence (selective CCBs with mainly vascular effects [C08CA]: Odds ratio [95% confidence interval (CI)]: 1.22 [1.04 to 1.43]; Figure 1A; selective CCBs with direct cardiac effects [C08D]: OR [95% CI]: 1.39 [1.07 to 1.81]; Figure 1B). Additional adjustment for SBP (Table S5, model 3, available at https://www.aaojournal.org) did not meaningfully change the results. These associations persisted in sensitivity analyses only including studies with objectively ascertained glaucoma cases (Table S6, available at https://www.aaojournal.org) and in sensitivity analyses only including open-angle glaucoma cases (Table S7, available at https://www.aaojournal.org). When additionally adjusting the previous associations for ethnicity (Table S8, available at https://www.aaojournal.org), the association of glaucoma prevalence with selective CCBs with direct cardiac effects (C08D) was reduced to some extent (OR [95% CI]: 1.25 [0.93 to 1.67]), but the association with selective CCBs with mainly vascular effects (C08CA, OR [95%]: 1.26 [1.07 to 1.47]) was not. This association persisted in sensitivity analyses only including studies with objectively ascertained glaucoma cases. When assessing antihypertensive use as solely monotherapy and not in combination with other antihypertensives (Table S9, available at https://www.aaojournal.org), the use of selective CCBs with direct cardiac effects (C08D) was associated with a higher glaucoma prevalence (model 2, OR [95% CI]: 1.96 [1.23 to 3.12]). This association was stronger when analyzing only objectively ascertained glaucoma cases (model 2, OR [95% CI]: 2.15 [1.30 to 3.54]). When grouping the CCBs together, use of any CCB was associated with a 23% higher prevalence of glaucoma (Table S10, model 2, OR [95% CI]: 1.23 [1.08 to 1.39], available at https://www.aaojournal.org). This associations persisted, with significant *P*-values, in sensitivity analyses only including studies with objectively ascertained glaucoma cases.

The association between CCB use and glaucoma did not change after additional adjustment for systemic beta-blocker use (which was significantly associated with IOP in the present study – see below), in both the primary meta-analyses including all studies with objective and self-reported glaucoma cases (Table S11, model 2[b], all CCBs: OR [95% CI]: 1.25 [1.09 to 1.42], available at

https://www.aaojournal.org) and sensitivity analyses including only studies with objectively ascertained glaucoma cases. Additional adjustment for simultaneous use of the two medications (i.e. modelling an interaction) showed no strong evidence for a significant interaction between systemic beta-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 glaucoma cases, that did not retain statistical significance in sensitivity analyses: RAS inhibitors (Table S10, model 2, OR [95% CI]: 1.13 [1.03 to 1.24], available at https://www.aaojournal.org), statins (Table 4, model 2, OR [95% CI]: 1.10 [1.00 to 1.21]), NSMRIs (Table 4, model 2, OR [95% CI]: 1.50 [1.15 to 1.96]), and insulin (Table 4, model 2, OR [95% CI]: 1.54 [1.09 to 2.18]). None of the other antihypertensive medications, lipid-lowering medications, antidepressants, and antidiabetic medications were associated with glaucoma prevalence (Table 4).

Intraocular pressure

In the meta-analyses of our maximally-adjusted multivariable models (Table 4), systemic beta-blocker use was associated with a lower IOP (non-selective beta-blockers [C07AA]: Beta [95% CI]: -0.55 [-0.94 to -0.16] mmHg; Figure 2A; selective beta-blockers [C07AB]: Beta [95% CI]: -0.39 [-0.62 to -0.15] mmHg; Figure 2B). Additional adjustment for ethnicity did not meaningfully change these associations (Table S12, available at https://www.aaojournal.org). When assessing antihypertensive use as solely monotherapy and not in combination with other antihypertensives (Table S13, available at https://www.aaojournal.org), both non-selective beta-blockers (C07AA, Beta [95% CI]: -0.54 [-0.94 to -0.15] mmHg) and selective beta-blockers (C07AB, Beta [95% CI]: -0.45 [-0.74 to -0.16] mmHg) were associated with a lower IOP. When grouping the systemic beta-blockers together, use of any systemic beta-blocker was associated with a 0.33 mmHg lower IOP (Table S10, model 2, all systemic beta-blockers: Beta [95% CI]: -0.33 [-0.57 to -0.08] mmHg, available at https://www.aaojournal.org). A suggestive association was observed for high-ceiling diuretics (C03C) and lower IOP (Table 4, Beta [95% CI]: -0.30 [-0.47 to -0.14] mmHg); while this association retained statistical significance after adjustment for SBP (Table S14, model 3, Beta [95% CI]: -0.21 [-0.37; -0.04] mmHg, available at https://www.aaojournal.org) or ethnicity (Table S12, Beta [95% CI]: -0.31 [-0.51 to -0.11] mmHg, available at https://www.aaojournal.org), it was no longer significant when additionally adjusting for use

of beta-blockers and CCBs (Table S15, model 3, Beta [95% CI]: -0.14 [-0.31; 0.02] mmHg, available at https://www.aaojournal.org). Moreover, monotherapy of high-ceiling diuretics (C03C) was not significantly associated with lower IOP (Table S13, model 2, Beta [95% CI]: -0.32 [-0.71 to 0.06] mmHg, available at https://www.aaojournal.org).

Although monotherapy of aldosterone antagonists (C03D) tended to be associated with a higher IOP (Table S13, model 2, Beta [95% CI]: 1.21 [0.27 to 2.14] mmHg, available at https://www.aaojournal.org), none of the other antihypertensive medications, e.g., alpha-agonists, CCBs, ACEIs and ARBs were associated with IOP (Table 4 and Table S10, available at https://www.aaojournal.org). Other lipid-lowering medications (C10AX), but not statins and fibrates, showed a tendency towards being associated with a lower IOP (Table 4, Beta [95% CI]: -0.39 [-0.78 to 0.00] mmHg), but this association did not retain statistical significance after adjusting for total cholesterol level (Table S14, model 4, Beta [95% CI]: -0.40 [-0.81; 0.01] mmHg, available at https://www.aaojournal.org). Use of SSRIs was associated with a lower IOP (Table 4, Beta [95% CI]: -0.23 [-0.45; -0.01] mmHg); however, this association was no longer significant when additionally adjusting for SBP (Table S14, model 3, Beta [95% CI]: -0.15 [-0.37; 0.06], available at https://www.aaojournal.org). Use of other antidepressants or antidiabetic medications were not associated with IOP (Table 4). Additional adjustment of aforementioned analyses with SBP (Table S14, model 3, available at https://www.aaojournal.org) or total cholesterol (Table S14, model 4, available at https://www.aaojournal.org) did not meaningfully change the results, unless stated otherwise.

DISCUSSION

In this large study examining glaucoma prevalence and IOP in more than 140000 participants from 11 populations across eight European countries, we identified associations between CCB use and high glaucoma prevalence. Non-selective and selective beta-blockers were associated with lower IOP. A suggestive association was observed between use of high-ceiling diuretics and lower IOP. Our findings confirm the known IOP-lowering effect of systemic beta-blockers, quantifying the effect on a population level, and identify other potential systemic medication modifiers of glaucoma risk. While our novel findings require further studies to determine whether the associations are causal, these findings will be of interest to physicians caring for glaucoma patients 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 OAG (OR [95% CI]: 1.80 [1.04; 3.20]).[16] At the time, only data from the first cohort of the Rotterdam Study (RS-I) was available, with a maximal follow-up of 6.5 years. In the meta-analysis described in the present study, we were able to include participants from all three independent cohorts of the Rotterdam Study (RS-I, RS-II, and RS-III) 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 glaucoma cases. Zheng et al. analyzed US health insurance data in a case-control design and showed a strong and highly significant association between CCB use and POAG (OR [95% CI]: 1.26 [1.18; 1.35]).[8] The association retained statistical significance after adjustment of other medications, e.g., systemic beta-blockers (OR [95% CI]: 1.23 [1.14; 1.33]). Similarly, Asefa et al.[17] and Langman et al.[18] reported an adverse association between use of CCBs and glaucoma prevalence (OR [95% CI]: 1.19 [1.01; 1.40] and 1.34 [1.24; 1.44], respectively). CCBs may exert direct effects on the retina; previously, use of CCBs has been associated with a thinner macular retinal nerve fiber layer and thinner ganglion cell-inner plexiform layer.[19]

Some studies have suggested that CCBs more effectively lower blood pressure when taken at bedtime than morning dosing.[20-24] Simultaneously, nocturnal systemic hypotension may be associated with increased risk of glaucoma progression.[25-27] This may thus explain the association between CCBs and increased glaucoma prevalence, if CCBs are preferentially taken 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 Ca^{2+} may be responsible for apoptotic and necrotic cell death in many cell lines, including (retinal) neurons. As the primary effect of a CCB is inhibition of intracellular Ca^{2+} influx[28, 29], previous studies have suggested that CCBs harbor neuroprotective effects. By inducing vasodilation, they can restore impaired blood flow in local ischemic tissues and they can directly inhibit Ca^{2+}-related cell death pathways. This could potentially rescue ischemic RGCs.[30, 31] However, in ischemic tissue, vasodilation may already be maximized and autoregulation of blood flow may be impaired, while it is preserved in non-ischemic areas. Therefore, CCB-induced vasodilation may result in diversion of blood flow, which could worsen damage in ischemic tissue.[32]

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 glaucoma cases. The literature has reported contradicting findings for both ACEIs and ARBs: protective effects,[33] no effects,[16, 17, 34] and harmful effects.[8, 17, 18] None of the other antihypertensive medications were associated with glaucoma in the present study. Contradicting findings have been reported for diuretics: while some studies showed no association,[16, 17] a case-control study in the UK showed an association with increased glaucoma prevalence.[34]

Systemic beta-blockers were significantly associated with lower IOP, which is in line with previous findings.[10, 11, 35, 36] Additionally, we found a suggestive association between use of high-ceiling diuretics (often prescribed to heart failure patients) and lower IOP. However, this association was not apparent when adjusting for use of systemic beta-blockers, CCBs and SBP. It is thus possible that the association between use of high-ceiling diuretics and lower IOP is partly explained 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, 35] CCBs,[10, 35] alpha-agonists,[10, 35] ACEIs,[10, 35] and ARBs.[10, 35] Although use of systemic beta-blockers was significantly associated with lower IOP, we did not find a significant association with glaucoma prevalence. Previous research has suggested that the IOP-lowering effect of systemic beta-blockers would translate to a reduced risk of incident glaucoma.[35] In line with this theory, a protective effect of systemic beta-blockers on glaucoma risk was reported by Zheng et al. (OR [95% CI]: 0.77 [0.72 to 0.83])[8] and Langman et al. (OR [95% CI]: 0.77 [0.73 to 0.83]).[18] Similarly, Owen et al. reported lower prevalence of oral beta-blocker use in the five years before diagnosis in glaucoma cases than in controls (adjusted OR [95% CI]: 0.87 [0.80 to 0.94]).[34] After stratification, this effect was present for selective beta-blockers (adjusted OR [95% CI]: 0.81 [0.74 to 0.88]) but not for non-selective beta-blockers (adjusted OR [95% CI]: 1.08 [0.94 to 1.24]). However, it is possible that systemic beta-blockers do not reduce the risk of glaucoma per se, but limit the detection of glaucoma given that elevated IOP is often a trigger for diagnosing glaucoma. Moreover, BP, IOP and optic nerve head perfusion are complexly correlated and can influence glaucoma development and progression in different ways. High BP may cause an increased production (due to elevated ciliary blood flow and capillary pressure) and decreased outflow (due to increased episcleral venous pressure) of aqueous humor, causing an increase in IOP. Having a low BP, however, whether spontaneous or secondary to antihypertensive treatment, may reduce perfusion of the optic nerve, leading to ischemic damage. The BP-lowering effect of systemic beta-blockers may thus balance out

the IOP-lowering effect on glaucoma risk, explaining the null-association between use of systemic beta-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. In the literature, it has been described that NSMRIs have anticholinergic effects on the eye, including mydriasis and cyclopegia, which in turn may precipitate angle-closure.[37] Cases studies have reported angle-closure and increased IOP with NSMRI use.[38-40] As the majority of the objectively ascertained glaucoma cases in the present study were classified as 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. reported a greater risk of glaucoma incidence in SSRI-users analyzing health insurance data.[41] In contrast, Gündüz et al. showed that IOP was significantly lower in SSRI users compared to patients not using SSRIs.[42] Protective associations of SSRIs and SNRIs with glaucoma risk have also been reported.[8] Further, Chen et al. reported that long-term use of SSRIs did not affect the risk of glaucoma in patients suffering from depression.[43] Similar findings were reported by a recent systemic review and meta-analysis on the risk of glaucoma and serotonergic antidepressants[44]: SSRI use was not associated with glaucoma risk, but lower IOP was found in participants exposed to antidepressants for more than 6 months. Another literature review confirmed this meta-analytical finding,[37] as do our results showing no association with SSRI use for both glaucoma and IOP. One factor responsible for the inconsistent results might be the presence of multiple distinct receptor subtypes located at the level of iris-ciliary body complex[45-47], and their different modes of action.[45-48] Moreover, previous research has reported an adverse association between glaucoma severity and depression.[49-52] Thus, differences in glaucoma severity in earlier published reports on the association between antidepressants use and glaucoma may additionally 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 our 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 was potentially 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[53]). 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.[54] Statin use was not associated with glaucoma incidence (OR [95% CI]: 0.94 [0.83 to 1.06]) or with IOP. Similarly, other studies investigating the association between use of statins and glaucoma[12, 33, 55] or IOP[10, 12, 35] also failed to find significant associations. However, others did find protective effects of statins on the risk of glaucoma.[56-58] Research into the association between antidiabetic medications and glaucoma or IOP are scarce. For metformin specifically, a protective association with glaucoma has been reported by Lin et al.[59] and Vergroesen et al.,[60] while George et al. did not find any significant association between metformin use and POAG incidence.[61] Insulin and sulfonylureas have been associated with higher mean IOP.[11] We were limited by sample size in the analyses for the antidiabetic medications, as the prevalence of glaucoma in a population-based study is often only 1-8% and the prevalence of DM in such populations is only 3-18%. This makes the number of participants with glaucoma and DM even lower, leaving the sample of diabetic participants with glaucoma and treated with e.g. metformin very limited. Moreover, since the majority of the data in our study was collected over 10 years ago, we were only able to examine 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. Our cross-sectional observational study is not able to determine whether the association identified is 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 since CCBs are frequently prescribed in the management of arterial hypertension; about 30-40% of patients with hypertension are prescribed a CCB.[62] We were

unable to assess the potential effect of changes in antihypertensive prescribing patterns following the SPRINT trial[53] given 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 non-objectively ascertained glaucoma cases. For the non-objectively ascertained glaucoma cases it was not determined which glaucoma subtype was present. Therefore, we performed sensitivity analyses excluding non-objectively ascertained glaucoma cases; this decreased the sample size and thus limited the statistical power. Also, not all objectively ascertained glaucoma cases underwent gonioscopy (Table 1). This made it less feasible to robustly discriminate 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 open-angle glaucoma cases (Table S7, available at https://www.aaojournal.org). This did not change the observed associations. In the majority 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. Non-selective and selective beta-blockers were associated with lower IOP. A potentially harmful association of CCBs for glaucoma is particularly noteworthy, as 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 hypertensive patients with, or at risk of, glaucoma.

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Figure 1. Forest plot of meta-analyzed associations of calcium channel blockers (CCBs) with glaucoma prevalence including the ten studies with objectively and non-objectively ascertained glaucoma cases, with data per Anatomical Therapeutic Chemical code: **A**) Selective CCBs with mainly vascular effects. **B**) CCBs with direct cardiac effects. Abbreviations: SE = standard error; N = number; OR = odd ratio; 95% CI = 95% confidence interval.

Figure 2. Forest plot of meta-analyzed associations of systemic beta-blockers with intraocular pressure: **A**) Non-selective beta-blockers. **B**) Selective beta-blockers. Abbreviations: SE = standard error; N = number; MD = mean difference; 95% CI = 95% confidence interval.

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Table 1. Descriptive data for the contributing studies

	Glaucoma ascertainment	*Glaucoma subtypes included*	*IOP measurements*	*Medication data ascertainment*	*BP ascertainment*	*Total cholesterol*	*Diabetes ascertainment*
ALIENOR	Objective: ISGEO glaucoma classification; Visual field test (Octopus 101); optic nerve head examination; slit-lamp; gonioscopy	OAG (100%); unknown whether primary or secondary	NCT (KT 800); 1 measurement per eye	ATC codes from medical prescriptions and medication containers	OMRON M4	NA	Fasting blood glucose ≥7.0 mM or use of antidiabetic medications
COIBMRA	Objective: Diagnosis by the Research Center based on optic nerve head examination (color fundus and SD-OCT Spectralis)	POAG (100%, but not confirmed)	NCT (Tonoref II); mean of ≥3 measurements per eye (up to 5 readings taken if any outliers)	ATC codes from self-reported medication	Unknown	NA	Use of antidiabetic medications or self-reported
EPIC	Objective: Diagnosis by glaucoma specialist based on the ISGEO glaucoma classification; Visual field test (Humphrey 750i); optic nerve head examination (HRT II & TRC-NW6S); gonioscopy	POAG (86.5%), PACG (8.0%), secondary glaucoma (5.5%)	NCT (AT555 or ORA); best signal value of ≥3 IOPg measurements per 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
GHS	Objective: ISGEO glaucoma classification; Visual field test (FDT); optic nerve head examination (Visucam PRO NM and Spectralis); slit-lamp	OAG (100%); unknown whether primary or secondary	NCT (NT-2000); mean of 3 measurements per 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 hours of fasting
LIFE-Adult	Non-objective: 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, or HbA1c ≥6.5%, taking into account use of antidiabetic medications or self-reported
LIFELINES	Non-objective: Glaucoma definition algorithm which was based on self-reported incisional surgery for glaucoma, glaucoma treatment, and glaucoma-related complaints	Unknown	NCT (ORA); mean of 1-2 measurements per 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, HbA1c ≥6.5%, or self-reported

MONTRACHET	Objective: ISGEO glaucoma classification; Visual field test (FDT & Humphrey SITA 24-2); optic nerve head examination (TRC-NW6S & SD-OCT); gonioscopy	POAG (95%), PEXG (5%)	NCT (Tonoref II); 1 measurement per eye	ATC codes from self-reported medication	Standard cuff	Blood sample collected at visit	Self-reported
RS	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 per 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 non-fasting >11.1 mmol/L)
TES	Objective: Visual field test (HFA II); optic nerve head examination (HRT); gonioscopy; slit-lamp	POAG (62.8%), PACG (6.4%), PEXG (27.6), secondary glaucoma (3.2%)	GAT; mean of 3 measurements per eye	ATC codes from medical prescriptions and medication containers	Omron 705CP	NA	Self-reported
TROMSØ	Non-objective: Self-reported	Unknown	NCT (ICare rebound tonometer); mean of 4 measurements per eye	ATC codes from self-reported medication, validated against the Norwegian Prescription Drug Registry	Dinamap Vital Signs Monitor	Blood sample collected at visit	Non-fasting blood glucose ≥11.1 mmol/l, HbA1c >6.5%, or self-reported
UEMS	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 per 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

ISGEO glaucoma classification: classification for glaucoma developed at the biennial congress of the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) held in Leeuwenhorst, The Netherlands, in 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):238-42. Abbreviations: ALIENOR = Alienor Study; COIMBRA = Coimbra Eye Study; EPIC = EPIC-Norfolk Eye Study; GHS = Gutenberg Health Study; LIFE-Adult = Leipzig Research Centre for Civilization Diseases (LIFE) Adult Study; LIFELINES = Lifelines; MONTRACHET = Montrachet Study; RS = Rotterdam Study; TES = Thessaloniki Eye Study; TROMSØ = Tromsø Eye Study; UEMS = Ural Eye and Medical Study; IOP = intraocular pressure; BP = blood pressure; FDT = frequency doubling technology; HFA = Humphrey field analyzer; OCT = optical coherence tomography; (P)OAG = (primary) open-angle glaucoma; (P)ACG = (primary) angle-closure glaucoma; PEXG = pseudo exfoliation glaucoma; NCT = non-contact tonometry; GAT = Goldmann applanation tonometer; ATC = Anatomical Therapeutic Chemical; NA = not available.

Table 2. Baseline characteristics of participants included in the glaucoma and/or IOP analyses, presented as mean (standard deviation) unless stated otherwise.

	Glaucoma, N (%)	*IOP, mmHg*	*Age, years*	*Female sex, N (%)*	*BMI, kg/m²*	*DM, N (%)*	*SBP, mmHg*	*Cholesterol, mmol/l*	*European, N (%)*[a]	*Visit year*
ALIENOR (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 (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 (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
GHS (N=14479)	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)	11829 (99.1)	2007-2012
LIFE-Adult (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=86841)	3838 (4.4)	15.3 (3.8)	50.3 (5.1)	35459 (40.8)	25.4 (5.0)[b]	2911 (3.4)	124 (20)[b]	5.1 (1.1)	78028 (98.3)	2006-2017
MONTRACHET (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
RS (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
TES (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 (N=8012)	234 (3.0)	13.9 (3.5)	61.1 (10.5)	3649 (45.5)	NA[c]	462 (6.0)	133.4 (20.2)	5.5 (1.1)	NA	2015-2016
UEMS (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)[d]	2015-2017

[a] Ethnicity was not available for all participants, % is based on number of participants of whom ethnicity data was available. [b] Data presented as median (interquartile range). [c] Data was only available on categorical level: BMI 0-25 kg/m² (N=2507 [31.4%]), 25-30 kg/m² (N=3592 [45.0%]), >30 kg/m² (N=1889 [23.6%]). [d] Represents the number of participants with Russian ethnicity. Abbreviations: ALIENOR = Alienor Study; COIMBRA = Coimbra Eye Study; EPIC = EPIC-Norfolk Eye Study; GHS = Gutenberg Health Study; LIFE-Adult = Leipzig Research Centre for Civilization Diseases (LIFE) Adult Study; LIFELINES = Lifelines; MONTRACHET = Montrachet Study; RS = Rotterdam Study; TES = Thessaloniki Eye Study; TROMSØ = Tromsø Eye Study; UEMS = Ural Eye and Medical Study. N = number; IOP = intraocular pressure; BMI = body mass index; DM = diabetes mellitus; SBP = systolic blood pressure; NA = not available.

Table 4. Meta-analyzed associations of commonly used systemic medications with glaucoma prevalence (objectively and non-objectively ascertained glaucoma cases) and intraocular pressure (model 2).

	Glaucoma			*Intraocular pressure (mmHg)*		
	N	**OR (95% CI)**	**P**	**N**	**Beta (95% CI)**	**P**
Antihypertensive medications						
Alpha-agonists (C02A)	127762	1.36 (0.75; 2.47)	0.31	35600	0.02 (-0.36; 0.41)	0.90
Low-ceiling diuretics: thiazides (C03A)	134548	1.05 (0.88; 1.25)	0.62	40089	0.06 (-0.09; 0.22)	0.42
Low-ceiling diuretics: others (C03B)	120703	1.28 (0.87; 1.88)	0.21	36010	-0.05 (-0.33; 0.23)	0.73
High-ceiling diuretics (C03C)	137214	1.06 (0.82; 1.37)	0.67	41016	-0.30 (-0.47; -0.14)	<0.001*
Aldosterone antagonists (C03C)	116388	1.01 (0.62; 1.65)	0.97	41015	-0.20 (-0.49; 0.08)	0.17
Non-selective beta-blockers (C07AA)	136286	1.19 (0.90; 1.57)	0.21	41018	-0.55 (-0.94; -0.16)	0.006*
Selective beta-blockers (C07AB)	137214	1.04 (0.95; 1.15)	0.38	41016	-0.39 (-0.62; -0.15)	0.001*
Selective CCBs: vascular effects (C08CA)	137219	1.22 (1.04; 1.43)	0.01*	41021	0.03 (-0.08; 0.14)	0.60
Selective CCBs: direct cardiac effects (C08D)	127681	1.39 (1.07; 1.81)	0.01*	41016	0.03 (-0.31; 0.37)	0.86
Angiotensin-converting-enzyme inhibitors (C09A)	137214	1.13 (0.99; 1.29)	0.06	41016	0.04 (-0.10; 0.19)	0.57
Angiotensin II receptor blockers (C09C)	137214	1.08 (0.95; 1.23)	0.24	41016	0.09 (-0.13; 0.32)	0.42
Lipid-lowering medications						
Statins (C10AA)	137260	1.10 (1.00; 1.21)	0.04*	41059	-0.07 (-0.19; 0.05)	0.26
Fibrates (C10AB)	112482	1.11 (0.64; 1.95)	0.71	27842	-0.18 (-0.52; 0.16)	0.31
Other lipid-lowering medications (C10AX)	112233	1.20 (0.79; 1.82)	0.40	41059	-0.39 (-0.78; 0.00)	0.05
Antidepressants						
Non-selective monoamine reuptake inhibitors (N06AA)	135854	1.50 (1.15; 1.96)	0.003*	41060	0.14 (-0.17; 0.45)	0.38
Selective serotonin reuptake inhibitors (N06AB)	137655	1.26 (0.87; 1.84)	0.22	41060	-0.23 (-0.45; -0.01)	0.04*
Other antidepressants (N06AX)	130002	1.50 (1.10; 2.03)	0.01*	41060	-0.14 (-0.39; 0.12)	0.29
Antidiabetic medications[a]						
Insulin (A10A)	7792	1.54 (1.09; 2.18)	0.01*	4046	0.14 (-0.19; 0.47)	0.40
Biguanides (A10BA)	8090	0.84 (0.62; 1.14)	0.26	4006	0.07 (-0.13; 0.28)	0.48
Sulfonylureas (A10BB)	8090	0.94 (0.73; 1.22)	0.66	4006	0.12 (-0.20; 0.44)	0.45

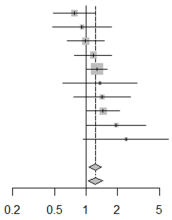
Random-effects meta-analyses of logistic and linear regression analyses assessing the association between systemic medications and glaucoma prevalence (including ten studies with objectively and non-objectively ascertained glaucoma cases, with medication data per Anatomical Therapeutic Chemical code) and intraocular pressure, 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; [a] Only participants with diabetes mellitus were included in the analyses and these analyses were therefore not adjusted for diabetes diagnosis. Abbreviations: CCBs = calcium channel blockers; N = number; OR = odds ratio; 95% CI = 95% confidence interval.

A

Model 2: C08CA: selective CCBs with mainly vascular effects

Study	Beta	Experimental SE	Total N	OR	95%-CI	Weight (fixed)	Weight (random)
Tromsø Eye Study	-0.26	0.2367	7655	0.77	[0.49; 1.23]	8.6%	9.9%
Gutenberg Health Study	-0.09	0.3274	11970	0.91	[0.48; 1.74]	4.5%	5.6%
Thessaloniki Eye Study	-0.01	0.2081	2362	0.99	[0.66; 1.49]	11.1%	12.2%
Rotterdam Study	0.16	0.2062	8268	1.17	[0.78; 1.75]	11.3%	12.4%
Lifelines	0.24	0.1156	86841	1.27	[1.01; 1.60]	36.1%	27.3%
Alienor Study	0.30	0.4114	869	1.35	[0.60; 3.03]	2.9%	3.7%
Montrachet Study	0.35	0.3207	866	1.42	[0.76; 2.66]	4.7%	5.8%
EPIC-Norfolk Eye Study	0.37	0.1850	8603	1.45	[1.01; 2.08]	14.1%	14.7%
LIFE-Adult-Study	0.66	0.3272	8855	1.94	[1.02; 3.68]	4.5%	5.6%
Coimbra Eye Study	0.88	0.4756	930	2.40	[0.94; 6.09]	2.1%	2.8%
Fixed effect model			**137219**	**1.23**	**[1.07; 1.40]**	**100.0%**	--
Random effect model				**1.22**	**[1.04; 1.43]**	--	**100.0%**

Heterogeneity: I^2 = 17%, τ^2 = 0.0109, p = 0.29

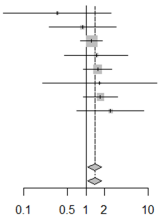


B

Model 2: C08D: CCBs with direct cardiac effects

Study	Beta	Experimental SE	Total N	OR	95%-CI	Weight (fixed)	Weight (random)
Alienor Study	-1.06	1.0241	869	0.35	[0.05; 2.57]	1.7%	1.7%
Montrachet Study	-0.12	0.6298	866	0.88	[0.26; 3.04]	4.5%	4.5%
Lifelines	0.21	0.2069	86841	1.24	[0.82; 1.85]	41.5%	41.5%
Gutenberg Health Study	0.38	0.6003	11970	1.46	[0.45; 4.75]	4.9%	4.9%
Rotterdam Study	0.43	0.2697	8268	1.54	[0.91; 2.62]	24.4%	24.4%
LIFE-Adult-Study	0.51	1.0811	8855	1.67	[0.20; 13.92]	1.5%	1.5%
Thessaloniki Eye Study	0.54	0.3222	2357	1.72	[0.91; 3.23]	17.1%	17.1%
Tromsø Eye Study	0.91	0.6320	7655	2.48	[0.72; 8.57]	4.4%	4.4%
Coimbra Eye Study	.	.	.			0.0%	0.0%
EPIC-Norfolk Eye Study	.	.	.			0.0%	0.0%
Fixed effect model			**127681**	**1.39**	**[1.07; 1.81]**	**100.0%**	--
Random effect model				**1.39**	**[1.07; 1.81]**	--	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.76

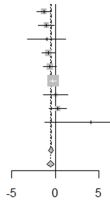


A

Model 2: C07AA: non-selective beta-blockers

Study	Beta	Experimental SE	Total N	MD	95%-CI	Weight (fixed)	Weight (random)
EPIC-Norfolk Eye Study	-1.29	0.4290	7947	-1.29	[-2.13; -0.45]	9.6%	13.0%
Thessaloniki Eye Study	-1.03	0.4560	2243	-1.03	[-1.93; -0.14]	8.5%	12.1%
Coimbra Eye Study	-0.98	1.1070	926	-0.98	[-3.15; 1.19]	1.4%	3.0%
Gutenberg Health Study	-0.82	0.3770	14476	-0.82	[-1.56; -0.08]	12.5%	15.0%
Alienor Study	-0.65	0.3730	933	-0.65	[-1.38; 0.08]	12.7%	15.2%
Rotterdam Study	-0.26	0.1990	8212	-0.26	[-0.65; 0.13]	44.7%	24.4%
Tromsø Eye Study	0.02	0.7180	5005	0.02	[-1.39; 1.43]	3.4%	6.3%
Montrachet Study	0.32	0.5100	866	0.32	[-0.68; 1.32]	6.8%	10.4%
Lifelines	4.07	2.7080	410	4.07	[-1.24; 9.38]	0.2%	0.5%
Fixed effect model			**41018**	**-0.49**	**[-0.75; -0.23]**	**100.0%**	--
Random effect model				**-0.55**	**[-0.94; -0.16]**	--	**100.0%**

Heterogeneity: I^2 = 40%, τ^2 = 0.1247, p = 0.10



B

Model 2: C07AB: selective beta-blockers

Study	Beta	Experimental SE	Total N	MD	95%-CI	Weight (fixed)	Weight (random)
EPIC-Norfolk Eye Study	-1.05	0.1510	7947	-1.05	[-1.35; -0.75]	8.4%	13.4%
Lifelines	-0.83	0.7300	410	-0.83	[-2.26; 0.60]	0.4%	2.3%
Tromsø Eye Study	-0.44	0.1740	5005	-0.44	[-0.78; -0.10]	6.4%	12.5%
Montrachet Study	-0.42	0.2500	866	-0.42	[-0.91; 0.07]	3.1%	9.7%
Thessaloniki Eye Study	-0.37	0.1880	2241	-0.37	[-0.74; 0.00]	5.4%	11.9%
Alienor Study	-0.36	0.1930	933	-0.36	[-0.74; 0.02]	5.2%	11.8%
Coimbra Eye Study	-0.19	0.3620	926	-0.19	[-0.90; 0.52]	1.5%	6.6%
Rotterdam Study	-0.12	0.0810	8212	-0.12	[-0.28; 0.04]	29.3%	15.8%
Gutenberg Health Study	-0.08	0.0690	14476	-0.08	[-0.22; 0.05]	40.4%	16.1%
Fixed effect model			**41016**	**-0.24**	**[-0.33; -0.16]**	**100.0%**	--
Random effect model				**-0.39**	**[-0.62; -0.15]**	--	**100.0%**

Heterogeneity: I^2 = 80%, τ^2 = 0.0830, p < 0.01