Change in Systemic Medication and its Influence on Intraocular Pressure – Results From the Gutenberg Health Study

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Purpose. The purpose of this study was to investigate the relationship between the change in systemic medication and intraocular pressure (IOP) on a population-based level.

Methods. The Gutenberg Health Study is a population-based prospective observational cohort study in Germany. As part of the baseline examination (2007–2012) and 5-year follow-up examination (2012–2017), IOP was measured by non-contact tonometry. Systemic medication was recorded at both time points. Multivariable regression analyses were carried out to analyze associations. Moreover, we calculated the dose-response relationship for the dosage change of selective beta-blockers with IOP change over 5 years.

Results. The analysis population included 19,161 eyes of 9633 participants. IOP change was lower in participants with new intake of selective beta-blockers (−0.31 mm Hg, $P < 0.001$) and increased in those with discontinuation of selective beta-blocker intake (+0.28 mm Hg, $P = 0.02$). Associations between IOP change and statins and calcium channel blockers (CCBs) could be attributed to co-medications. There was a dose-response relationship for change in selective beta-blocker intake and change in IOP (−0.16 mm Hg/100 mg, $P = 0.02$).

Conclusions. Use of systemic selective beta-blockers is associated with an IOP change on a population level, whereas the association with other systemic medications on IOP change could be explained by co-medication use or change in blood pressure. Patients undergoing IOP monitoring and management should routinely be asked about changes in systemic medications.

Keywords: intraocular pressure (IOP), systemic medication, epidemiology

Advancing age, particularly above 75 years, is associated with various chronic illnesses. As a result, elderly individuals frequently use five or more drugs, referred to as polypharmacy.[1] Therefore, it is of importance to understand how systemic medications, commonly administrated in older patients, influence intraocular pressure (IOP). In particular, both selective and nonselective beta-blockers are utilized in the treatment of increased IOP. Nonselective beta-blockers, such as timolol and carteolol, inhibit both beta-1 and beta-2 receptors throughout the body. On the other hand, selective beta-blockers primarily target beta-1 receptors, with betaxolol being a notable example.[2]

Apart from beta-blockers, we focused on the possible effects of statins,[3] diuretics,[4] angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors,[5] calcium channel blockers (CCBs),[6] and various antidepressive drugs,[7] including monoamine reuptake inhibitors and selective serotonin reuptake inhibitors (SSRIs).[8] A recent cross-sectional meta-analysis of 11 European population-based studies showed an influence of beta-blockers on IOP, and potentially for loop diuretics, whereas other systemic medications were not associated with IOP alteration. This study also demonstrated that the intake of CCBs is associated with a higher prevalence of glaucoma. No other systemic medications were found to be related to glaucoma.[4] An analysis of the Rotterdam Study, involving 3842 participants, identified a higher incidence of open-angle glaucoma in those taking calcium channel antagonists, whereas beta-blockers showed a non-significant trend toward reducing the risk of developing glaucoma.[9] Drugs typically administrated locally for the reduction of IOP, such as beta-blockers, are also often given systemically for regulation of blood pressure and chronic heart failure.[10,11] For a long time, there was evidence[12] that the usage of such drugs have a measurable impact on IOP, even if their concentration in the eyes by systemic administration is lower than after topical application.

Various systemic drugs have been proposed to influence the development of ocular hypertension and glaucoma.[13]

Our study advances the understanding of the associations between changes in IOP and systemic medication use, overcoming several limitations of previous research. Unlike prior studies, which were predominantly cross-sectional, ours is the first, to our knowledge, that uses a longitudinal design. This approach allows us to track and analyze IOP changes over time within the same individuals, thereby offering a more detailed perspective on how systemic medications affect IOP.

Methods

The Gutenberg Health Study

The Gutenberg Health Study (GHS) is a prospective, monocentric cohort study based on the population of the city of Mainz and the district Mainz-Bingen in Germany.[14] The participants between the ages of 35 and 74 years were included stratified by sex, place of residence (urban/rural), and age decade. At baseline examination, 15,010 participants were included.[15]

The primary aim of this study was to provide new insights into risk stratification for various diseases in the general population, with special focus on the cardiovascular system.[14] The GHS database is currently the largest collection of data for eye diseases and associated risk factors in Germany and one of the largest worldwide. Recruitment started in 2007 and lasted until early 2012. The first follow-up examinations took place 5 years later, between 2012 and 2017, and included 12,423 participants. The GHS was conducted according to the principles of "Good Clinical Practice," the "Good Epidemiological Practice," and the Declaration of Helsinki.[16,17] Informed consent for participation was obtained from all participants. Approval for the conduction of the study was given by the Ethics Committee of the State Medical Association of Rhineland-Palatinate and the Data Protection Officer of the University Medical Center Mainz.

Measurement of Intraocular Pressure

Eye examinations were performed by medical staff and qualified personnel at the study center. IOP was measured with the Nidek NT-2000 (Nidek Co., Japan) non-contact tonometer. The mean value of three consecutive measurements per eye was assessed and this was considered as the measured IOP. All patients' examinations began with the right eye, followed by the left eye. Examination at baseline and at 5-year follow-up examination took place in the same season and at the same day and time (98% within 2 hours).

Assessment of Medication

Medication classes included in the study were chosen based on the prevalence of antihypertensive and cardiovascular drugs among the sample population. Participants were requested to bring the packaging of all their medications to their study visit to verify the medication intake. Drugs taken by participants were registered according to the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization.[18] In Supplementary Table S1, we listed the active substances with ATC codes, for which an association with IOP change is suspected through previous cross-sectional studies.[4,19] Participants were grouped in those with no medication during the study, new intake, discontinued drug intake, and continuous intake during the study. An analysis was only performed if a drug was either newly received or discontinued in at least 100 participants, which corresponds to approximately 1% of the expected analysis population. For this reason, nonselective beta-blockers were not included in the statistical analysis, as they did not meet the minimum case threshold.

Within this study, the ATC codes C09B and C09D represent combination drugs; specifically, C09B refers to ACE inhibitors combined with other medications, and C09D to ARBs also in combination with other drugs. Before performing statistical analysis, these combinations were grouped into their corresponding drug classes.

Inclusion/Exclusion Criteria

The only inclusion criterion was having at least one IOP measurement in one eye at both time points of the study. Exclusion criteria were diagnosed glaucoma, taking antiglaucoma medication, or any eye surgery between both examinations.

Statistical Analysis

For descriptive analysis, absolute and relative frequencies were computed in categorical parameters. For continuous

variables, mean and standard deviation were computed for approximately normal-distributed data, otherwise we used median and interquartile range. The change in IOP between baseline and follow-up was computed on eye level. Multivariable linear regression analyses were performed using generalized estimating equations (GEEs) to address the collinearity between the right and left eyes. The analysis incorporated medication classes categorized into four groups: new medication intake, discontinued intake, and continued intake, with "no medication use at both time points" serving as the reference category. Two models analyzing the medication classes separately were constructed (uni-medication models), each adjusting for a set of covariates. The first model included adjustments for age, sex, baseline body mass index (BMI), BMI difference, and diabetes. In the second model, systolic blood pressure difference was additionally incorporated. The adjustment variables were selected based on a previous analysis of the GHS regarding IOP. For this reason, baseline systolic blood pressure was not included in our analyses, as it did not demonstrate a significant association with IOP change in a multivariable context in our earlier univariable analysis.[20] Subsequently, multivariable models incorporating all medication classes were calculated (multi-medication models), adjusting for the same factors. Namely age, sex, baseline BMI, BMI difference, and diabetes in model 3, with an additional adjustment for systolic blood pressure difference in model 4.

In addition, we meticulously examined an effect modification for CCBs with an interaction term in the uni-medication analysis. In a previous cross-sectional study of the GHS, no significant association was found for this medication.[21] However, due to indications from the uni-medication analysis, we decided to investigate this potential association in more detail.

In an additional set of analyses, we included only participants who were taking a single class of the specified medications and excluded those who were on more than one class. This approach was adopted to ensure that the observed effects could be attributed as closely as possible to one medication class without the confounding influence of multiple medications. This way, we could better understand if the medication's effect on IOP stands on its own. Moreover, one analysis was conducted within sex-stratified subgroups to identify potential variations with usage of the multi-medication model. Finally, we calculated the dose-response relationship for the dosage change of beta-blockers (selective) with IOP change over 5 years in the right eye. Metoprolol was used as a reference for assigning weights to various beta-blocker subgroups. A table of equivalence dosage for various beta-blockers was used for standardization on Metoprolol dosage.[22]

R software version 4.0.3 (R Core Team) was used for the statistical evaluation. The analysis was conducted using the following R packages: ggplot2, tableone, ggpubr, and geepack.

Results

Analysis Population

Of the original cohort of 15,010 participants, we examined 12,423 at the 5-year follow-up examination. There were 1683 participants (11.21%) who dropped out of the study, 357 had died (2.38%) prior to the follow-up appointment, 447 (2.98%) could no longer be contacted, and 100 participants (0.67%) were excluded because they no longer met the health criteria for a visit at the study center.

Of those who took part at the 5-year follow-up, 1377 (11.08% of those examined at follow-up) had no IOP measurement in either eye at both time points. There were 1272 participants (10.24%) who were excluded because of the usage of topical eye medication, eye surgery during the 5-year interval, or newly diagnosed glaucoma.

Exclusion of participants with missing information on the systemic medication reduced the number of cases by 118 and by missing values regarding other analysis variables again by 23. Thus, the analysis population included 9633 individuals.

Participants' Characteristics

Of the analysis population, we included 19,161 eyes of 9633 participants. The description of the study population is shown in Table 1. The mean change in IOP was +0.73 (2.04) mm Hg for the right and +0.67 (2.04) mm Hg for the left eye over 5 years.

Because selective beta-blockers are a major focus of the analysis, we additionally compared the descriptive parameters between the groups using beta-blockers (new intake, discontinued intake, and continuous intake) and the group not taking these medications (Supplementary Table S2). The comparison revealed that individuals who have taken or are currently taking selective beta-blockers tend to be older and have a higher prevalence of conditions, such as arterial hypertension and diabetes. Furthermore, systolic and diastolic blood pressure, as well as BMI, were found to be higher compared to the group not using these medications.

Uni-Medication Analysis

Beta-Blockers. Five hundred eighty-six participants (6.1%) reported a new intake of selective β-adrenoceptor antagonists (beta-blockers), 934 participants (9.7%) had continuous intake of selective beta-blockers, and 207 participants (2.1%) stopped the intake of beta-blockers within the 5-year interval between examinations. Participants who were new on selective beta-blockers showed in model 1 (adjusted for age, sex, BMI baseline, BMI difference, and diabetes) a lower IOP change by an average of −0.39 mm Hg (95% confidence interval [CI] = −0.55 to −0.22, $P < 0.001$) over 5 years compared to the study participants without the intake of selective beta-blockers; Table 2. When discontinuing beta-blocker use, IOP change increased by 0.29 mm Hg (95% CI = 0.04 to 0.53, $P = 0.02$). We saw comparable results in model 2 with additional adjustment for 5-year differences of systolic blood pressure.

After exclusion of participants with other co-medications that could potentially influence IOP, namely ACE inhibitors, angiotensin II receptor blockers, diuretics, and calcium channel inhibitors, the association between the new intake or discontinuation of selective beta-blocker and IOP change was no longer evident; Supplementary Table S3. The number of cases of medication intake decreased significantly due to the elimination of co-medication (Supplementary Table S4).

The dosage change of selective beta-blockers showed a significant relationship between the dosage and IOP change in the right eye (B = −0.16 mm Hg/100 mg, $P = 0.02$; Fig. 1).

Table 1. Participants' Characteristics ($N = 9633$, Baseline Examination) Absolute Frequencies of the Intake Patterns of the Medications for Which we Calculated GEE Models

	Overall	Men	Women	Sex-Specific Difference, *P* Value
Anthropometric data (baseline)	9633	4921	4712	
Age, y, mean (SD)	53.30 (10.5)	53.58 (10.6)	53.02 (10.4)	0.009
Age categories: *n*				
35–44 y	2378 (24.7%)	1.169 (23.8%)	1.209 (25.7%)	
45–54 y	2891 (30.0%)	1.471 (29.9%)	1.420 (30.1%)	
55–64 y	2610 (27.1%)	1.326 (26.9%)	1.284 (27.2%)	
65–74 y	1754 (18.2%)	955 (19.4%)	799 (17.0%)	
Cardiovascular parameters				
Arterial hypertension	4412 (45.8%)	2516 (51.1%)	1896 (40.2%)	<0.001
Diabetes	675 (7%)	436 (8.9%)	239 (5.1%)	<0.001
Systolic blood pressure, mm Hg, mean (SD), baseline	130.16 (16.85)	133.0 (15.6)	127.2 (17.6)	<0.001
Systolic blood pressure, mm Hg, mean (SD), follow-up	130.21 (16.51)	132.42 (15.16)	127.91 (17.53)	<0.001
Diastolic blood pressure, mm Hg, mean (SD), baseline	82.31 (9.27)	83.84 (9.15)	80.7 (9.13)	<0.001
Diastolic blood pressure, mm Hg, mean (SD), follow-up	80.68 (9.31)	82.00 (9.24)	79.30 (9.17)	<0.001
Body-mass-index, kg/m^2, mean (SD), baseline	27.06 (4.78)	27.6 (4.1)	26.5 (5.3)	<0.001
Body-mass-index, kg/m^2, mean (SD), follow-up	27.44 (4.98)	27.92 (4.33)	26.95 (5.54)	<0.001
Ophthalmic parameters				
Intraocular pressure, mm Hg, right eye, mean (SD), baseline	14.04 (2.78)	14.10 (2.86)	13.96 (2.69)	0.01
Intraocular pressure, mm Hg, right eye, mean (SD), follow-up	14.77 (2.92)	14.87 (3.03)	14.65 (2.79)	<0.001
Intraocular pressure, mm Hg, left eye, mean (SD), baseline	14.19 (2.81)	14.31 (2.89)	14.06 (2.71)	<0.001
Intraocular pressure, mm Hg, left eye, mean (SD), follow-up	14.85 (2.93)	14.98 (3.03)	14.71 (2.83)	<0.001
Medication intake				
β-Adrenoceptor antagonists, selective: *n*				0.67
No intake	7.905 (82.1%)	4017 (81.6%)	3889 (82.5%)	
New intake	586 (6.1%)	303 (6.2%)	283 (6%)	
Discontinued intake	207 (2.1%)	110 (2.2%)	97 (2.1%)	
Continuous intake	934 (9.7%)	491 (10%)	443 (9.4%)	
β-Adrenoceptor antagonists, nonselective: *n*				1.00
No intake	9581 (99.5%)	4689 (95.3%)	4683 (99.4%)	
New intake	18 (0.2%)	6 (0.1%)	12 (0.3%)	
Discontinued intake	17 (0.2%)	8 (0.2%)	9 (0.2%)	
Continuous intake	17 (0.2%)	9 (0.2%)	8 (0.2%)	
Thiazide diuretics: *n*				<0.001
No intake	8.068 (83.8%)	4036 (82%)	4032 (85.6%)	
New intake	604 (6.3%)	339 (6.9%)	265 (5.6%)	
Discontinued intake	234 (2.4%)	141 (2.9%)	93 (2%)	
Continuous intake	727 (7.5%)	405 (8.2%)	322 (6.8%)	
Loop diuretics: *n*				0.34
No intake	9.359 (97.2%)	4766 (96.9%)	4593 (97.5%)	
New intake	154 (1.6%)	88 (1.8%)	66 (1.4%)	
Discontinued intake	33 (0.3%)	14 (0.3%)	19 (0.4%)	
Continuous intake	87 (0.9%)	53 (1.1%)	34 (0.7%)	
Angiotensin-converting enzyme (ACE) inhibitors: *n*				<0.001
No intake	7871 (81.7%)	3841 (78.1%)	4030 (85.5%)	
New intake	615 (6.4%)	379 (7.7%)	236 (5%)	
Discontinued intake	319 (3.3%)	186 (3.8%)	133 (2.8%)	
Continuous intake	828 (8.6%)	515 (10.5%)	313 (6.6%)	
Angiotensin II receptor blocker (ARB): *n*				<0.001
No intake	8051 (83.6%)	4060 (82.5%)	3991 (84.7%)	
New intake	730 (7.6%)	366 (7.4%)	364 (7.7%)	
Discontinued intake	103 (1.1%)	56 (1.1%)	47 (1%)	
Continuous intake	749 (7.8%)	439 (8.9%)	310 (6.6%)	
Calcium channel blocker: *n*				<0.001
No intake	8509 (88.3%)	4238 (86.1%)	4271 (90.6%)	
New intake	563 (5.8%)	332 (6.7%)	231 (4.9%)	
Discontinued intake	119 (1.2%)	70 (1.4%)	49 (1%)	
Continuous intake	442 (4.6%)	280 (5.7%)	161 (3.4%)	
HMG-CoA reductase inhibitors (statins): *n*				<0.001
No intake	8161 (84.7%)	4011 (81.5%)	4150 (88.1%)	
New intake	532 (5.5%)	328 (6.7%)	204 (4.3%)	
Discontinued intake	206 (2.1%)	122 (2.5%)	84 (1.8%)	
Continuous intake	734 (7.6%)	460 (9.3%)	274 (5.8%)	

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Table 1. Continued

	Overall	Men	Women	Sex-Specific Difference, *P* Value
Nonselective monoamine reuptake inhibitors: *n*				<0.001
No intake	9342 (97%)	4831 (98.2%)	4511 (95.7%)	
New intake	126 (1.3%)	38 (0.8%)	88 (1.9%)	
Discontinued intake	80 (0.8%)	32 (0.7%)	48 (1%)	
Continuous intake	85 (0.9%)	20 (0.4%)	65 (1.4%)	
Selective serotonin reuptake inhibitors: *n*				<0.001
No intake	9.337 (96.9%)	4817 (97.9%)	4520 (95.9%)	
New intake	125 (1.3%)	44 (0.9%)	81 (1.7%)	
Discontinued intake	88 (0.9%)	33 (0.7%)	55 (1.2%)	
Continuous intake	83 (0.9%)	27 (0.5%)	56 (1.2%)	
Other antidepressants: *n*				0.03
No intake	9.403 (97.6%)	4833 (98.2%)	4570 (97%)	
New intake	122 (1.3%)	45 (0.9%)	77 (1.6%)	
Discontinued intake	50 (0.5%)	19 (0.4%)	31 (0.7%)	
Continuous intake	58 (0.6%)	24 (0.5%)	34 (0.7%)	

Data from the German population-based Gutenberg Health Study (2007–2017, $N = 9633$).

Diuretics. Neither continuous, discontinued, nor new uptake of thiazide diuretics was associated with IOP change in any of the models.

Regarding loop diuretics, new intake was associated with a lower IOP change in model 1 (B = −0.35, 95% CI = −0.69 to −0.00, $P = 0.05$), but not after adjustment for a change in systolic blood pressure.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blocker. Continuous intake of ACE inhibitors was associated with a lower IOP change by an average of −0.20 mm Hg (95% CI = −0.34 to −0.06, $P = 0.01$). This association remained in model 2 with −0.17 mm Hg IOP change (95% CI = −0.32 to −0.03, $P = 0.01$) after adjustment for change in systolic blood pressure. Discontinuation of these drugs showed no influence on IOP change. The new intake of angiotensin II receptor blockers was associated with a lower IOP change in model 1 (B = −0.15 mm Hg, 95% CI = −29 to 0.00, $P = 0.05$), however, not after adjustment for a change in systolic blood pressure.

When excluding the effect of co-medication, the association between new intake or continuous intake of ACE inhibitors and IOP change was not present.

Calcium Channel Inhibitors. New intake of calcium channel inhibitors was associated with a decrease in IOP of −0.42 mm Hg (95% CI = −0.58 to −0.26, $P < 0.001$) on average. Similarly, in model 2, the IOP change was associated with new intake of calcium channel inhibitors (B = −0.29 mm Hg, 95% CI = −0.45 to −0.13, $P < 0.001$). The continuous intake or stop of medication showed no association with IOP change.

The negative association between the new intake of calcium channel inhibitors and IOP change disappeared in model 1 and model 2, when participants with a co-medication were excluded (model 1: B = −0.06, $P = 0.77$ and model 2: B = 0.01, $P = 0.96$).

We investigated the potential effect modification within the medication groups involving CCBs. Notably, an effect modification was evident when examining the discontinuation of angiotensin II receptor blockers and the new intake of CCBs in both model 1 (B = −1.40, $P = 0.002$) and model 2 (B = −1.36, $P = 0.004$).

Statins. Concerning statins, new usage was associated with a lower IOP change of −0.27 mm Hg (95% CI = −0.44 to −0.09, $P = 0.003$) in model 1 and −0.21 mm Hg in model 2 (95% CI = −0.39 to −0.04, $P = 0.02$). Continuous intake as well as discontinuation of the drug was not associated with IOP change. After exclusion of co-medication, new intake of statins and IOP change were not associated (model 1: B = −0.03, $P = 0.87$ and model 2: B = −0.01, $P = 0.96$).

Antidepressants. Regarding nonselective monoamine reuptake inhibitors, participants who continuously took the medication had a positive IOP change compared to those without intake (B = 0.44, 95% CI = 0.01 to 0.88, $P = 0.05$) in model 2. New intake and discontinuation of these drugs showed no effect on IOP change.

Concerning SSRIs, there was a significant association with IOP change for discontinuation of the drug with an increasing IOP of 0.43 mm Hg over 5 years (95% CI = 0.12 to 0.74, $P = 0.01$) in model 2.

The association between continuous use of nonselective monoamine reuptake inhibitors with IOP change was not observed when participants with co-medication were excluded (model 1: B = 0.44, $P = 0.08$ and model 2: B = 0.41, $P = 0.11$). Furthermore, the association between discontinuation of SSRIs remained evident in model 2 after exclusion of co-medication (model 1: B = 0.38, 95% CI = −0.02 to 0.77, $P = 0.06$ and model 2: B = 0.39, 95% CI = −0.01 to 0.78, $P = 0.05$).

Multi-Medication Modeling. Models 3 and 4 demonstrated a significant association with changes in IOP over 5 years concerning the new intake and the discontinuation of selective beta-blockers (Fig. 2, Supplementary Table S5). The new intake of selective beta-blockers was associated with a decrease in IOP over 5 years (B = −0.28, $P = 0.001$), whereas discontinuation was associated with an increase (B = 0.33, $P = 0.01$).

Continuous use of ACE inhibitors was also linked to a negative change in IOP pressure over 5 years (B = −0.18, $P = 0.03$). Furthermore, a negative association was observed with the new intake of CCBs (B = −0.25, $P = 0.003$). In the case of nonselective monoamine reuptake

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Table 2. Uni-Medication Association Analysis Between Systemically Acting Drugs and a Change in Intraocular Pressure Over 5 Years

	Model 1		Model 2	
Reference: No Medication	**IOP Change Over 5 y in mm Hg (95% CI)**	***P* Value**	**IOP Change Over 5 y in mm Hg (95% CI)**	***P* Value**
Selective beta-blockers				
New intake	−0.39 (−0.55 to −0.22)	<0.001	−0.31 (−0.48 to −0.15)	<0.001
Discontinued	0.29 (0.04 to 0.53)	0.02	0.28 (0.04 to 0.53)	0.02
Continuous intake	−0.13 (−0.25 to 0.00)	0.05	−0.11 (−0.24 to 0.01)	0.08
Thiazide diuretics				
New intake	−0.08 (−0.24 to 0.08)	0.33	0.07 (−0.09 to 0.24)	0.38
Discontinued	−0.16 (−0.41 to 0.09)	0.22	−0.22 (−0.47 to 0.03)	0.09
Continuous intake	−0.07 (−0.22 to 0.07)	0.33	−0.05 (−0.20 to 0.09)	0.48
Loop diuretics				
New intake	−0.35 (−0.69 to 0.00)	0.05	−0.24 (−0.58 to 0.11)	0.18
Discontinued	−0.12 (−0.83 to 0.60)	0.75	−0.14 (−0.85 to 0.57)	0.69
Continuous intake	−0.08 (−0.42 to 0.25)	0.62	−0.04 (−0.37 to 0.29)	0.81
ACE inhibitors				
New intake	−0.14 (−0.29 to 0.01)	0.07	−0.02 (−0.17 to 0.13)	0.77
Discontinued	−0.13 (−0.34 to 0.08)	0.23	−0.13 (−0.34 to 0.08)	0.22
Continuous intake	−0.20 (−0.34 to −0.06)	0.01	−0.17 (−0.32 to −0.03)	0.01
Angiotensin II receptor blockers				
New intake	−0.15 (−29 to 0.00)	0.05	−0.04 (−0.17 to 0.13)	0.62
Discontinued	−0.04 (−0.34 to 0.08)	0.86	−0.10 (−0.34 to 0.08)	0.61
Continuous intake	−0.02 (−0.32 to −0.03)	0.76	0.01 (−0.32 to −0.03)	0.93
Calcium channel blocker				
New intake	−0.42 (−0.58 to −0.26)	<0.001	−0.29 (−0.45 to −0.13)	<0.001
Discontinued	0.20 (−0.14 to 0.54)	0.26	0.13 (−0.21 to 0.47)	0.44
Continuous intake	−0.06 (−0.26 to 0.14)	0.56	−0.01 (−0.21 to 0.18)	0.90
Statins				
New intake	−0.27 (−0.44 to −0.09)	0.003	−0.21 (−0.39 to −0.04)	0.02
Discontinued	−0.01 (−0.26 to 0.25)	0.96	−0.01 (−0.27 to 0.25)	0.95
Continuous intake	−0.05 (−0.21 to 0.11)	0.53	−0.02 (−0.18 to 0.13)	0.78
Nonselective monoamine reuptake inhibitors				
New intake	0.23 (−0.06 to 0.52)	0.13	0.23 (−0.06 to 0.52)	0.12
Discontinued	0.26 (−0.10 to 0.62)	0.16	0.24 (−0.12 to 0.60)	0.19
Continuous intake	0.42 (−0.02 to 0.86)	0.06	0.44 (0.01 to 0.88)	0.05
Selective serotonin reuptake inhibitors				
New intake	0.11 (−0.43 to 0.22)	0.51	−0.09 (−0.41 to 0.23)	0.57
Discontinued	0.43 (0.13 to 0.74)	0.01	0.43 (0.12 to 0.74)	0.01
Continuous intake	0.23 (−0.19 to 0.66)	0.29	0.26 (−0.16 to 0.68)	0.23
Other antidepressants				
New intake	0.10 (−0.41 to 0.23)	0.59	0.10 (−0.41 to 0.23)	0.58
Discontinued	0.47 (0.12 to 0.74)	0.09	0.45 (0.12 to 0.74)	0.10
Continuous intake	0.47 (−0.16 to 0.68)	0.09	−0.09 (−0.16 to 0.68)	0.68

Data from the German population-based Gutenberg Health Study (2007–2017, $N = 9633$ individuals). Linear GEE models were calculated. Model 1 controlling for age, sex, BMI baseline, BMI difference, and diabetes. Model 2 controlling for age, sex, BMI baseline, BMI difference, diabetes, and systolic blood pressure difference.

inhibitors, their continuous use was associated with an increase in IOP (B = 0.45, $P = 0.04$). A positive association was also observed between discontinuation of selective serotonin reuptake inhibitors and IOP change (B = 0.34, $P = 0.05$).

In addition, we stratified the regression models by sex, revealing sex-specific differences in the previously mentioned associations (Supplementary Table S6). In men, an association was observed between changes in IOP over 5 years and the new intake of CCBs, continuous use of ACE inhibitors, and the continuous use of nonselective monoamine reuptake inhibitors.

In contrast, among women, we observed associations between changes in IOP over 5 years and the new intake of selective beta-blockers, as well as the initiation or discontinuation of other antidepressants.

Discussion

This study analyzed changes in IOP over a 5-year period and its association with systemic medication. IOP change was associated with various medications in uni-medication analysis, including selective beta-blockers, diuretics, ACE inhibitors, angiotensin II receptor blockers, CCBs, statins, and antidepressants. In the multi-medication model, the new intake and discontinuation of beta-blockers, as well as the continuous intake of ACE inhibitors, the new intake of CCBs and the discontinuation of SSRIs, were still associated with IOP changes in the general population.

The observed association between the new intake of selective beta-blockers and IOP change over a 5-year period aligns with various cross-sectional studies that investigated this relationship.[4,21,23] The association was present both

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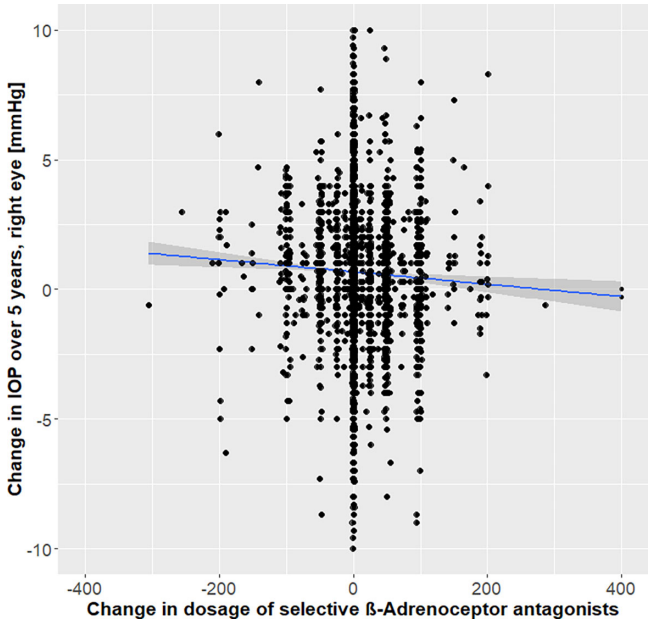

Figure 1. Dose-response relationship between change in dosage of selective beta-blockers and IOP change. Data from the German population-based Gutenberg Health Study (2007–2017). The dosage of selective beta-blockers was standardized to a common scale based on the equivalent dose of metoprolol.

in the uni-medication model and in the multi-medication model with all co-medications. In addition, we found a dose-response relationship of selective beta-blocker usage and IOP change. First reports about a dose-response influence of beta-blockers on IOP go back to 1976, when in 12 patients a dose-response relationship between propranolol (nonselective beta-blocker) and IOP was found.[24] The use of oral beta-blockers has been shown to reduce IOP in several studies.[25,26] Wettrell et al. investigated the effects of three adrenergic beta-blockers on healthy eyes. The authors demonstrated that a significant reduction in IOP was achieved immediately following the administration of the minimum oral dose. This reduction persisted for the entire duration of the treatment period, which lasted 8 days.[26] A further study, which examined the effect of orally administered beta-blockers on 46 individuals, showed that a reduction in IOP occurred both after 3 hours and after 24 hours, which was in the range of 20% to 40%.[25] Beyond the impact of beta-blockers on IOP, additional research has demonstrated that the use of oral selective beta-blockers may also reduce the risk of developing glaucoma.[9,27] Owen et al. conducted a case-control study involving 8778 cases diagnosed with or treated for glaucoma and matched them with 8778 glaucoma-free controls. The study found a lower prevalence of selective beta-blocker usage among the glaucoma cases compared to the controls.[27] Further, we showed that discontinuation of beta-blockers led to an increase in IOP. Beta-blockers are mostly used for the treatment of cardiovascular diseases[28–30] and can be classified into selective (cardioselective) ones, which inhibit β1-adrenoceptors, and nonselective beta-blockers, which inhibit both β1 and β2 adrenoceptors.[31,32] Given that beta-adrenoceptors are present in various tissues within the eye, including the ciliary body, and play a significant role in the regulation of aqueous humor production, beta-blockers have a targeted effect in this context. Specifically, these receptors contribute to the regulation of aqueous humor production by influencing the rate of fluid secretion.[33,34] Beta-blockers function by binding to these receptors, thereby inhibiting their activity. This inhibition reduces the secretion of aqueous humor from the ciliary epithelium, leading to a decrease in IOP.[35] The association of selective beta-blocker intake and IOP changes is no longer visible after excluding co-medication in the sensitivity analysis. This is likely due to the significantly reduced number of cases. In a previous cross-sectional study of the GHS, a descriptively lower IOP in case of the use of selective beta-blockers was observed (-0.12 mm Hg, $P = 0.054$), nevertheless, the difference was not statistically significant.[21] This is likely due to the fact that a smaller number of participants could be included in the longitudinal study, resulting in lower statistical power. Additionally, we have a comparatively lower average age, which could also lead to a reduction in medication use.

In our analysis, an association between the new intake of statins with IOP change was observed. In the multi-medication model, which integrated all co-medications, the previously observed association ceased to exist. This suggests the involvement of at least one more medication, likely due to its blood pressure-lowering effect. This finding is consistent with other studies that showed no association between usage of statins and IOP.[21,23] Khawaja et al.[23] initially demonstrated an association between IOP and statins in their cross-sectional study. However, this association could also be explained by the concurrent use of systemic beta-blockers.

An association was observed between the new intake of ACE inhibitors and a lower IOP in both the uni-medication and multi-medication model. However, this association was no longer evident in the sensitivity analysis, which could also be attributed to the reduced number of cases. A prior cross-sectional analysis from the GHS did not find this association between baseline IOP and ACE inhibitors.[21] However, a significant IOP reduction has been demonstrated in experimental animal models with the administration of topical ACE inhibitors, and it is suspected that this modification increases the uveoscleral outflow.[5,36] A clinical study in patients with ocular hypertension or primary open angle glaucoma showed a lower IOP following the topical application of ACE inhibitors.[37] With respect to angiotensin II receptor blockers, the potential association with IOP change could be explained by co-medications, which is in line with other cross-sectional studies.[21,23]

Although an association with a lower IOP change in case of new intake of CCBs was demonstrated, this association could also be explained by co-medication. Our effect medication analysis revealed that angiotensin II receptor blockers appeared to be the main contributing factors for this finding. This result is consistent with previous literature, which reported no association between CCBs and IOP.[4,23]

Last, we found an association between discontinuation of SSRIs and an increase in IOP change in uni-medication and multi-medication analysis, as well as after exclusion of co-medication. It has been shown that in some patients with depression, the reason for discontinuing SSRI intake was the occurrence of unspecified visual disturbances.[7] Several articles describe the association between SSRIs on IOP.[7,38] The reviews describe that limited numbers of case reports have suggested that an adverse event associated with the use of this drug might be angle-closure. This could suggest a possible association between changes in IOP and the usage of this medication.[7] However, the causality between taking the drug

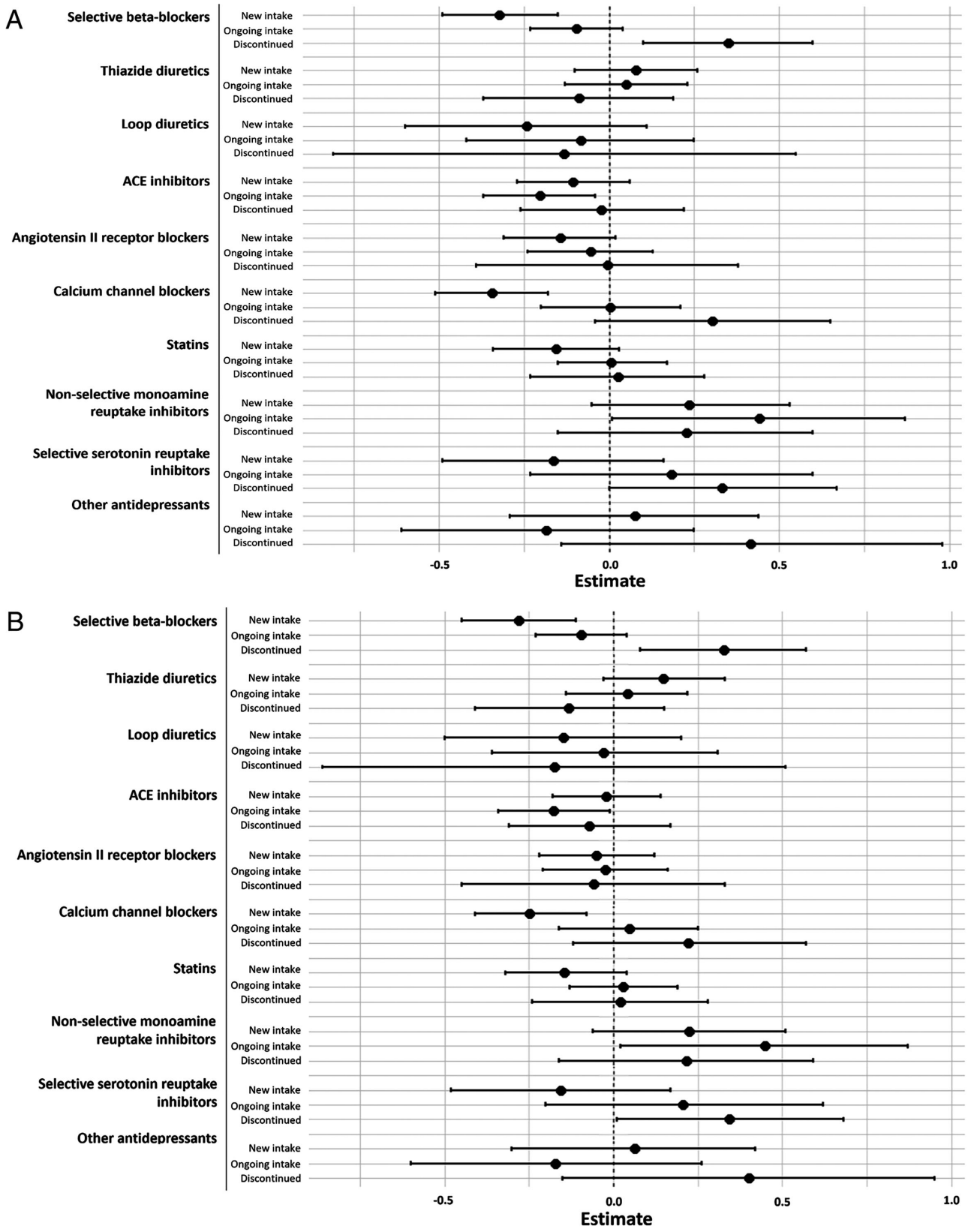

Figure 2. Associations between systemically acting drugs and a change in intraocular pressure over 5 years. Data from the German population-based Gutenberg Health Study (2007–2017, $N = 9633$ individuals, multi-medication analysis). Linear GEE models were calculated. (**A**) Model 3 controlling for co-medication, age, sex, baseline body mass index, body mass index difference over 5 years, and diabetes. (**B**) Model 4 controlling for co-medication, age, sex, baseline body mass index, body mass index difference over 5 years, diabetes, and systolic blood pressure difference over 5 years. Detailed data in Supplementary Table S5.

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and the occurrence of angle-closure has not been proven. Given that our results were only marginal after exclusion of co-medication, this finding should be interpreted with caution.

In women, IOP changes were associated with "other antidepressants" like mirtazapine. Studies indicate that women generally respond better to serotonergic antidepressants, although postmenopausal women show poorer responses,[39–41] whereas there are also studies contradicting these findings.[42–45] To our knowledge, there are no studies specifically examining sex differences in the effects of antidepressants on IOP. Furthermore, there was a significant association between selective beta-blockers and the change in IOP in women, which was not significant in men. This effect is likely due to different baseline characteristics, as literature suggests a similar response to the medication in women and men.[46] Moreover, sex differences in drug metabolism and hormonal influences could contribute to the observed variations.[47] There is a need for further studies comparing the effects of medications on IOP between sexes.

In 2023, a meta-analysis of 11 population-based studies was conducted, exploring the impact of various medications on glaucoma and IOP. Similar to findings in this study, an association was observed between lower IOP and the use of systemic beta-blockers (both selective and nonselective), whereas no association was found with CCBs, ACE inhibitors, angiotensin II receptor blockers, statins, or antidepressants. A weak association with high-ceiling diuretics was identified, but it was nonsignificant after adjusting for other systemic medications.[4] These findings are in line with our results, except for the association with ACE inhibitors which was seen in our study. Another literature-based meta-analysis from 2023 including 10 cross-sectional and case-control studies also identified an association between lower IOP and the treatment with beta-blockers, although there was no association with CCBs, ACE inhibitors, angiotensin receptor blockers, or diuretics.[48]

Our investigation significantly advances the field's comprehension of the interactions between systemic medication use and IOP changes, thereby addressing critical gaps highlighted in earlier studies. Our longitudinal study design marks a departure from prior cross-sectional analyses, providing us with the unique capability to track IOP changes over time within the same individuals. This approach grants us a richer, more intricate view into the mechanisms by which systemic medications can affect IOP.

Strengths and Limitations

This study analyzed data from a large population-based representative sample. This analysis uniquely investigates the impact of new, discontinued, and continuous intake of systemic medications on IOP. One of the strengths of our approach is the longitudinal design, allowing us to compare within-individual differences over time, which provides a clearer picture of the medication effects and natural variations in IOP. Moreover, this study is among the first to examine how co-medications may drive IOP changes, offering insights into the complex interactions between various cardiovascular drugs. These aspects underscore the study's significant step forward from previous research, by providing a nuanced understanding of IOP dynamics in a large, well-characterized cohort.

However, our study has some limitations. First, the included GHS participants mainly were of Caucasian origin. Therefore, the results cannot be generalized to other ethnicities. Additionally, whereas IOP measurements were taken three times per eye during each visit to enhance accuracy, these measurements were all conducted within a short time frame. Therefore, although the average of these three readings was used to increase the reliability of the data, we could not account for potential intra- and inter-day fluctuations in IOP. To minimize environmental effects, the GHS aimed to examine the study participants at a similar time of day and the same season at baseline and 5-year examination. Furthermore, although noncontact tonometry is commonly used to assess IOP in clinical settings, it is not entirely consistent with Goldmann applanation tonometry, which is considered as reference standard. Within the GHS, tonometry was measured with the same device at baseline and follow-up examination to minimize a systemic bias due to different measurement techniques. Although our study excluded participants with diagnosed glaucoma, it did include individuals with narrow angles, a factor that should be considered when interpreting the impact on IOP and medication effects. Last, this was an exploratory study, and no adjustment for multiple testing was conducted, which should also be taken into account when interpreting the study data.

Conclusions

In summary, there was an approximate 0.7 mm Hg increase in IOP over a 5-year period in the population aged 35 to 74 years. New intake of systemic selective beta-blockers was associated with a reduction in IOP. Discontinuation of systemic beta-blockers led to an increase in IOP, whereas associations between IOP changes and statins, or CCBs could be attributed to the influence of co-medications.

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