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# Systemic Medication and Intraocular Pressure in a British Population

## *The EPIC-Norfolk Eye Study*

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***Objective:*** To determine the association between systemic medication use and intraocular pressure (IOP) in a population of older British men and women.

***Design:*** Population-based, cross-sectional study.

***Participants:*** We included 7093 participants from the European Prospective Investigation into Cancer–Norfolk Eye Study. Exclusion criteria were a history of glaucoma therapy (medical, laser, or surgical), IOP asymmetry between eyes of >5 mmHg, and missing data for any covariables. The mean age of participants was 68 years (range, 48–92) and 56% were women.

***Methods:*** We measured IOP using the Ocular Response Analyzer. Three readings were taken per eye and the best signal value of the Goldmann-correlated IOP value considered. Participants were asked to bring all their medications and related documentation to the health examination, and these were recorded by the research nurse using an electronic case record form. The medication classes examined were angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, α-blockers, β-blockers, calcium channel blockers, diuretics, nitrates, statins, insulin, biguanides, sulfonylureas, aspirin, and other nonsteroidal anti-inflammatory drugs. We examined associations between medication use and IOP using multivariable linear regression models adjusted for age, sex, and body mass index. Models containing diabetic medication were further adjusted for glycosylated hemoglobin levels.

***Main Outcome Measures:*** Mean IOP of the right and left eyes.

***Results:*** Use of systemic β-blockers (−0.92 mmHg; 95% CI, −1.19, −0.65; $P<0.001$) and nitrates (−0.63 mmHg; 95% CI, −1.12, −0.14; $P = 0.011$) were independently associated with lower IOP. The observed associations between statin or aspirin use with IOP were no longer significant after adjustment for β-blocker use.

***Conclusions:*** This is the first population-based study to demonstrate and quantify clinically significant differences in IOP among participants using systemic β-blockers or nitrates. Lower IOP observed in participants using statins or aspirin was explained by concurrent systemic β-blocker use. The study findings may have implications for the management of glaucoma patients with comorbidity, and may provide insight into the pathophysiologic processes underlying IOP. *Ophthalmology 2014;121:1501-1507 © 2014 by the American Academy of Ophthalmology.*


*Supplemental material is available at www.aaojournal.org.*

Raised intraocular pressure (IOP) is an important risk factor for the incidence[1] and progression[2] of glaucoma. The risk of developing open-angle glaucoma in a healthy population has been shown to increase by 16% per 1-mmHg increase in IOP.[1] Little is known regarding the influence of systemic medication on IOP, other than for β-blockers.[3–5] If a systemic medication does have an influence on IOP, this may give insight into the physiologic or pathologic mechanisms underlying IOP, and may aid the management of glaucoma patients with systemic comorbidity. Furthermore, for systemic medications found to have an influence on glaucoma risk, such as statins[6,7] or calcium channel blockers,[8] it would be of interest to know whether these medications influence IOP, or whether their effect on glaucoma risk is largely IOP independent. To date, no population-based study has systematically examined the association between common classes of systemic medication and IOP.

The aim of this study was to examine the association between the use of common systemic medications and IOP in a British population.

## Methods

### Participants

The European Prospective Investigation into Cancer (EPIC) study is a pan-European prospective cohort study designed to investigate



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the etiology of major chronic diseases.[9] EPIC-Norfolk, one of the UK arms of EPIC, recruited and examined 25,639 participants aged 40 to 79 between 1993 and 1997 for a baseline examination.[10] Recruitment was via general practices in the city of Norwich and the surrounding small towns and rural areas, and methods have been described in detail previously.[10] Because virtually all residents in the United Kingdom are registered with a general practitioner through the National Health Service, general practice lists serve as population registers. Ophthalmic assessment formed part of the third health examination and this has been termed the EPIC-Norfolk Eye Study.[11] In total, 8623 participants were seen for the ophthalmic examination, between 2004 and 2011. The EPIC-Norfolk Eye Study was carried out following the principles of the Declaration of Helsinki and the Research Governance Framework for Health and Social Care. The study was approved by the Norfolk Local Research Ethics Committee (05/Q0101/191) and East Norfolk & Waveney NHS Research Governance Committee (2005EC07L). All participants gave written, informed consent.

### Measurements

We measured IOP with a noncontact instrument, the Ocular Response Analyzer (ORA; Reichert, Corp, Buffalo, NY). The ORA uses a short (20-ms) pulse of air to indent the cornea and measure inward and outward applanation pressures using an electrooptical system.[12] The average of inward (P1) and outward (P2) applanation forces has been calibrated to derive a measure equivalent to IOP measured by Goldmann applanation tonometry; this is termed Goldmann-correlated IOP.[13] In this study, 3 ORA readings were taken per eye and the best signal value of the Goldmann-correlated IOP used (based on the best quality pressure waveform as assessed by the ORA software). Height and weight were measured with participants wearing light clothing and no shoes. Height was measured to 0.1 cm using a stadiometer, and weight was measured to the nearest 0.1 kg using digital scales (Tanita UK Ltd, Middlesex, UK). Body mass index (BMI) was calculated as weight/height$^2$. Blood pressure (BP) and heart rate were measured with the participant seated resting using an objective measurement device (Accutorr Plus; Datascope Patient Monitoring, Mindray UK, Ltd, Huntington, UK) on 2 separate occasions during the health examination and the mean of the 2 measurements considered. Participants were asked to bring all their medications and related documentation to the health examination, and these were recorded by the research nurse using an electronic case record form.

### Statistical Analysis

The classes of medication to be tested were decided a priori, based on the most common medications taken in the cohort; these were angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, α-blockers, β-blockers, calcium channel blockers, diuretics, nitrates, statins, diabetic medication (insulin, biguanides, and sulfonylureas), aspirin, and nonsteroidal anti-inflammatory drugs excluding aspirin. Lists of the medications in these classes are provided in Appendix 1 (available at www.aaojournal.org).

The mean IOP of the right and left eyes of each participant was used for analyses. If data were only available for 1 eye, then the IOP of that eye was considered for the participant. Participants with an intereye IOP difference of >5 mmHg were excluded from analyses, because the asymmetry may have been caused by undetected ocular disease or may have been owing to an artifact. We further excluded participants reporting a history of glaucoma medication or a glaucoma procedure. Comparisons of IOP in participants taking medication versus those not taking medication were undertaken for each class of drug using the independent samples $t$ test. To test whether any differences in IOP were independent of possible confounders, we used multivariable linear regression models with IOP as the dependent variable, and medication, age, gender, and BMI as explanatory variables. Models containing diabetic medications were further adjusted for blood glycosylated hemoglobin level. Considering the multiple statistical tests conducted and the exploratory nature of these analyses, we highlighted results significant at the 5% level after Bonferroni correction.

Given that many participants were taking >1 class of medication, we repeated regression analyses further adjusting for a particular class of drug, 1 at a time, for each drug found to be significantly associated with IOP in the original regression analyses. We also included all drugs found to be significant in individual analyses together in 1 multivariable regression model, adjusted for possible confounders.

To determine whether any association between antihypertensive medication and IOP was mediated by a change in heart rate or BP, we repeated regression analyses further adjusted for heart rate, and systolic BP (SBP) or diastolic BP.

Stata version 12.1 (StataCorp LP, College Station, TX) was used for all statistical analyses.

## Results

Of the 8623 participants attending the Eye Study, there were complete data for IOP and covariables from 7650 participants after exclusion of participants reporting a history of glaucoma medication use (n = 276) or a glaucoma procedure (n = 66). After further excluding participants with an intereye IOP asymmetry of >5 mmHg (n = 557), there were data from 7093 participants (82% of those attending the Eye Study) that were used for the main analyses. The mean age of included participants was 68 years (range, 48−92) and 56% were women. Compared with included participants, excluded participants were significantly older ($P<0.001$), had higher SBP ($P = 0.008$), and more were men ($P = 0.002$). Included and excluded participants did not have significantly different BMI ($P = 0.74$) or heart rate ($P = 0.29$).

Table 1 summarizes the number of participants taking each class of medication at the time of the health examination, and provides a comparison of the mean IOP between those taking and not taking each medication. Participants taking β-blockers ($P<0.001$), nitrates ($P<0.001$), statins ($P = 0.002$), or aspirin ($P<0.001$) had lower IOP on average than participants not taking each medication. Participants using biguanides or sulfonylureas had a higher IOP on average than participants not taking the medication, although there were no significant differences after correction for multiple testing.

After adjustment for possible confounders (age, gender, BMI, and blood glycosylated hemoglobin level), β-blocker ($P<0.001$), nitrate ($P<0.001$), statin ($P = 0.003$), and aspirin ($P<0.001$) use remained significantly associated with lower IOP (Table 2). When these 4 drugs were included in the same multivariable model, only the use of β-blockers (−0.92 mmHg; 95% CI, −1.19 to −0.65; $P<0.001$) or nitrates (−0.63 mmHg; 95% CI, −1.12 to −0.14; $P = 0.011$) remained significantly associated with IOP (Fig 1). Further analysis identified concurrent use of β-blockers as the explanation for the single medication associations observed between IOP and statins or aspirin; these associations lost significance when further adjusted for β-blocker use, but remained significant after further adjustment for nitrate use (Appendix 2; available at www.aaojournal.org).

The magnitude of IOP-lowering associated with systemic β-blocker or nitrate use was reduced after further adjustment for SBP or HR, but remained significant (Table 3). Results were similar if adjustment was for diastolic BP rather than SBP (Table 3).