Systemic medications and other risk factors of open-angle glaucoma

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Michael W. Marcus

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The eye is the lamp of the body. If your eyes are good, your whole body will be full of light.

Matthew 6:22

To Nelleke, the apple of my eyes

CONTENTS

General introduction

Glaucoma is a progressive neurodegerative disease characterized by optic neuropathy and progressive visual field defects in which elevated intraocular pressure (IOP) is regarded as the major risk factor.[1-2] Other risk factors that have been consistently reported in the literature include age,[3-5] race, [6-9] family history,[10-12] myopia[13-15] and central corneal thickness.[16-18] Because IOP is – thus far - the only modifiable risk factor, therapeutic strategies are majorly targeted towards IOP reduction as a protective measure against optic nerve damage. However, elevated IOP alone cannot explain all observations. Glaucomatous damage can progress after IOP lowering, can also occur with normal IOP (normal tension glaucoma; NTG), and the IOP can also increase without any signs or damage to the visual field (ocular hypertension).[19-22] There is growing evidence in the literature that impaired blood flow and neuroprotection may also play an important role in the pathogenesis of glaucoma.[23-26]

Although there are several clinical presentations of glaucoma, the two most important variants are the open-angle glaucoma (OAG) and the angle closure glaucoma (ACG). This classification is based on the anatomy of the anterior chamber angle of the eye as viewed by gonioscopy. OAG is the most common form of glaucoma in the western world and the studies presented in this thesis are focused primarily on OAG. In OAG, there is an increased outflow resistance at the level of the trabecular meshwork resulting in an imbalance between the production and outflow of the aqueous humor – with an increase in IOP as the result. OAG affects about 45 million people worldwide and this number is expected to increase to approximately 59 million by the year 2020.[27-28] Because of the insidious nature of this disease, only half of the people with OAG in the developed countries are likely to be known to the healthcare system while the number is expected to be less for developing countries.[29] With the ageing population, OAG will eventually lead to increased medical consumption and costs.

In the United States, the total annual cost of therapeutic management of glaucoma is estimated to be nearly $2.5 billion.[30] In order to reduce the health burden of OAG, effective public health measures should be put in place. Before embarking on public health programs, knowledge of the risk factors is important for promoting awareness for prevention and early detection of OAG. Furthermore, a good understanding of these risk factors could facilitate the treatment and management of the progression of glaucomatous visual field loss – and help to unravel its pathophysiology.

The research presented in this thesis was designed to decipher the effect of some systemic medications and some other risk factors of OAG. The studies presented in the first three chapters are based on the Rotterdam Study, a prospective population-based cohort study of age related disorders in the elderly. Our study population comprised of 3939 of the original 7983 participants aged 55 years and older from the Rotterdam study. In **chapter 1** we studied whether the use of cholesterol-lowering drugs is associated with a reduced risk of OAG. In **chapter 2** we explored the association between corticosteroid use and incident OAG. In **chapter 3** we studied whether antithrombotics could reduce the risk of OAG.

The central theme of **chapters 4, 5 and 6** is the use of statistical methodology, systematic review and meta-analysis to elucidate other risk factors of OAG. **Chapter 4** describes the risk factors associated with visual field progression in OAG by comparing different statistical approaches in the Groningen Longitudinal Glaucoma Study (GLGS), a prospective cohort study in a clinical setting. **Chapter 5** presents a systematic review and meta-analysis to examine the association between myopia and OAG. **Chapter 6** reviews the current state of knowledge of the effect of systemic medications on OAG.

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Cholesterol-lowering drugs and incident open-angle glaucoma: a population-based cohort study

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ABSTRACT

Background: Open-angle glaucoma (OAG) is a progressive neurodegenerative disease that may lead to blindness. An elevated intraocular pressure (IOP) is its major risk factor. OAG treatment is currently exclusively directed towards the lowering of the IOP. IOP lowering does not prevent disease progression in all patients and thus other treatment modalities are needed. Earlier studies reported cholesterol-lowering drugs to have neuroprotective properties. The aim of this study was to determine the associations between the use of cholesterol-lowering drugs and incident OAG.

Methodology / Principal Findings: Participants in a prospective population-based cohort study underwent ophthalmic examinations, including IOP measurements and perimetry, at baseline and follow-up. The use of statins and non-statin cholesterol-lowering drugs (NSCLDS) was monitored continuously during the study. Associations between the use of cholesterol-lowering drugs and incident OAG and IOP at follow-up were analyzed with Cox regression and multiple linear regression respectively. During a mean follow-up of 9.8 years, 108 of 3939 eligible participants (2.7%) developed OAG. The hazard ratio for statin use was 0.54 (95% confidence interval 0.31-0.96; P=0.034) and for NSCLDS 2.07 (0.81-5.33; P=0.13). The effect of statins was more pronounced with prolonged use (hazard ratio 0.89 [0.41-1.94; P=0.77] for use two years or less; 0.46 [0.23-0.94; P=0.033] for use more than two years; P-value for trend 0.10). The analyzes were adjusted for age and gender, baseline IOP and IOP-lowering treatment, the family history of glaucoma, and myopia. There was no effect of statins on the IOP.

Conclusions / Significance: Long-term use of statins appears to be associated with a reduced risk of OAG. The observed effect was independent of the IOP. These findings are in line with the idea that statins have neuroprotective properties and may open a way to a new OAG treatment modality.

INTRODUCTION

Open-angle glaucoma (OAG) is a progressive neurodegenerative disease that leads to glaucomatous optic neuropathy and eventually, through glaucomatous visual field loss, to loss of sight. Together with age-related maculopathy it is the most common cause of irreversible blindness. An elevated intraocular pressure (IOP) is the major risk factor of OAG, and OAG treatment is currently exclusively directed towards the lowering of the IOP. However, OAG progression often continues despite an apparently sufficient reduction of the IOP. For that reason, the search for other OAG treatment modalities is a very active field of research.

Statins are selective inhibitors of 3-hydroxyl-3-methylglutaryl coenzyme A reductase (HMG-CoA) [1]. Currently, they are the most important lipid lowering medications for the treatment of hypercholesterolemia [2-4]. Previous studies have reported beneficial effects of statins on a variety of eye diseases, including age-related maculopathy, cataract and diabetic retinopathy [5-11]. Several observational studies addressed the effects of statins on OAG. Some reported a protective effect [12-14] whereas others did not [15,16]. Studies including animal models as well as clinical trials have reported neuroprotective properties of statins [17-22]. Since OAG is characterized by the loss of neuronal cells, the use of statins, and possibly non-statin cholesterol-lowering drugs (NSCLDs) as well, might modify the risk of OAG through neuroprotection. With the current recommendations of lower primary prevention thresholds [23,24], the use of statins and NSCLDs has increased markedly over the years [25]. For these reasons, it is expedient to clarify the associations between these drugs and OAG.

The aim of the present study was to determine the associations between the use of cholesterol-lowering drugs and incident OAG in a large prospective population-based cohort study.

METHODS

Ethics statement

All measurements were conducted after the Medical Ethics Committee of the Erasmus University Rotterdam had approved the study protocol and all participants had given written informed consent in accordance with the declaration of Helsinki.

Study population

The present study was performed as part of the Rotterdam Study, a prospective population-based cohort study investigating age-related disorders. The study population consisted of 7983 individual's aged 55 years and older living in the Ommoord district of Rotterdam, the Netherlands [26]. For this study, data from 3939 participants who did not have OAG (see below) at baseline and who completed at least one follow-up examination were used. The baseline examination took place from 1991 to 1993; follow-up examinations were performed from 1997 to 1999 and from 2002 to 2006.

Ophthalmic assessment

Participants underwent similar eye examinations at baseline and at the two follow-up rounds [27]. These examinations included refraction, measurement of the best-corrected visual acuity, Goldman applanation tonometry (Haag-Streit AG, Bern, Switzerland), fundoscopy, fundus photography of the posterior pole, simultaneous stereoscopic fundus photography of the optic disc, and visual field testing.

At each visit, three IOP measurements were taken on each eye and the median value of these three measurements was recorded [28]; the higher median of both eyes was used

in the analysis. The visual field of each eye was screened using a 52-point supra-threshold test that covered the central visual field with a radius of 24° (Humphrey Field Analyzer [HFA]; Carl Zeiss, Oberkochen, Germany) [27,29]. Visual field loss was defined as non-response to a light stimulus of 6 dB above a threshold-related estimate of the hill of vision in at least three contiguous test points, or four including the blind spot. In participants with reproducible abnormalities on supra-threshold testing, Goldmann perimetry (Haag-Streit AG, Bern, Switzerland; baseline and first follow-up) or full-threshold HFA 24-2 testing (second follow-up) was performed on both eyes. Visual field loss was considered to be glaucomatous visual field loss only if reproducible and after excluding all other possible causes [29,30].

Incident open-angle glaucoma

We defined incident OAG as no glaucomatous visual field loss in both eyes at baseline and glaucomatous visual field loss in at least one eye at follow-up [30]. All identified cases were examined by an experienced ophthalmologist (PTVMdJ and RCWW) who performed gonioscopy and a dilated ophthalmic exam. Cases with a history or signs of angle closure or secondary glaucoma were excluded.

Medication data

Data on cholesterol-lowering drugs prescriptions for all participants were obtained from seven fully automated pharmacies using a centralized computer network in the study district, from January 1, 1991, onward. This included the product name, Anatomical Therapeutic Chemical (ATC) code, duration of use, and the date of first prescription. Cholesterol-lowering drugs were classified as statins (C10AA; simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin) or NSCLDs (C10AB, C10AC, C10AD, C10A; fibrates, bile acid-binding resins or nicotinic acid and derivatives).

The use of cholesterol-lowering drugs was recorded as the number of days with use during follow-up. Usage before baseline was not taken into account.

Other covariates

Other covariates included age, gender, smoking, diabetes mellitus, cardiovascular diseases, the use of antihypertensive drugs, body mass index, total cholesterol, IOP, IOP-lowering treatment, and family history of glaucoma. All these covariates were measured at baseline. Smoking status was self reported and categorized as ever or never smoker. Data on diabetes mellitus and cardiovascular disorders such as angina pectoris, atrial fibrillation, myocardial infarction, heart failure, hypertension, and stroke were obtained from the participants through interviews, electrocardiogram readings, and non-fasting and fasting serum blood glucose levels. Diabetes was defined as the use of antidiabetic medication or by a non-fasting or post-load plasma glucose level above 200 mg/dl (11.1 mmol/l). Hypertension was defined as the use of antihypertensive medication for the indication of hypertension or as a systolic blood pressure of 140 mmHg or more, or a diastolic pressure of 90 mmHg or more. Body mass and height were measured at the research center. Total serum cholesterol was measured in non-fasting blood. IOP-lowering treatment was defined as the use of IOP-lowering medication or a history of glaucoma surgery or laser trabeculoplasty. The family history of glaucoma was determined by interviews and was considered positive if the participant reported a history of glaucoma in parents, siblings or offspring. Myopia was defined as a spherical equivalent refractive error of -4 D and more myopia [30]. Eyes with a cataract extraction before baseline were excluded from this analysis. In cases with one eye with incident OAG, the refraction of that eye was used. In participants without OAG or OAG in both eyes, the refraction of a random eye was used.

Statistical analysis

Differences in baseline characteristics between participants with and without incident OAG and differences in baseline characteristics between cholesterol-lowering drug users and non-users were evaluated using chi-square tests for categorical variables and t-tests for normally distributed continuous variables. To determine the associations between the use of cholesterol-lowering drugs and incident OAG, the use of statins or NSCLDs was initially defined as any use during follow-up and the associations were initially analyzed with chi-square tests. Subsequently, a Cox proportional hazards model was used to calculate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the associations between the use of statins or NSCLDs and incident OAG. Follow-up duration was used as the time axis in the model. For participants without incident OAG, the follow-up duration was counted from the baseline visit to the last visit with reliable perimetry. For incident OAG cases, the follow-up ended at the first visit in which glaucomatous visual field loss was detected. The cholesterol-lowering drugs, age and gender, and other covariates with $P<0.20$ in the univariate comparisons were included in the multivariate analysis. Subsequently, the cholesterol-lowering drugs, age and gender, and other covariates with $P<0.05$ in the initial multivariate model were included in the final model. The use of cholesterol-lowering drugs was entered in the model as any use during follow-up. To allow for the evaluation of a possible dose-response relationship, we also performed analysis after making three nominal categories based on the duration of medication use, being no use, cumulative use during two years or less, and cumulative use during more than two years (see Discussion section). The dose-response relationship was evaluated with a trend test. To explore the influence of cholesterol-lowering drugs on the IOP, we conducted a multiple linear regression analysis with IOP at follow-up as the dependent variable. This analysis was adjusted for IOP-lowering treatment at follow-up and for the same covariates as the final Cox model except for baseline IOP and IOP-lowering treatment at baseline.

RESULTS

During a mean follow-up of 9.8 years, 108 of 3939 eligible participants (2.7%) developed OAG. Table 1A depicts the baseline characteristics of the study population for participants with and without incident OAG. Participants with incident OAG were older, more often male, more often had a positive family history of glaucoma, and more often had myopia. They also had a higher IOP and more frequently received IOP-lowering treatment. There was no difference between the groups regarding total serum cholesterol levels. Table 1B shows the baseline characteristics for cholesterol-lowering drug users and non-users. Participants using cholesterol-lowering drugs were younger, smoked less frequently and more often had diabetes mellitus, a myocardial infarction or hypertension. They also used more often antihypertensive drugs and had a higher total serum cholesterol level and a slightly higher IOP.

Table 2 presents the results of the univariable analyses for the use of statins and NSCLDs at any time during follow-up. These univariable comparisons revealed no significant differences between participants with and without incident OAG. Amongst the 811 participants using statins at any time during follow-up, the median duration of use was 1424 days, with a range from 8 to 4114 days; amongst the 113 participants using NSCLDs, the median duration of use was 298 days, with a range from 7 to 3544 days.

Table 3 presents the final multivariate model, adjusting for age and gender, baseline IOP and IOP-lowering treatment, the family history of glaucoma, and myopia. Participants using statins had a significant risk reduction (HR 0.54; 95% CI 0.31 to 0.96; P=0.034). The use of NSCLDs was not significantly associated with incident OAG (HR 2.07; 95% CI 0.81 to 5.33; P=0.13). There was a trend towards a reduced risk of incident OAG with prolonged statin use.The HR was 0.89 (95% CI 0.41 to 1.94, P=0.77) for use during two

years or less and 0.46 (95% CI 0.23 to 0.94, P=0.033) for use during more than two years. The overall P-value for trend was 0.10.

The protective effect of statins could be either caused by an IOP-lowering effect of statins or by a direct protective effect of statins on the neural tissue. To differentiate between these two possibilities, we conducted a multiple linear regression analysis with IOP at follow-up as the dependent variable. Table 4 shows the results. As can be seen in this table, there was no significant IOP-lowering effect of statins.

DISCUSSION

In this large prospective population-based study, the use of statins was associated with a reduced risk of OAG. This effect was independent of the IOP. The risk reduction tended to increase with the duration of cumulative use, which supports the observed association, but this trend did not reach statistical significance. The use of NSCLDs was not associated with the development of OAG.

The association between the use of statins and OAG we found is consistent with the results of McGwin et al. (odds ratio 0.60; 95% CI 0.39 to 0.92) [12]. They performed a nested case-control study in a clinical administrative database. In contrast, Owen et al. found no evidence for a protective effect of statins (odds ratio 0.97; 95% CI 0.88 to 1.06) [15]. They employed a case-control study design in a primary care database. Similarly, Iskedjidan et al. did not find a significant association between the use of statins and OAG [16]. They performed a retrospective population-based evaluation in an administrative prescription claims database. The designs of the latter two studies might have complicated the classification of OAG, and the resulting misclassification might have biased the effect estimate. The trend of the effect seen in our study is consistent with

previously published studies. McGwin et al. reported a significant reduction in the risk of OAG in patients using statins for more than 23 months [12]. De Castro et al. reported that the use of statins was associated with a slower progression of glaucomatous optic nerve atrophy [14]. In their clinical retrospective cohort study, patients using statins for two years showed less optic nerve head changes than patients not using statins. Nagaoka, et al studied the effect of statins on the retinal circulation and the IOP [31]. They found an IOP decrease after the administration of statins. At first sight, this seems to corroborate with our findings. However, our data suggested the protective effect of statins to be IOP independent. A possible explanation for this discrepancy might be that they studied the effects of statins up to one week after the initial administration whereas we found the most pronounced effect in those OAG cases that used statins for more than two years. Leung et al. reported that the use of simvastatin was associated with visual field stabilization in patients with normal tension glaucoma (relative risk 0.36; 95% CI 0.14 to 0.91; P=0.030) [13]. In their prospective cohort study, 256 patients with normal tension glaucoma of whom thirty-one were taking simvastatin and 225 were not taking simvastatin were followed-up for 36 months.

The use of NSCLDs was not associated with incident OAG in our study. This result contradicts the result of the study by McGwin et al. who found a protective effect among those who used NSCLDs (odds ratio 0.59; 95% CI 0.37 to 0.97) [12]. This discrepancy might be attributed to the low number of users of NSCLDS in our study, as depicted by the wide CIs.

Strengths of our study include its prospective design, the large number of participants, the long follow-up period and the population-based setting, which minimizes selection bias. An inextricable limitation of the population-based design is the limited number of OAG cases – due to the low prevalence of OAG - and the limited number of participants using NSCLDs. Information bias was prevented by prospectively collected and completely

automated pharmacy records of all prescriptions. Although this approach guarantees accurate prescription data, it cannot be guaranteed that all participants actually took their medication. Such exposure misclassification is usually similar in cases and controls and leads to conservative risk estimates. Hence, it may have contributed to the lack of effect of NSCLDs, but not to the protective effect of statins.

Several other factors have been reported to be a risk factor for the incidence of OAG, including myopia [32], pseudoexfoliation [33], central corneal thickness [34], and age [30]. Of these factors, only pseudoexfoliation and age may be associated with statin use and may thus be confounding factors in our analysis [35-37]. Pseudoexfoliation is relatively rare in the Netherlands and in our study population (which might or might not be due to underreporting) – hampering a meaningful adjustment for pseudoexfoliation in our analysis. However, the absence of adjustment should have resulted in an increased risk whereas we found a protective effect. Age is associated with statin use but we adjusted our models for that. Age as a linear covariable – as we did – might result in under-adjustment, but in that case an increased risk should have been the result, not a protective effect. We included only participants aged 55 years and older. This is not a limitation for this specific study question, as both statin use at younger age is relatively rare and the prevalence of OAG below 55 years of age is very low (0.1-0.2%; to be compared to 1-2% above 55 years of age [27]. Finally, myopia appeared to occur – presumably by chance – slightly more frequent amongst cholesterol-lowering drug users compared to non-users (P=0.063; Table 1B) and was included in the final model.

A possible limitation of this study is potential misclassification of exposure. However, such misclassification will be random because the outcome is – inextricably - gathered irrespective of exposure status. To appreciate this approach, it is important to realize that glaucoma development often takes more than a decade and cannot be detected in the earliest stages. Some factors slow down or accelerate the disease development, and thus

make it less likely or more likely that the disease can be detected at a certain point in time (being our follow-up examination). Cumulative exposure stratified into biologically plausible nominal categories as we used in our analyses is the best proxy for studying the overall influence of the use of medication on the rate of glaucoma development during follow-up. Details of this technique were published earlier [38]. Because the exposure misclassification is random, it will tend to bias the results towards the null hypothesis. This might mean that the significant protection we found is an underestimation of the true effect.

Our finding of a protective effect of statins may offer potential therapeutic possibilities for OAG or its prevention. We showed the effect to be independent of the IOP. Hence, the protective effect of statins could be caused by lowering serum cholesterol or by (other) neuroprotective properties of statins on neuronal cells, as mentioned in the Introduction section [17-22]. Our incident OAG cases did not have an elevated serum cholesterol level at baseline (Table 1), but that observation does not exclude a beneficial effect of a further lowering of this level - cardiovascular trials have shown beneficial effects of further lowering cholesterol levels even if initially already within normal limits [39,40]. Studies with serum cholesterol level monitoring during follow-up should enable the uncovering of more details of the mechanism underlying the protective effect of statins. Given the current level of evidence and the fact that statins are widely available and thoroughly investigated drugs, a neuroprotective OAG treatment could become reality and a randomised clinical trial seems to be a viable next step.

In conclusion, we confirmed that statins appear to have a protective effect on OAG. Due to our study design, we were able to add that this protective effect is IOP independent. Hence, statins should be further explored as a new class of medications for the treatment of OAG, especially for those patients in whom disease progression continues despite an apparently sufficient IOP reduction.

Table 1 Baseline characteristics of participants with and without incident open-angle glaucoma (A) and of cholesterol-lowering drug users (either statins or NSCLDs, or both) and non-users (B), with univariable comparisons (mean values with standard deviation between brackets unless stated otherwise)

A	Incident open-angle glaucoma (N=108)	No incident open-angle glaucoma (N=3831)	P-value
Age (year)	684(7.1)	65.7(6.8)	<0.001
Gender (%female)	49.1	58.7	0.046
Smoking (%)	33.3	33.4	0.98
Diabetes mellitus (%)	8.4	6.9	0.54
Angina pectoris (%)	1.9	3.1	0.46
Atrial fibrillation (%)	2.8	2.1	0.63
Myocardial infarction (%)	13.2	9.7	0.23
Heart failure (%)	0.9	1.2	0.81
Hypertension (%)	52.9	47.1	0.49
Blood pressure lowering drugs (%)	28.0	26.0	0.63
Stroke (%)	2.8	1.2	0.16
Body mass index (kg/m^2)	25.8(2.9)	26.3(3.5)	0.12
Total cholesterol (mmol/l)	6.5(1.1)	6.7(1.2)	0.17
IOP (mmHg)	17.3(4.7)	15.0(3.1)	<0.001
IOP-lowering treatment (%)	15.7	2.3	<0.001
Family history of glaucoma (%)	16.7	8.1	0.002
Myopia	9.5	4.9	0.033

B	CLD users (N=848)	Non-users (N=3091)	P-value
Age	64.3(5.5)	66.1(7.1)	<0.001
Gender (%female)	56.6	58.9	0.23
Smoking (%)	27.5	35.0	<0.001
Diabetes mellitus (%)	10.2	6.1	<0.001
Angina pectoris (%)	3.8	2.8	0.15
Atrial fibrillation (%)	2.4	2.1	0.57
Myocardial infarction (%)	15.3	8.2	<0.001
Heart failure (%)	1.2	1.2	0.97
Hypertension (%)	58.7	47.1	<0.001
Blood pressure lowering drugs (%)	38.3	22.6	<0.001
Stroke (%)	1.4	1.2	0.65
Body mass index (kg/m^2)	26.5(3.5)	26.2(3.5)	0.055
Total cholesterol (mmol/l)	7.4(1.3)	6.5(1.1)	<0.001
IOP (mmHg)	15.3(3.2)	15.0(3.2)	0.044
IOP-lowering treatment (%)	2.0	2.9	0.18
Family history of glaucoma (%)	9.7	8.0	0.13
Myopia	6.3	4.7	0.063

CLD= cholesterol-lowering drugs; NSCLDs= non-statin cholesterol-lowering drugs; IOP = intraocular pressure.

Table 2 Univariable analyses of the use of cholesterol-lowering medication at any time during follow-up and the development of open-angle glaucoma

	Incident open-angle glaucoma (N=108)	No incident open-angle glaucoma (N=3831)	P-value
Statins (n[%])	16(14.8)	795(20.8)	0.13
NSCLDs (n[%])	5(4.6)	108(2.8)	0.27

NSCLDs = non-statin cholesterol-lowering drugs.

Table 3 Final multivariable model of the risk of developing open-angle glaucoma for cholesterol-lowering medication

	Hazard ratio	95% confidence interval	P-value
Statins	0.54	0.31-0.96	0.034
NSCLDs	2.07	0.81-5.33	0.13
Age (per year)	1.07	1.04-1.10	<0.001
Gender (female)	0.56	0.38-0.83	0.004
IOP (per mmHg)	1.12	1.08-1.18	<0.001
IOP treatment	3.39	1.82-6.32	<0.001
Family history of glaucoma	1.85	1.08-3.15	0.024
Myopia	2.30	1.19-4.43	0.013

NSCLDs = non-statin cholesterol-lowering drugs; IOP = intraocular pressure.

Table 4 Multiple linear regression analysis with intraocular pressure at follow-up as the dependent variable

	beta	95% confidence interval	P-value
Statins	-0.006	-0.262 - 0.249	0.96
Age (year)	-0.011	-0.026 - 0.005	0.18
Gender (female)	-0.269	-0.479 – -0.060	0.012
IOP-lowering treatment at follow-up	1.761	1.340 - 2.181	<0.001
Family history of glaucoma	0.378	0.001 - 0.755	0.050
Myopia	0.597	0.124 - 1.069	0.013

IOP = intraocular pressure.

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Corticosteroids and open-angle glaucoma in the elderly: a population-based cohort Study

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ABSTRACT

Background: Data on corticosteroid-induced open-angle glaucoma in population-based cohort study in the elderly are limited.

Objective: To determine whether there is an association between corticosteroid use and the incidence of open-angle glaucoma in the general elderly population.

Methods: In a prospective population-based cohort study among 3939 participants aged 55 years and above, ophthalmic examinations including measurement of the intraocular pressure (IOP), assessment of the optic nerve head and perimetry were performed at baseline and after an average follow-up duration of 9.8 years. The use of corticosteroids was monitored continuously during follow-up. Corticosteroids were stratified into five groups: ophthalmic steroids, inhaled steroids, nasal steroids, oral steroids and steroid ointments. Associations between the use of corticosteroids and incident open-angle glaucoma were assessed using logistic regression models; associations between the use of corticosteroids and IOP at follow-up were analyzed with multiple linear regression.

Results: During follow-up, 108 participants (2.8%) developed glaucomatous visual field loss. The odds ratio of the use of ophthalmic steroids was 1.04 (95% confidence interval[CI] 0.66-1.65; *P*=0.86), inhaled steroids 0.79 (0.42-1.48; *P*=0.46), nasal steroids 1.26 (0.74-2.13; *P*=0.40), oral steroids 1.03 (0.65-1.64; *P*=0.89), and steroid ointments 0.70 (0.47-1.05; *P*=0.086). These analyzes were adjusted for age, gender, high myopia and family history of glaucoma. The use of corticosteroids was not associated with an increased IOP at follow-up.

Conclusions: The use of any class of steroids was not associated with the incidence of open-angle glaucoma in this population of elderly.

INTRODUCTION

The usage of corticosteroids for inflammatory disease dates back to the 1950's.[1] Currently, corticosteroids are applied successfully in many fields of medicine, including ophthalmology, and belong to the most frequently prescribed drugs.[2] However, they can produce a plethora of adverse ocular effects such as corticosteroid-induced glaucoma[3-8] and cataract.[9-11]

Individuals who develop an increase in intraocular pressure (IOP) after steroid therapy are referred to as steroid responders.[12-14] In the literature, several risk factors have been identified for steroid responders. They include the presence of primary open-angle glaucoma (OAG)[15] or its family history,[16-18] age,[19-21] diabetes mellitus,[22] high myopia,[23] and rheumatoid arthritis.[24] Glaucoma may develop if the IOP elevation is of sufficient magnitude and duration. In that case, a progressive degeneration of the optic nerve and a corresponding decline of the visual field may ensue: steroid-induced glaucoma.[25-27]

The ocular hypertensive response in steroid–induced glaucoma has been shown to occur with ophthalmic steroids,[28-30] inhaled steroids,[31-33] nasal steroids,[31,34] oral steroids,[35-37] and steroid ointments.[38-41] Most of these studies are case reports or small case series; two studies were performed in health-insurance-plan databases.[31,37] In population-based epidemiology, steroid-induced glaucoma has only been addressed by the Blue Mountains eye study.[33] They did not find any harmful effect for ophthalmic or oral steroids; for inhaled steroids, an effect was seen in a subgroup of patients with a positive family history of glaucoma.[33] Hence, it is largely unknown if the adverse effects of steroids are limited to a few susceptible individuals or contribute to the burden of OAG in the population. The aim of this study was to explore the associations between steroid use and incident OAG in a population-based setting.

METHODS

Study population

The present study was performed as part of the Rotterdam Study, a prospective population-based cohort study of age-related disorders. The study population consisted of 7983 individuals aged 55 years and older living in a district of Rotterdam, the Netherlands.[42] For this study, data from 3939 participants who did not have glaucoma at baseline and who completed at least one follow-up examination were used. The baseline examination took place from 1991 to 1993; follow-up examinations were performed from 1997 to 1999 and from 2002 to 2006. All measurements were conducted after the Medical Ethics Committee of the Erasmus University Rotterdam had approved the study protocol and all participants had provided written informed consent in accordance with the declaration of Helsinki.

Ophthalmic assessment

Participants underwent similar eye examinations at baseline and at the two follow-up rounds. These examinations included refraction, measurement of the best corrected visual acuity, Goldmann applanation tonometry (Haag-Streit AG, Bern, Switzerland), fundoscopy, fundus photography of the posterior pole, simultaneous stereoscopic fundus photography of the optic disc, and visual field testing.

At each visit, three intraocular pressure (IOP) measurements were taken on each eye and the median value of these three measurements was recorded.[43] In the analyzes we used the highest median of the baseline IOP measurements of both eyes. The visual field of each eye was screened using a 52-point supra-threshold test that covered the central visual field with a radius of 24° (Humphrey Field Analyzer [HFA]; Carl Zeiss, Oberkochen,

Germany).[44,45] Visual field loss was defined as non-response to a light stimulus of 6 dB above a threshold-related estimate of the hill of vision in at least three contiguous test points, or four including the blind spot. In participants with reproducible abnormalities on supra-threshold testing, Goldmann perimetry (Haag-Streit AG, Bern, Switzerland; baseline and first follow-up) or full-threshold HFA 24-2 testing (second follow-up) was performed on both eyes. Visual field loss was considered to be glaucomatous visual field loss only if reproducible and after excluding all other possible causes.[44,46]

Incident open-angle glaucoma

We defined an incident OAG case as a participant with no glaucomatous visual field loss in both eyes at baseline and glaucomatous visual field loss in at least one eye at follow-up.[46] Cases with a history or signs of angle closure (gonioscopy was performed in all identified cases) or secondary glaucoma (except for steroid-induced glaucoma) were excluded.

Medication data

Data on corticosteroid prescriptions for all participants were obtained from seven fully automated pharmacies using a centralized computer network in the Ommoord district of Rotterdam, the Netherlands, from January 1, 1991, onward. This included the product name, Anatomical Therapeutic Chemical (ATC) code, number of prescriptions, and the date of first prescription. Corticosteroids were classified as ophthalmic steroids (S01BA, S01CA), inhaled steroids (R03BA), nasal steroids (R01AD), oral steroids (ATC codes H02AB, H02BX), and steroid ointments (D07AA, D07AB, D07AC, D07AD). The number of prescriptions during follow-up was used as a proxy for cumulative dose. Usage before baseline was not taken into account.

Other covariables

Other covariables included age, gender, diabetes mellitus, rheumatoid arthritis, IOP, IOP-lowering treatment, family history of glaucoma, and myopia. All covariables were measured at baseline. Information on the presence of diabetes mellitus was elicited from the participants through interviews and blood samples. Diabetes was defined as the use of antidiabetic medication or by a non-fasting or post-load plasma glucose level above 200 mg/dL (11.1 mmol/L). The presence of rheumatoid arthritis was assessed using The Stanford Health Assessment Questionnaire based on the International Classification of Impairments, Disabilities and Handicaps guidelines.[47] IOP-lowering treatment was defined as the use of IOP-lowering medication or a history of glaucoma surgery or laser trabeculoplasty. The family history of glaucoma was determined by interviews and was considered positive if the participant reported a history of glaucoma in parents, siblings or offspring. For myopia, the spherical equivalent refractive error was calculated as sphere+(cylinder/2) in diopters (D). Refraction was stratified into three categories: -4 D and more myopia (high myopia), between (but not including) -4 and 0 D (low myopia), and 0 D and a positive refractive error. Eyes with a cataract extraction before baseline were excluded from this analysis. In cases with one eye with incident OAG, the refraction of that eye was used. In participants without OAG or OAG in both eyes, the refraction of a random eye was used.

Statistical analyses

Differences in baseline characteristics between participants with and without incident OAG were evaluated using chi-square tests for categorical variables and t-tests for normally distributed continuous variables. The use of corticosteroids was initially categorized as any use during follow-up and analyzed with chi-square tests. Associations between incident OAG and the use of corticosteroids were assessed using logistic

regression models. Effect estimates were presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). In addition to the five groups of steroids, all factors that were associated with incident OAG in the univariate analyses at a *P*-value of 0.20 or less and age and gender were included in the multivariate models. Collinearity between the various groups of steroids was assessed by calculating Spearman's correlation coefficients. Furthermore, multicollinearity diagnostic statistics produced by linear regression analysis was carried out using PROC REG with options variance inflation factor (VIF) and tolerance (TOL).[48] Because many participants got only a few prescriptions during the entire follow-up period (see Results section), we evaluated dose-response relationships by stratifying steroid use as no steroid use, use less than or equal to the median number of prescriptions and use more than the median number of prescriptions, where the median number of prescriptions was determined within the subgroup of steroid users. To explore direct effects of the steroids on the IOP, we conducted a multiple linear regression analysis with IOP at follow-up as the dependent variable. In this analysis, steroid use was defined as use more than the median number of prescriptions; the analysis was adjusted for the same covariables as the logistic regression models except for baseline IOP and IOP-lowering treatment at baseline. All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). A *P*-value of 0.05 or less was considered statistically significant.

RESULTS

During a mean follow-up of 9.8 years (range 5.0-13.9 years), 108 participants (2.7%) developed OAG. Table 1 depicts the baseline characteristics of the study population. Participants with incident OAG were older, more often male, had a higher IOP at baseline, more frequently received IOP-lowering treatment, and more often had high myopia or a positive family history of glaucoma.

Table 2 presents the results of the univariable analyses for the use of steroids at any time during follow-up, for all five groups of steroids. There were no significant differences between participants with and without incident OAG. The median (95% central range) of the number of prescriptions per participant as determined within the subgroup of steroid users was 2 (1-17) for ophthalmic steroids, 7 (1-55) for inhaled steroids, 2 (1-31) for nasal steroids, 2 (1-31) for oral steroids and 3 (1-37) for steroid ointments.

In the multivariable logistic regression analysis for all corticosteroid classes in our study population, none of the classes of steroids showed a significant association with incident OAG. This analysis was adjusted for age, gender, baseline IOP, IOP treatment, positive family history of glaucoma and high myopia. Formally speaking, baseline IOP and IOP-lowering treatment are not confounding factors in the association between steroid use and OAG. Moreover, since steroid use already at or before baseline might be more likely in those participants who used steroids during follow-up, these two variables might even be in the causal pathway. Table 3 shows the results of the multivariable logistic regression analysis after removing IOP and IOP-lowering treatment from the model. The risk of developing OAG remained insignificant for all classes of steroids.

We repeated the analysis as presented in Table 3 after recoding the use for all classes of steroids in no use, use smaller than or equal to the median number of prescriptions and used more than the median number of prescriptions. Table 4 presents the results. The risk of developing OAG was not significant for any of the steroid classes.

Family history, rheumatoid arthritis, high myopia and diabetes have been reported to be risk factors for steroid responders (see Introduction). In our study, only family history (P=0.002) and high myopia (0.033) showed a significant univariable association with OAG (Table 1). Interaction analyses with each class of steroid showed no significant effects for either the family history or high myopia.

In order to rule out the possibility of collinearity, we computed the correlation coefficients between the various steroid classes. These coefficients were consistently less than 0.5. Furthermore, we calculated the 'variance inflation factor' (VIF) for collinearity of each independent variable. None of the VIFs was larger than 2.5. This indicates that the steroid classes may be analysed simultaneously in a single multivariable model.

Table 5 shows the results of the multiple linear regression analysis with IOP at follow-up as the dependent variable. As can be seen in this table, there was no significant IOP-lowering effect for any of the steroid classes.

DISCUSSION

In the elderly, the use of corticosteroids - in whatever dosage form - appears not to be associated with an increased risk of incident OAG at the population level.

The lack of association between the use of ophthalmic steroids and OAG in our study is consistent with the results of the population-based Blue Mountains eye study.[33] In contrast, a positive association between the use of topical ophthalmic steroids and OAG (OR 1.72; 95% CI 1.55-1.92) was reported in a case-control study performed in a health-insurance-plan database.[37] The study population of that study consisted of 9793 glaucoma cases and 38325 controls, with a mean age of 74.9 and 74.7 years for cases and controls respectively. The small number of users amongst the cases in our study might have hampered the finding of a significant association between ophthalmic steroid use and OAG. This is illustrated by the fact that our 95% CI for ophthalmic steroids (0.66-1.65; Table 3) overlapped with that of Garbe et al. (1.55-1.92). However, another explanation of the discrepancy between the results of our study and that of Garbe et al. might be a selection bias in their case-control design.

Individuals on ophthalmic steroid therapy are more likely to visit an ophthalmologist and are therefore more likely to be diagnosed with ocular hypertension or OAG. Confounding by indication may also play a role - ophthalmic steroids may be prescribed as part of glaucoma treatment (laser or surgery). The cross-sectional design of Garbe et al. might be more sensitive to this type of bias than our longitudinal design.

The lack of association between inhaled and nasal steroids and OAG we found seem to agree with another study by Garbe et al.[31] In that case-control study, the use of inhaled and nasal steroids was not associated with an increased risk of ocular hypertension or glaucoma. However, they found an association in a subgroup of subjects with a prolonged administration of high doses of inhaled steroids. The small number of incident OAG cases with inhaled steroid use in our study limited the value of subgroup analysis, but our 95% CI for inhaled steroids for the subgroup with more than the median number of prescriptions (0.28-1.98; Table 4) appeared to overlap with that of Garbe et al. (1.01-2.06). In agreement with our findings, the Blue Mountains eye study did not find an association between inhaled steroid use and OAG. However, they found a positive association between inhaled steroids and elevated IOP or OAG in a subgroup of subjects with a positive family history of glaucoma.[33] In our data, the interaction between the family history of glaucoma and the use of inhaled steroids was not significant. As explained by the authors, a possible explanation for this finding by the Blue Mountain eye study might be due to the fact that they collected limited information on steroid use. The resulting missing data for steroid use might have induced a bias if the participants with and without missing data on corticosteroid use had different characteristics (differential misclassification).

The use of oral steroids was also not associated with OAG in our study. The Blue Mountains eye study reported, in agreement with our finding, no significant association between the use of oral steroids and glaucoma in a population-based cross-sectional

study.[33] The association between oral steroids and OAG was also investigated in the abovementioned health-insurance-plan database case-control study.[37] In that study, current use of oral steroids was shown to increase the risk of ocular hypertension or OAG (OR 1.41; 95% CI 1.22-1.63). As mentioned above, the discrepancy between this finding and our results might be either attributed to a selection bias in their case-control design (false-positive association) or to the limited number of incident OAG cases using oral steroids in our data (false-negative association). Here, our 95% CI (0.65-1.64) also overlapped with that of Garbe et al. (1.22-1.63).

Finally, we found no significant association between the use of steroid ointments and OAG. Thus far, this seems not to have been investigated in any other large study, but several case reports have raised concerns about a possible association between steroid ointments use and glaucoma.[6-8,38-41,49-52,57-59] Steroid ointments may reach the eye via systemic absorption through the skin, they may be directly absorbed into the eye if intentionally used at the lid margins, or contamination of the eye may occur through the hand after topical application on other locations.

One possible explanation for the absence of any significant effect in our study could be the simultaneous assessment of several groups of steroids in a single multivariable model. Although the collinearity analysis suggested that our approach was justified, we repeated our multivariable analysis as presented in Table 3, with one group of steroids at a time. None of the steroid types showed a significant change in OR. We also explored the association between any steroid use and incident OAG by combining all steroid groups (ophthalmic, inhaled, nasal, oral and steroid ointments) into a single variable. There was no significant association (OR 1.15; 95% CI 0.72-1.85; adjusted for age, gender, family history and myopia). It is also possible that the sensitivity to steroids is age dependent. Since most diseases that require a longstanding steroid treatment start well before the age of 55, a possible explanation for the absence of any clear effect of

corticosteroids in our study population could be that those who are sensitive to steroids develop OAG before the age of 55 and are therefore not represented in our study cohort because we excluded individuals with glaucoma at baseline. In the literature, we found 41 case reports together reporting on 74 cases.[3-8,28-30,32,34-36,38-41,49-72] The median age of these cases was 32 years, with a range from 3 weeks to 80 years. Sixty of the 74 cases (81%) had an age below the youngest age of 55 years of our study cohort. In the 74 cases, the OAG was presumed to be caused by ophthalmic steroids in 38 cases,[3-5,8,28-30,53-55,60-62,66-69,71,72] by inhaled steroids in one case,[32] by nasal steroids in two cases,[34] by oral steroids in eight cases,[35,36,53,56,63-65] and by steroid ointments in 31 cases.[6-8,38-41,49-52,57-59] Armaly reported that steroid-induced effects were greater in older eyes compared with younger eyes and in glaucomatous eyes compared with non-glaucomatous eyes.[21,54,55] Lam et al. reported that the ocular hypertensive response to topical steroids is dose and age dependent with a peak in children aged six years or younger compared with children older than six.[73] Yamashita et al. reported on the use of systemic corticosteroids in five children with acute lymphoblastic leukemia who were followed up to age six. In these children, the steroid use was associated with an IOP elevation that was strong enough to develop glaucomatous optic neuropathy.[19] Kwok et al. performed a randomized control trial in 19 patients. In their study, 56% of the studied children were high responders to topical dexamethasone and they concluded that the ocular-hypertensive response to topical dexamethasone in children occurs more frequently, more severely, and more rapidly than that reported in adults.[20] Jones and Rhee suggested in a review article that age is a risk factor which appears to occur in a bimodial distribution peaking at an age of six years and at late adulthood.[25] Finally, in a recently published nested case-control study using databases from the Quebec provincial health insurance plan, Gonzalez et al reported that current use and continuous use of inhaled steroids did not result in an increased risk of glaucoma or raised intra-ocular pressure requiring treatment in subjects aged 66 years and older.[74]

Obviously, the effect of age is difficult to address, since those who are classified as steroid responder at young age may be glaucoma patients at old age.

The strength of the current study is its design, a prospective population-based cohort study. This design minimizes the risk of biased results. Further, the use of a fully automated system for prescription-only drugs ensures very accurate and complete data since it by-passes the need of participants correctly remembering and reporting their past and present medication use. Obviously, although, very accurate prescription data were available, it cannot be guaranteed that all participants actually took their medication. Moreover, especially with ointments, it is difficult to estimate the dosage reliably from the number of prescriptions. A limitation of the population-based design is the limited number of incident OAG cases and the limited numbers of users in some corticosteroid classes. The number of cases could be increased by including our possible OAG cases, being those who had reached the 97.5th percentile of the disc-area adjusted cup-to-disc ratio in at least one eye at follow-up but did not have glaucomatous visual field loss.[46] This might improve the statistical power but might also induce random misclassification of the outcome measure. Adding these cases did not change any of the results presented in this study significantly (data not shown). Finally, we were unable to investigate whether the risk varies with age because our study cohort included only individuals aged 55 years and older (see previous paragraph).

In conclusion, steroid-induced glaucoma, albeit a dangerous and potentially blinding entity in some groups of patients, does not contribute significantly to the glaucoma burden in the general elderly population.

Table 1: Baseline characteristics of participants with and without incident open-angle glaucoma (mean values with standard deviation in brackets unless stated otherwise)

		Incident open-angle glaucoma (N=108)	No open-angle glaucoma (N=3831)	P-value
Age (year)		68.4(7.1)	65.7(6.8)	<0.001
Gender (n[%] female)		53(49.1)	2248(58.7)	0.046
Diabetes mellitus (n[%])†		9(8.4)	264(6.9)	0.54
Rheumatoid arthritis (n[%])‡		3(2.8)	81(2.1)	0.65
IOP (mmHg)		17.3(4.7)	15.0(3.1)	<0.001
IOP-lowering treatment (n[%])		17(15.7)	88(2.3)	<0.001
Positive family history of glaucoma (n[%])*		18(16.7)	311(8.1)	0.002
Myopia (n[%])**	Low	22(21.0)	770(20.3)	0.88
	High	10(9.5)	186(4.9)	0.033

IOP = intraocular pressure; † = 30 participants had missing data on diabetes mellitus; ‡ = 33 participants had missing data on rheumatoid arthritis; * = 8 participants had missing data on their family history of glaucoma; ** = 47 participants had missing data on myopia due to prior cataract surgery.

Table 2: Univariable analyses of the use of each class of corticosteroids at any time during follow-up and the development of incident open-angle glaucoma (number of participants with percentage in brackets)

	iOAG (N=108)	No -OAG (N=3831)	Odds ratio	95% confidence interval	P-value
Ophthalmic steroids	30(27.8)	848(22.1)	1.35	0.88-2.08	0.17
Inhaled steroids	13(12.0)	559(14.6)	0.80	0.45-1.44	0.46
Nasal steroids	18(16.7)	603(15.7)	1.07	0.64-1.79	0.79
Oral steroids	31(28.7)	1142(29.8)	0.95	0.62-1.45	0.80
Steroid ointments	51(47.2)	2100(54.8)	0.74	0.50-1.08	0.12

iOAG= incident open-angle glaucoma

Table 3: Multivariable analysis of the risk of developing incident open-angle glaucoma for all classes of corticosteroids adjusted for age, gender, positive family history of glaucoma and high myopia

	Odds ratio	95% Confidence Interval	P-value
Ophthalmic steroids	1.04	0.66-1.65	0.86
Inhaled steroids	0.79	0.42-1.48	0.46
Nasal steroids	1.26	0.74-2.13	0.40
Oral steroids	1.03	0.65-1.64	0.89
Steroid ointments	0.70	0.47-1.05	0.086
Age (per year)	1.06	1.04-1.09	<0.001
Gender (female)	0.63	0.43-0.93	0.022
Positive family history of glaucoma	2.24	1.31-3.84	0.003
High myopia	2.22	1.13-4.38	0.021

Table 4: Dose-response effects: multivariable analysis of the risk of developing incident open-angle glaucoma for all classes of corticosteroids for use less than or equal to the median number of prescriptions (upper row) and use more than the median number of prescriptions (lower row), adjusted for age, gender, positive family history of glaucoma and high myopia

	Odds ratio	95% Confidence Interval	P-value
Ophthalmic steroids	0.81	0.44-1.46	0.48
	1.52	0.84-2.77	0.17
Inhaled steroids	0.95	0.45-2.02	0.89
	0.74	0.28-1.98	0.55
Nasal steroids	1.27	0.66-2.44	0.47
	1.24	0.55-2.78	0.61
Oral steroids	1.34	0.80-2.23	0.27
	0.68	0.32-1.45	0.31
Steroid ointments	0.82	0.51-1.30	0.39
	0.60	0.35-1.01	0.055
Age (per year)	1.07	1.04-1.09	<0.001
Gender (female)	0.62	0.42-0.92	0.017
Positive family history of glaucoma	2.24	1.31-3.85	0.003
High myopia	2.24	1.13-4.42	0.020

Table 5: Multiple linear regression analysis with intraocular pressure at follow-up as the dependent variable

	beta	95% Confidence Interval	P-value
Ophthalmic steroid	0.490	-0.336 to 0.433	0.80
Inhaled steroids	-0.348	-0.792 to 0.096	0.13
Nasal steroids	0.159	-0.268 to 0.586	0.47
Oral steroids	-0.212	-0.539 to 0.115	0.20
Steroid ointments	0.006	-0.234 to 0.246	0.96
Age (per year)	-0.005	-0.020 to 0.011	0.57
Gender (female)	-0.296	-0.508 to -0.085	0.006
Positive family history of glaucoma	0.513	0.134 to 0.892	0.008
High myopia	0.666	0.189 to 1.142	0.006

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3

Antithrombotic medication and incident open-angle glaucoma

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ABSTRACT

Purpose: To determine the associations between the use of antithrombotic drugs and incident open-angle glaucoma (OAG).

Methods: Ophthalmic examinations including measurements of the intraocular pressure (IOP) and perimetry were performed at baseline and follow-up in 3939 participants of the prospective population-based Rotterdam Study who did not have OAG at baseline. The use of antithrombotic drugs was monitored continuously during follow-up. Antithrombotics were stratified into anticoagulants and platelet aggregation inhibitors. Associations between incident OAG and the use of antithrombotics were assessed using Cox regression models; associations between antithrombotics and IOP at follow-up were analyzed with multiple linear regression.

Results: During a mean follow-up of 9.8 years, 108 participants (2.7%) developed OAG. The hazard ratio for anticoagulant use was 0.90 (95% confidence interval 0.55 to 1.48; P=0.69) and for platelet aggregation inhibitors 0.80 (0.53 to 1.21; P=0.28). There was no trend towards a reduced or increased risk of incident OAG with prolonged anticoagulant use (P-value for trend 0.84) or platelet aggregation inhibitor use (0.59). The analyses were adjusted for age, gender, baseline IOP and IOP-lowering treatment, family history of glaucoma and myopia. There was a significant IOP-lowering effect of anticoagulants (-0.31 mmHg; 95% confidence interval -0.58 to -0.04 mmHg; P=0.025) but not of platelet aggregation inhibitors (P=0.06). The IOP-lowering effect of anticoagulants disappeared after additional adjustment for the use of systemic beta-blockers.

Conclusions: Use of anticoagulants or platelet aggregation inhibitors appears not to be associated with incident OAG.

INTRODUCTION

Open-angle glaucoma (OAG) is an insidious disease characterized by irreversible loss of retinal ganglion cells and cupping of the optic disc, ultimately resulting in loss of sight. The prevalence of OAG in the 40+ population is approximately 2%.[1] An elevated IOP is an important risk factor for OAG and the therapeutic management of OAG is currently targeted towards the lowering of IOP. However, OAG progression often continues despite an apparently sufficient reduction of the IOP. As this IOP-independent progression is at best partially understood, more research is needed to elucidate the pathogenesis of OAG, which may result in the development of other therapeutic strategies.

Impaired blood flow has been postulated to be involved in the pathogenesis of OAG.[2,3] Treatment with antithrombotic drugs such as anticoagulants and platelet aggregation inhibitors (PAIs) is a frequently used prophylaxis against impaired blood flow.[4] Moreover, PAIs have been suggested to have neuroprotective properties.[5] Some clinicians already prescribe PAIs based on a "it does not hurt to try" principle. However, two recent trials in Alzheimer's disease (like OAG a neurodegenerative disease) showed no effect of PAIs (aspirin) on cognitive functioning whereas it increased the risk of serious bleeds.[6,7] For all these reasons, it seems logical to study the potential role of these drugs in the management of OAG, as suggested earlier.[8] Thus far, one study addressed the effect of PAIs(acetylsalicyclic acid; ASA) on IOP[9] and two studies the effect of ASA on the progression of OAG.[10,11] As these studies gave equivocal results (see Discussion), another look at this issue seemed warranted. Moreover, we did not find any study addressing the effects of anticoagulants or of PAIs other than ASA on OAG.

The aim of this study was to determine the associations between the use of anti-coagulants or PAIs and the development of OAG in a prospective population-based cohort study.

METHODS

Study population

The present study was performed as part of the Rotterdam Study, a prospective population-based cohort study investigating age-related disorders. The study population consisted of 7983 individuals aged 55 years and older living in the Ommoord district of Rotterdam, the Netherlands.[12] For this study, data from a subset of 3939 participants who did not have OAG (see below) at baseline and who completed at least one follow-up examination were used. The baseline examination took place from 1991 to 1993; follow-up examinations were performed from 1997 to 1999 and from 2002 to 2006. All measurements were conducted after the Medical Ethics Committee of the Erasmus University Rotterdam had approved the study protocol and all participants had given written informed consent in accordance with the declaration of Helsinki.

Ophthalmic assessment

Participants underwent similar eye examinations at baseline and at the two follow-up rounds. These examinations included refraction, measurement of the best-corrected visual acuity, Goldmann applanation tonometry (Haag-Streit AG, Bern, Switzerland), fundoscopy, fundus photography of the posterior pole, imaging of the optic disc, and visual field testing.

At each visit, three IOP measurements were taken on each eye and the median value of these three measurements was recorded [13] ; the higher median of both eyes was used in the analysis. The visual field of each eye was screened using a 52-point supra-threshold test that covered the central visual field with a radius of 24° (Humphrey Field Analyzer [HFA]; Carl Zeiss, Oberkochen, Germany).[14,15]

Visual field loss was defined as non-response to a light stimulus of 6 dB above a threshold-related estimate of the hill of vision in at least three contiguous test points, or four including the blind spot. In participants with reproducible abnormalities on supra-threshold testing, Goldmann perimetry (Haag-Streit AG, Bern, Switzerland; baseline and first follow-up) or full-threshold HFA 24-2 testing (second follow-up) was performed on both eyes. Visual field loss was considered to be glaucomatous visual field loss only if reproducible and after excluding all other possible causes.[14,16]

Incident open-angle glaucoma

We defined incident OAG as no glaucomatous visual field loss in both eyes at baseline and glaucomatous visual field loss in at least one eye at follow-up. [16] All identified cases were examined by an experienced ophthalmologist (PTVMdJ and RCWW) who performed gonioscopy and a dilated ophthalmic exam. Cases with a history or signs of angle closure or secondary glaucoma were excluded.

Medication data

Data on antithrombotic drugs prescriptions for all participants were obtained from seven pharmacies using a centralized computer network in the Ommoord district of Rotterdam, the Netherlands, from January 1, 1991, onward. This included the product name, Anatomical Therapeutic Chemical (ATC) code, duration of use, and the date of first prescription. Antithrombotic drugs were classified based on ATC system according to pharmacological subgroup into anticoagulants (B01AA; coumarin derivatives) and PAIs (B01AC; abciximab, ASA, carbasalate calcium, clopidogrel, dipyridamole, eptifibatide, prasugrel, tirofiban). The use of antithrombotics was recorded as the number of days with use during follow-up. Usage before baseline was not taken into account.

Other covariables

Other covariables included age, gender, smoking, diabetes mellitus, cardiovascular diseases, the use of antihypertensive drugs, the use of statins, body mass index, total cholesterol, IOP, IOP-lowering treatment, and family history of glaucoma. All these covariables were measured at baseline. Smoking status was self-reported and categorized as ever or never smoker. Data on diabetes mellitus and cardiovascular disorders such as angina pectoris, atrial fibrillation, myocardial infarction, heart failure, hypertension and stroke were obtained from the participants through interviews, electrocardiogram readings, and non-fasting and fasting serum blood glucose levels. Diabetes was defined as the use of antidiabetic medication or by a non-fasting or post-load plasma glucose level above 200 mg/dl (11.1 mmol/l). Hypertension was defined as the use of antihypertensive medication for the indication of hypertension or as a systolic blood pressure of 140 mmHg or more, or a diastolic pressure of 90 mmHg or more. The use of antihypertensive medication and statins was determined using the pharmacy computer system as described above. Body mass and height were measured at the research center. Total serum cholesterol was measured in non-fasting blood. IOP-lowering treatment was defined as the use of IOP-lowering medication or a history of glaucoma surgery or laser trabeculoplasty. The family history of glaucoma was determined by interviews and was considered positive if the participant reported a history of glaucoma in parents, siblings or offspring. Myopia was defined as a spherical equivalent refractive error of -4 D and more myopia. Eyes with a cataract extraction before baseline were excluded from this analysis. In cases with one eye with incident OAG, the refraction of that eye was used. In participants without OAG or OAG in both eyes, the refraction of a random eye was used.

Statistical analysis

Differences in baseline characteristics between participants with and without incident OAG and differences in baseline characteristics between anti-thrombotic drug users and non-users were evaluated using chi-square tests for categorical variables and t-tests for normally distributed continuous variables. To determine the associations between the use of anti-thrombotic drugs and incident OAG, the use of anticoagulants or PAIs was initially defined as any use during follow-up and the associations were initially analyzed with chi-square tests. Subsequently, a Cox proportional hazards model was used to calculate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the associations between the use of anticoagulants or PAIs and incident OAG. Follow-up duration was used as the time axis in the model. For participants without incident OAG, the follow-up duration was counted from the baseline visit to the last visit with reliable perimetry. For incident OAG cases, the follow-up ended at the first visit in which glaucomatous visual field loss was detected. The antithrombotic drugs, age and gender, and other covariables with $P<0.20$ in the univariate comparisons were included in the multivariate analysis. Subsequently, the antithrombotic drugs, age and gender, and other covariables with $P<0.05$ in the initial multivariate model were included in the final model. The use of antithrombotic drugs was entered in the model as any use during follow-up. To allow for the evaluation of a possible dose-response relationship, we also performed analysis after making three nominal categories based on the duration of medication use, being no use, cumulative use during two years or less, and cumulative use during more than two years (see Discussion). The dose-response relationship was evaluated with a trend test. To explore direct effects of the antithrombotics on the IOP, we conducted a multiple linear regression analysis with IOP at follow-up as the dependent variable. This analysis was adjusted for IOP-lowering treatment at follow-up and for the same covariates as the final Cox model except for baseline IOP and IOP-lowering treatment at baseline. All analyzes were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and $P \leq 0.05$ is significant.

RESULTS

During a mean follow-up of 9.8 years, 108 participants (2.7%) developed OAG. Table 1A depicts the baseline characteristics of the study population for participants with and without incident OAG. Participants who developed OAG were older and more often male, more often had a positive family history of glaucoma, and more often had myopia. They also had a higher IOP and more frequently received IOP-lowering treatment. Table 1B shows the baseline characteristics of the study population for antithrombotic drug users and non-users.

Table 2 presents the results of the univariable analyses for the use of antithrombotic drugs at any time during follow-up. There was no significant difference between OAG cases who used either anticoagulants or PAIs and the controls. Amongst the 722 participants using anticoagulants at any time during follow-up, the median duration of use was 231 days, with a range from 1 to 3823 days; amongst the 1388 participants using PAIs, the median duration of use was 1112 days, with a range from 7 to 4411 days.

Table 3 presents the final model, adjusting for age, gender, baseline IOP and IOP-lowering treatment, the family history of glaucoma and myopia. Participants using anticoagulants and PAIs had non-significant risk reductions with HRs of 0.90 and 0.80, respectively. There was no trend towards a reduced or increased risk of incident OAG with prolonged anticoagulant use (HR 0.84 [95% CI 0.46-1.53; P=0.57] for usage during two years or less; HR 1.04 [95% CI 0.48-2.27; P=0.92] for usage during more than two years; P-value for trend 0.84) or PAI use (HR 0.78 [95% CI 0.42-1.45; P=0.44] for usage during two years or less; HR 0.81 [95% CI 0.51-1.31; P=0.40] for usage during more than two years; P-value for trend 0.59).

Table 4 shows the results of the multiple linear regression analysis with IOP at follow-up as the dependent variable. As can be seen in this table, there was a significant IOP-lowering effect of anticoagulants but this effect was not seen in PAIs.

DISCUSSION

This study did not demonstrate any association between the use of either anticoagulants or PAIs and incident OAG. Interestingly, the use of anticoagulants seemed to be associated with a lower IOP.

In a retrospective cohort study performed in a clinical setting, de Castro et al examined the effect of ASA on the optic nerve head as assessed longitudinally with confocal scanning laser ophthalmoscopy in 76 OAG suspects.[11] They did not find an effect of ASA use after a follow-up of 23 months, which is in agreement with our findings. Linden et al conducted a double blind, placebo controlled randomized, crossover study amongst 28 patients with OHT or OAG to determine the short-term effect of a single dosis of 500 mg ASA on the IOP. There was no statistically significant difference between the placebo treated and the ASA treated patients.[9] This is in agreement with our observation that the usage of PAIs was not associated with the IOP at follow-up. Bell et al found, in a retrospective observational case-control study amongst 64 patients undergoing trabeculectomy and 74 controls, an association between ASA use and an increased frequency of glaucoma surgery, suggesting a harmful effect (Bell 2004).[10] The major limitation of their study as reiterated by the authors was that they equated the frequency of glaucoma surgery with the progression of glaucoma. This assumption might have biased the effect estimate. Although they found a significant harmful effect whereas we did not, the 95% CI for ASA use in their study (1.10-4.79) overlaps with our 95% CI for PAIs use (0.53-1.21).

Although we did not find a significant beneficial or harmful effect of anticoagulants or PAIs on the incidence of OAG, there was a significant IOP-lowering effect of anticoagulants. Interestingly, the anticoagulant heparin has been associated with an increased outflow facility in human and monkey trabecular meshwork [17-19], providing at least a glimpse of a possible biological explanation for this unexpected finding. Although our finding may thus support a hypothesis regarding IOP regulation, the clinical significance is at most modest, as the R^2 was only 0.03 (that is, the percentage of the IOP at follow-up explained by the anticoagulant use in the regression model was 3%) and the effect estimate was only approximately -0.3 (that is, those using anticoagulants had - on average – a 0.3 mmHg lower IOP than those not using anticoagulants). The combination of a significant IOP-lowering effect and no effect on the incidence of OAG might point to a harmful IOP-independent effect of anticoagulants on OAG. However, with a 12% increase in OAG risk per mmHg increase in IOP (Table 3), the effect of a 0.3 mmHg lowering of the IOP is amply within the 95% CI as reported in Table 3. Apart from a possible biological mechanism explaining the IOP-lowering effect of anticoagulants, confounding by, for example, the use of systemic beta-blockers at follow-up could be a possible confounding factor. If we adjusted the analysis as presented in Table 4 for beta-blocker use at follow-up, the IOP-lowering effect of anticoagulants was no longer significant (effect estimate -0.031 mmHg; P=0.78).

In an earlier study, we reported that the use of statins was associated with a reduced risk of OAG (chapter 1). Therefore, the use of statins may be regarded as a confounder in the present study. In the present study, we corrected – in accordance with the assumptions of the Cox model - for the use of statins at baseline. As the use of statins increases rapidly with age, we explored adjusting for statin use during follow-up as well. No changes were observed in the HRs of either the anticoagulants or the PAIs.

Strengths of our study include its prospective and population-based design, the large number of participants and the long follow-up period. Information bias was prevented by prospectively and completely automated collected pharmacy records of all prescriptions. Although this approach guarantees accurate prescription data, a complete overview of medication prescriptions does not guarantee that all participants actually took their medication. In this respect it is important to mention that the monitoring of the users of anticoagulants is well organized in the Netherlands (by means of regular blood sampling and the provision of personalized dosing schemes). Also, especially the PAIs that irreversibly block the platelet aggregation (like ASA) have a long therapeutic half-life (approximately 10 days; determined by the physiological turnover of platelets). This should make the effect of these drugs resistant against an irregular intake. Nevertheless, non-compliance may have resulted in a too conservative risk estimate, inhibiting the discovery of small harmful or protective effects.

A possible limitation of this study is potential misclassification of exposure. This misclassification will be random because the outcome is – inextricably - gathered irrespective of exposure status. To appreciate this approach, it is important to realize that OAG development often takes more than a decade and cannot be detected in the earliest stages. Some factors slow down or accelerate the disease development, and thus make it less likely or more likely that the disease can be detected at a certain point in time (being our follow-up examination). Cumulative exposure stratified into biologically plausible nominal categories as we used in our analyses is the best proxy for studying the overall influence of the use of medication on the rate of glaucoma development during follow-up.[20] Because the exposure misclassification is random, it will tend to bias the results towards the null hypothesis. This might have hampered the detection of small protective or harmful effects in our study.

To the best of our knowledge, this is the first study examining the effects of the use of anticoagulants on OAG, and the first population-based study examining the effects of PAIs on OAG. Given no clear protective or harmful effects, our study does not support prescribing or withdrawing either anticoagulants or PAIs in patients with OAG.

Table 1 Baseline characteristics of participants with and without incident open-angle glaucoma (A) and of antithrombotic users (either anticoagulants or platelet aggregation inhibitors, or both) and non-users (B), with univariable comparisons (mean values with standard deviation between brackets unless stated otherwise)

A	Incident open-angle glaucoma (N=108)	No incident open-angle glaucoma (N=3831)	P-value
Age	68.4(7.1)	65.7(6.8)	<0.001
Gender (%female)	49.1	58.7	0.046
Smoking (%)	33.3	33.4	0.98
Diabetes mellitus (%)	8.4	6.9	0.54
Angina pectoris (%)	1.9	3.1	0.46
Atrial fibrillation (%)	2.8	2.1	0.63
Myocardial infarction (%)	13.2	9.7	0.23
Heart failure (%)	0.9	1.2	0.81
Hypertension (%)	52.9	47.1	0.49
Stroke (%)	2.8	1.2	0.16
Use of antihypertensive drugs (%)	28.0	26.0	0.63
Use of statins (%)	0.9	2.1	0.39
Body mass index (kg/m^2)	25.8(2.9)	26.3(3.5)	0.12
Total cholesterol (mmol/l)	6.5(1.1)	6.7(1.2)	0.17
IOP (mmHg)	17.3(4.7)	15.0(3.1)	<0.001
IOP-lowering treatment (%)	15.7	2.3	<0.001
Family history of glaucoma (%)	16.7	8.1	0.002
Myopia	9.5	4.9	0.033

B	Antithrombotic users (N=1748)	Non-users (N=2191)	P-value
Age	67.3(6.9)	64.5(6.6)	<0.001
Gender (%female)	55.0	61.1	<0.001
Smoking (%)	32.6	34.1	0.31
Diabetes mellitus (%)	9.2	5.2	<0.001
Angina pectoris (%)	4.7	1.8	<0.001
Atrial fibrillation (%)	3.8	0.8	<0.001
Myocardial infarction (%)	15.1	5.5	<0.001
Heart failure (%)	2.0	0.5	<0.001
Hypertension (%)	57.3	43.5	<0.001
Stroke (%)	2.3	0.5	<0.001
Use of antihypertensive drugs (%)	35.5	18.5	<0.001
Use of statins (%)	32.2	11.3	<0.001
Body mass index (kg/m^2)	26.6(3.5)	26.1(3.5)	<0.001
Total cholesterol (mmol/l)	6.7(1.2)	6.7(1.2)	0.82
IOP (mmHg)	15.1(3.2)	15.0(3.2)	0.35
IOP-lowering treatment (%)	2.5	2.8	0.47
Family history of glaucoma (%)	8.0	8.6	0.50
High myopia	5.1	5.0	0.95

IOP = intraocular pressure.

Table 2 Univariable analyses of the use of antithrombotic drugs at any time during follow-up and the development of open-angle glaucoma

	iOAG (N=108)	No-iOAG (N=3831)	P-values
Anticoagulants (n[%])	21(19.4)	701(18.3)	0.76
PAIs (n[%])	40(37.0)	1348(35.2)	0.69

iOAG= incident open-angle glaucoma; PAIs= platelet aggregation inhibitors

Table 3 Final multivariable model of the risk of developing open-angle glaucoma for antithrombotic drugs

	Hazard ratio	95% confidence interval	P-value
Anticoagulants	0.90	0.55-1.48	0.69
Platelet aggregation inhibitors	0.80	0.53-1.21	0.28
Age (per year)	1.08	1.05-1.11	<0.001
Gender (female)	0.57	0.39-0.85	0.005
IOP (per mmHg)	1.12	1.08-1.18	<0.001
IOP treatment	3.24	1.73-6.08	0.002
Family history of glaucoma	1.82	1.06-3.11	0.029
Myopia	2.09	1.08-4.04	0.028

IOP = intraocular pressure.

Table 4 Multiple linear regression analysis with intraocular pressure at follow-up as the dependent variable

	beta	95% confidence interval	P-value
Anticoagulants	-0.31	-0.58 to -0.04	0.025
Platelet aggregation inhibitors	-0.21	-0.44 to 0.008	0.06
Age (year)	-0.006	-0.021 to 0.010	0.49
Gender (female)	-0.30	-0.51 to -0.09	0.006
IOP-lowering treatment at follow-up	1.76	1.34 to 2.18	<0.001
Family history of glaucoma	0.37	-0.01 to 0.75	0.054
Myopia	0.60	0.13 to 1.08	0.012

IOP = intraocular pressure.

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4

Risk factors for visual field progression in the Groningen Longitudinal Glaucoma Study - a comparison of different statistical approaches

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ABSTRACT

***Purpose**:* To identify risk factors for visual field progression in glaucoma and to compare different statistical approaches to this risk factor analysis.

***Patients and Methods**:* We included 221 eyes of 221 patients. Progression was analyzed using Nonparametric Progression Analysis applied to Humphrey Field Analyzer (HFA) data. Risk factors were analyzed using the statistical approaches from the Advanced Glaucoma Intervention Study (AGIS), the Early Manifest Glaucoma Trial (EMGT) and the Canadian Glaucoma Study (CGS). Four intraocular pressure (IOP) variables (baseline IOP, mean IOP during follow-up, IOP fluctuation, and pre-treatment IOP) and eight other risk factors were investigated.

***Results**:* On average 7.2 reliable fields were available after a mean follow-up of 5.4 years; 89 eyes progressed. With the AGIS approach, age (odds ratio 1.03 per year; 95% confidence interval 1.00-1.06; *P*=0.044) predicted progression. With an additional stepwise selection procedure, mean IOP during follow-up (1.16 per mmHg; 1.05-1.29; *P*=0.003), baseline HFA mean deviation (MD; 2.72 for better versus worse than -6 dB; 1.50-4.95; *P*=0.001) and age (1.03; 1.01-1.06; *P*=0.010) predicted progression. With the EMGT approach, baseline IOP (hazard ratio 1.07; 1.02-1.11; *P*=0.010), baseline Frequency Doubling Perimeter (FDT) MD (1.75; 1.14-2.70; *P*=0.013) and age (1.03; 1.01-1.05; *P*=0.006) predicted progression, and with the CGS approach, baseline IOP (1.07; 1.02-1.11; *P*=0.010), baseline FDT MD (1.75; 1.14-2.70; *P*=0.013) and age (1.03; 1.01-1.05; *P*=0.012).

***Conclusions**:* IOP, disease stage and age appeared to be robust independent risk factors for visual field progression in glaucoma. The IOP variable that was significant depended on the statistical approach applied.

INTRODUCTION

Over the past few decades, a number of studies have contributed to elucidating the risk factors associated with or predictive for glaucoma progression.[1-14] A good understanding of these risk factors is a prerequisite for estimating the risk of progression in individual patients. Knowledge of individual progression risks enables custom-made glaucoma care.

Elevated intraocular pressure (IOP) is an established risk factor for glaucoma progression. Several other risk factors for progression have been identified with conflicting results.[1-14] These conflicting results might be attributed to variability in (1) the study design, (2) the study population, (3) the statistical approach applied, and (4) the outcome measure (progression definition) used.

The aim of this study was to identify risk factors associated with visual field progression in glaucoma and to determine the influence of the statistical approach applied. For this purpose we compared different statistical approaches in a single dataset, using a single outcome measure. The statistical approaches were adopted from the Advanced Glaucoma Intervention Study (AGIS),[10] the Early Manifest Glaucoma Trial (EMGT),[6] and the Canadian Glaucoma Study (CGS).[1] The selected progression definition (outcome measure) was the Nonparametric Progression Analysis (NPA).[15] The dataset was the cohort of the Groningen Longitudinal Glaucoma Study (GLGS).[15;16]

PATIENTS AND METHODS

Study population

The present study was performed within the Groningen Longitudinal Glaucoma Study (GLGS), a prospective cohort study performed in a clinical setting. The objectives,

methods, rationale and study design have been described earlier.[15;16] In short, all 875 glaucoma patients and glaucoma suspects who visited our glaucoma outpatient service between July 1, 2000, and June 30, 2001, and who provided informed consent were included in an institutional review board–approved observational prospective follow-up using conventional perimetry, frequency doubling perimetry (FDT; Carl Zeiss Meditec AG, Jena, Germany) and laser polarimetry (GDx; Laser Diagnostic Technologies, San Diego, CA, USA).

Out of the original 875 glaucoma patients and glaucoma suspects, 452 were classified as having glaucoma. Of the 452 glaucoma patients, the disease in 372 of them was classified using standard automated perimetry (Humphrey Field Analyzer [HFA]; Carl Zeiss Meditec Inc., Dublin, CA, USA). The Goldmann perimeter (Haag Streit AG, Bern, Switzerland) was used in 80 patients, who were excluded from the current analysis. Of the 372 patients classified using the HFA (for criteria see below), 221 patients who had undergone a follow-up period as measured from the last baseline test of at least 3 years and who had at least four reliable visual fields were included in the present study.

Perimetry

Perimetry was performed using the HFA 30-2 Swedish interactive threshold algorithm (SITA) fast strategy. An abnormal test result was defined as any one of the following: (1) a glaucoma hemifield test result outside normal limits, (2) a pattern standard deviation with $P<0.05$, or (3) three adjacent non-edge points with $P<0.05$ in the pattern deviation probability plot, with at least 1 point reaching $P<.01$ and with all points being on the same side of the horizontal meridian (LTG-P criterion).[17] A test result was considered unreliable if false-positive classifications exceeded 10% or if both false-negative classifications and fixation losses exceeded 10% and 20%, respectively.

For glaucoma at baseline, two consecutive reliable test results had to be abnormal in at least one eye. Defects had to be in the same hemifield, and at least one depressed test point of these defects had to have exactly the same location on both fields. Moreover, the defects had to be compatible with glaucoma and without any other explanation. The first test result was discarded because of a learning effect. Therefore, at least three tests had to be performed at baseline before glaucoma could be diagnosed. During the follow-up period, perimetry was performed at a frequency of one test per year. In case of suspected progression or unreliable test results, clinicians were allowed to increase the frequency of testing. This was a subjective decision; no formal tools or rules were used.

Progression detection

The method used to identify progression was the Nonparametric Progression Analysis (NPA).[15] In this methods, reliable follow-up test results are compared with two reliable baseline test results. NPA is based on a nonparametric ranking[18] of mean deviation (MD) values. The MD values of the follow-up fields are compared with the worse MD value of the two baseline fields. If the MD of a follow-up field is better than or equal to the MD of the worse baseline field, the field is considered stable. If the MD of a follow-up field is worse than the MD of the worse baseline field, the change is considered outside the normal variation (that is, suspected progression). Possible progression is diagnosed if this change is confirmed once (deterioration in two consecutive fields) and likely progression if confirmed more than once (deterioration in three or more consecutive fields). Following a reading of suspected, possible, or likely progression, MD readings better than the worse baseline MD are disallowed; in that case, the patient's condition is considered stable.[15] This was done by assessing progression from the final field backwards, and in this way we circumvented the fact that normally the specificity of event-based progression detection algorithms decreases with increasing numbers of follow-up fields. In NPA, the two baseline fields divide the MD probability space of a patient *a priori* in three equal

parts. Hence, if the eye is truly stable with no change in MD over time, the probability that the final field has an MD lower than that of both baseline fields is one-third. Therefore, the specificity of suspected progression in NPA is 0.67. Similarly, the specificities of possible (MD of the last two fields lower than that of both baseline fields) and likely progression (MD of the last three fields lower than that of both baseline fields) are 0.83 and 0.90, respectively.[18]

Risk Factors for Progression

The possible risk factors for progression as documented in the GLGS from the very beginning were age, gender, myopia, cardiovascular disease, family history of glaucoma, pre-treatment IOP, IOP at baseline, mean IOP during follow-up, IOP fluctuation (standard deviation during follow-up), and HFA, FDT and GDx test results. All risk factors were recorded at baseline except for the mean IOP and IOP fluctuation during follow-up. The pre-treatment IOP was defined as the highest IOP ever measured prior to the study, before any treatment was started. Myopia was defined as a spherical equivalent of -4 D or more of myopia in at least one eye. Cardiovascular disease was defined in terms of whether cardiovascular medication was used or not. Family history of glaucoma was considered to be positive if the participants reported a history of glaucoma in their parents, siblings or offspring. All IOP measurements were performed with Goldmann applanation tonometry (Haag Streit AG, Bern, Switzerland). FDT at baseline was performed using the C-20 full-threshold mode. The HFA and FDT variable used was the MD, dichotomized as better or worse than the median value in the study population, being -6 dB for both devices. The GDx variable used was "The Number".[16] New patients were scored as "untreated on inclusion" if treatment started after inclusion. This variable corrects for a possible bias resulting from the fact that some patients had not yet been treated at the time of inclusion.

Statistical Analysis

Only one eye per patient was included. If a patient met the criteria with both eyes, a randomly chosen eye was included. Visual field progression was defined as having at least a possible progression at the end of the follow-up. Three different statistical approaches for risk factor analysis were applied, taken from three different glaucoma studies: AGIS,[10] EMGT[6] and CGS[1].

In the AGIS,[10] associations between progression and various potential risk factors were assessed using multivariate logistic regression. Those factors that were associated with progression in univariate analyses (chi-square test, unpaired *t* test, or Wilcoxon rank sum test, depending on the type of data) at a *P* value of 0.20 or less were included in the final model. Furthermore, those clinically relevant variables such as age and gender that might potentially predict or confound the detection of progression were included. No selection other than univariate pre-selection was applied in the AGIS. In addition to this approach, we also added interaction terms and applied a stepwise variable selection.

In the statistical approach of the EMGT,[6] Cox proportional hazard models with Breslow adjustment for ties in time to progression were used to evaluate the constancy of the hazard ratio throughout the follow-up time period. Univariate analyses of the risk factors for progression were explored using chi-square tests for categorical variables and t-tests for continuous variables. Variable selection was carried out in two steps. First, all variables significant in the univariate analyses at a *P* value of 0.20 or less were included in the model. Second, a stepwise variable selection algorithm was used to assess the best statistical fit. Furthermore, separate models were used to explore and identify those baseline and follow-up factors significantly associated with glaucoma progression.

In the statistical approach derived from the CGS,[1] risk factors for progression were first explored using Kaplan-Meier survival analyses with the log-rank test for the univariate analyses. Since selection of variables in the final model was based solely on a stepwise procedure and not on the results of univariate analyses, we did not report the results of these univariate analyses. As in the CGS, IOP was the only time-dependent variable in our study and therefore was analyzed as a covariate in the multivariate analysis. Variables were entered into a Cox Proportional hazards model in a forward stepwise analysis if their *P* value was 0.10 or less and if the hazards were judged to be proportional when examining the negative log plots of the survivor functions. Interaction terms were explored and included in the model if the partial likelihood ratio test indicated a better model fit.

In order to assess the effect that the possible risk factors for glaucoma progression may have on the rate of progression (the MD slope, that is, the time derivative of MD), we performed a multiple linear regression analysis with rate of progression as the dependent variable and the factors that were found to be significantly associated with progression in the analyses described above as independent variables.

All statistical analyses were performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA), except for the statistical approach employed from the AGIS where PASW Statistics 17.0.2 (SPSS, Inc., Chicago, IL, USA) was used. Variables with a *P* value of 0.05 or less were considered statistically significant unless otherwise stated.

RESULTS

Table 1 shows the study population characteristics at baseline and during follow-up. The average follow-up duration (as measured from the last baseline field) was 5.3 years; on

average 5.1 reliable follow-up fields were available (7.1 fields including baseline). The average MD at baseline was –9.4 dB; the average MD slope was -0.25 dB/years. According to the NPA algorithm, 89 of the 221 patients showed at least possible progression.

Table 2 depicts the results of univariate risk factor analyses of all variables explored in the GLGS according to AGIS and EMGT statistical approach. Since variable selection in the CGS was solely based on a stepwise procedure, we did not present results for univariate analyses for the CGS statistical approach. Nine variables (age, gender, history of cardiovascular disease, HFA MD, FDT MD, GDx test result, baseline IOP, mean IOP during follow-up and IOP fluctuation) satisfied the criteria of the AGIS and EMGT statistical approaches. These variables were included in the logistic regression model and Cox proportional hazard model for the AGIS and EMGT approaches, respectively.

Table 3 presents the results of the multivariate analyses with dependent variable NPA progression, using the AGIS, EMGT and CGS statistical approaches. With the AGIS approach, age was the only independent predictor of NPA progression with an odds ratio (OR) of 1.03 per year of increase in age. An interaction term between mean IOP and IOP fluctuation added to the model was not significant. Applying a stepwise variable selection resulted in a model that had the HFA MD (OR 2.72 for better versus worse than -6 dB), mean IOP during follow-up (OR 1.16 per mmHg increase) and age (OR 1.03) as independent risk factors for progression. With the EMGT and CGS approaches, three variables were found to be independent predictors of NPA progression. The FDT MD, baseline IOP and age increased the risk of NPA progression by 75% for better versus worse than -6 dB, 7% per mmHg increase in baseline IOP and 3% per year of increase in age, respectively in both approaches. None of the interaction terms used in the CGS approach were significant.

Table 4 shows the results of a multiple linear regression analysis with the rate of progression as the dependent variable, and with mean IOP during follow-up, HFA MD and age as independent variables. The rate of progression worsened (that is, became more negative) by 0.04 dB/year per mmHg of increase in mean IOP during follow-up and was 0.18 dB/year more negative in patients with a baseline HFA MD of -6 dB or worse as compared to those with a better baseline MD. With baseline IOP in the model instead of mean IOP during follow-up, the rate of progression worsened by 0.02 dB/year per mmHg of increase in baseline IOP (95% CI -0.03 to -0.01 dB/year per mmHg; P=0.030).

DISCUSSION

IOP, baseline damage (as assessed with HFA or FDT) and age were found to be robust independent risk factors for glaucoma progression. The IOP variable that was significant depended on the statistical approach applied.

Intraocular pressure

Four IOP variables were included in our analyses. In all the analyses (except for the AGIS approach without stepwise selection) at least one of these variables was found to be a risk factor for glaucoma. This is not an unexpected finding, since IOP is a well-known risk factor for progression,[1;5;6;9;12;13] although there are reports that have failed to show such a relationship in normal tension glaucoma.[2;3] In our population, every mmHg increase in baseline or mean IOP increased the progression risk by 7% or 16 % respectively. This finding corroborates the increase of 12% per mmHg increase in average IOP during follow-up as reported in the EMGT[6] and the larger increase of 19% per mmHg increase in mean follow-up IOP as reported in the CGS[1]. Our findings further buttress the importance of controlling the IOP of glaucoma patients.

Using the AGIS statistical approach, none of the IOP variables were significant risk factors for progression, with IOP fluctuation closest to significance (P=0.091). After the additional stepwise variable selection, however, mean IOP during follow-up was a highly significant predictor of progression (P=0.003). If the analyses were repeated after excluding mean IOP during follow-up and including either baseline IOP or IOP fluctuation, the included IOP variable reached significance. Interestingly, the same phenomenon appeared both in the original AGIS analyses[10] and in a recent study in which IOP fluctuation was defined by the IOP range during follow-up.[8] These results would suggest that IOP fluctuation and either baseline IOP or average IOP during follow-up are not unrelated. In our study, IOP fluctuation was positively correlated with both the baseline IOP (r=0.40; P<0.001) and the mean IOP during follow-up (r=0.37; P<0.001). Because of the linear dependency among these variables, simultaneous inclusion in a model may lead to unstable coefficients of effect estimates. In order to rule out the possibility of collinearity, we carried out multicollinearity diagnostic statistics produced by linear regression analysis using Procedure Regression (PROC REG) with options variance inflation factor and tolerance in SAS.[19] None of the variance inflation factors was larger than 2.5 suggesting that there was no formal need to drop any IOP variable from the AGIS multivariate model as shown in Table 3. In addition, interaction terms were explored, but were found to be insignificant.

Baseline disease stage

Three methods of testing baseline disease stage were analyzed for their ability to predict glaucoma progression (HFA, FDT and GDx test results). We found HFA or FDT test results to be a significant risk factor for progression, but none of the final models showed FDT and HFA test results as both being significant risk factors in the same model. This is a plausible finding since FDT and HFA both measure functional visual field loss and, as to be expected, their scores were highly correlated (r=0.60; p<0.001).

Since multi-collinearity diagnostic statistics showed that none of the variance inflation factors was larger than 2.5 (see above), both variables could be analyzed in the same model.

An increased risk along with an increasing glaucoma stage was also reported in other studies.[5;7-9] The EMGT reported a HR of 1.55,[5] although in a later report the increase was not significant (HR 1.38, p=0.051).[6] In the CGS, using univariate analysis it seemed that a better baseline visual field was related to progression, but, in a multivariate regression analysis, this factor did not show significance.[1] The AGIS visual field score in the AGIS analyses showed no relationship with glaucoma progression.[10] It should be noted that the exclusion criteria in the AGIS, EMGT, and CGS were based, among other things, on visual field score, resulting in a narrowing of the baseline disease stage range. In our study, with a mean (SD; 95% central range) baseline MD of -9.4 dB (7.6 dB; -0.3 to -28.2 dB), such an exclusion criterion was not applied.

Variable "The Number" from the baseline GDx was not found to be a significant risk factor for progression. This variable remained insignificant even if HFA and FDT were excluded from the analyses. Some prior studies have shown that a smaller neuro-retinal rim or an enlarged cup-to-disk ratio predicts progression,[4;7;12;14;20] although not all studies have reported this association.[11]

Finally, the assessment of disease stage as a risk factor requires a careful consideration of the sensitivity and specificity of the outcome measure as a function of disease stage - especially because the MD variability increases with disease stage. The specificity of the outcome measure used in this study, NPA, is independent of the variability whereas the sensitivity decreases with variability.[18] Despite this decreasing sensitivity with increasing variability (that is, with disease stage), we found disease stage to be an independent risk factor, suggesting that it is a robust finding.

Hence, (perimetric) disease stage should be seen as a factor that requires careful consideration when making therapeutic decisions.

Other factors

Although many variables such as age, gender, myopia, family history of glaucoma, and the history of cardiovascular disease were explored, age was, in addition to IOP and disease stage, the only factor in our population that predicted progression in more than one analysis. For every yearly increment in age, the risk of progression increased by 3%. Several other investigators have reported a similar relationship between age and the progression of glaucoma,[1;5-8;10-12] whereas other studies were unable to confirm this association.[2;3;9;13;14] Family history and myopia seem to be associated with glaucoma[21-25] but not with its progression.[1;3;5;11] Gender was a significant factor for progression in a minority of studies and this varied in terms of whether men[11] or women[1;3] had a greater risk. A history of cardiovascular disease[1;5;10] would not seem to be an independent predictor of glaucoma progression.

Statistical Methodology

The various statistical approaches used constitute a major setback when comparing different risk factor analysis studies. In order to explore the influence of the statistical technique used on the results of risk factor analysis, we compared the statistical approaches employed by the AGIS, the EMGT, and the CGS in a single dataset and with a single outcome measure. In the CGS, a pre-selection was not performed and the CGS approach was more conservative in its use of a *P*-value of 0.10 as the selection criterion for the stepwise selection procedure whereas EMGT and AGIS used a *P*-value of 0.20 in the univariate pre-selection. The CGS and EMGT used Cox regression in contrast to the logistic regression used by AGIS.

The mathematical algorithms employed by these two models also differ. Interestingly, the answer to the ongoing discussion[26] of whether it is IOP fluctuation or another IOP variable that is the primary harmful factor in glaucoma progression depends, at least in our dataset, solely on the statistical approach used and which IOP variables were also analyzed in the same model. This underlines the importance of (1) a sound statistical design before the onset of the analyses to prevent "searching" for significance, (2) reticence in generalizing found risk factors, and (3) caution in the implementation of risk factors found in other reports. The significance of risk factors should always be seen in the light of previous (and later) reports. The risk factors found in our study are in agreement with the results of many other studies and this would tend to support the idea that they are indeed significant risk factors for glaucoma progression.

We compared the statistical approaches of AGIS, EMGT and CGS, but not their outcome measures. The outcome measures used in these three studies were the AGIS scoring system in AGIS,[27] the Glaucoma Progression Analysis (GPA) in the EMGT,[28] and the Glaucoma Chance Probability (GCP) in the CGS.[29] The use of a single outcome measure enabled a more direct comparison of the statistical approaches. Moreover, the AGIS scoring system is not readily available and the GCP cannot be run on SITA test results. We compared NPA and GPA in an earlier study.[15] NPA had a fairly good agreement with GPA in early glaucoma, while NPA was more sensitive than GPA in patients with advanced glaucoma. The latter finding can be explained by the fact that GPA uses pattern deviation analysis. This makes the use of NPA more appropriate in our dataset with many patients with advanced disease. We repeated the risk factor analyses with outcome measure GPA. Similar associations were found but, as to be expected, the associations were less profound and did not reach significance in some analyses.

Due to the finite number of visual field tests in our observational study, some cases with progression may have been misclassified as stable because confirmation was not yet

performed at the end of the study. Similarly, some stable cases may have been erroneously classified as cases with progression because falsification after possible or likely progression was not yet performed. The misclassified cases could have resulted in conservative risk estimates. An inherent property of all event-based progression detection algorithms is that the specificity decreases with an increasing number of tests. We circumvented this limitation by disallowing MD readings better than the worse baseline MD following a reading of suspected, possible, or likely progression (see Methods section, progression detection subsection). The number of visual fields differed slightly between cases and controls (Table 1) and this might have influenced our results. We explored this issue by repeating all analyses with the number of visual fields added as a covariate. No significant changes were found. As mentioned in the Methods section, the GLGS is an observational study. Hence, as in all observational studies, some confounding by indication cannot be excluded.

In conclusion, IOP, disease stage, and age seem to be significant independent risk factors for visual field progression in glaucoma. The results from risk-factor analyses may depend on the statistical approach applied.

Table 1 Patient characteristics (mean with standard deviation between brackets unless stated otherwise)

	All patients	**NPA progression**	
		Yes	No
Number of patients	221 (100%)	89 (40%)	132 (60%)
Baseline			
Age (yr)	66.4 (12.3)	68.8 (11.5)	64.8 (12.6)
Gender (% male)	55.2	48.3	59.8
Family history (%)	16.9	20.7	14.4
Myopia (%)	18.1	16.9	18.9
Cardiovascular disease (%)	36.7	43.8	31.8
HFA MD (dB)	-9.4 (7.6)	-10.0 (6.8)	-8.9 (8.0)
FDT MD (dB)	-6.9 (5.5)	-7.8 (5.3)	-6.3 (5.7)
GDx (The Number)	52.0 (24.1)	55.9 (23.4)	49.4 (24.3)
IOP at baseline (mmHg)	16.1 (4.7)	17.0 (5.5)	15.5 (4.1)
Untreated on inclusion (%)	10.9	13.5	9.1
pre-treatment IOP (mmHg)	30.3 (9.5)	30.2 (10.0)	30.4 (9.2)
Follow-up			
Follow-up duration (years)	5.3 (1.1)	5.3 (1.0)	5.3 (1.2)
Number of visual fields	7.1 (1.9)	7.5 (1.7)	6.9 (2.0)
HFA MD slope (dB/years)	-0.25 (0.56)	-0.69 (0.55)	0.04 (0.33)
Mean IOP (mmHg)	14.9 (2.9)	15.5 (3.0)	14.5 (2.9)
IOP fluctuation (mmHg)	2.8 (1.8)	3.2 (2.2)	2.5 (1.5)

HFA = Humphrey Field Analyzer; MD = mean deviation; FDT = Frequency Doubling Technique perimeter; GDx = nerve fiber analyzer; IOP = intraocular pressure.

Table 2 Univariate risk factor analyses for NPA progression according to the AGIS and EMGT statistical approaches

Variables	**AGIS approach p-value**	**EMGT approach p-value**
Baseline		
Age (yr)	0.008[†]	0.017[^]
Gender (% male)	0.091[‡]	0.091[‡]
Family history (%)	0.224[‡]	0.224[‡]
Myopia (%)	0.693[‡]	0.693[‡]
Cardiovascular disease (%)	0.069[‡]	0.069[‡]
HFA MD (% < -6 dB)	0.013[‡]	0.013[‡]
FDT MD (% < -6 dB)	0.017[‡]	0.017[‡]
GDx (The Number)	0.052[†]	0.048[^]
IOP (mmHg)	0.148[†]	0.021[^]
Untreated on inclusion (%)	0.303[‡]	0.303[‡]
pre-treatment IOP (mmHg)	0.762[†]	0.906[^]
Follow-up		
Follow-up Duration (yr)	0.960[†]	NA
Mean IOP (mmHg)	0.017[^]	0.017[^]
IOP fluctuation (mmHg)	0.045[†]	0.005[^]

HFA = Humphrey Field Analyzer; MD = mean deviation; FDT = Frequency Doubling Technique perimeter; GDx = nerve fiber analyzer; IOP = intraocular pressure; [†] = Wilcoxon rank sum test; [‡] = Chi-square test; [^] = Unpaired *t* test.

Table 3 Odds ratios and hazard ratios for the logistic regression model (AGIS) and Cox proportional hazards models (EMGT, CGS), for dependent variable progression according to the NPA

	Odds ratio	**95% confidence interval**	***P* value**
AGIS approach			
Age (years)	1.03	1.00 – 1.06	0.044
Gender (% male)	0.63	0.35 – 1.14	0.127
Cardiovascular disease (%)	1.47	0.80 – 2.71	0.220
HFA MD (% < -6 dB)	1.77	0.81 – 3.86	0.154
FDT MD (% < -6 dB)	1.54	0.73 – 3.27	0.261
GDx (The Number)	1.01	0.99 – 1.02	0.483
Baseline IOP (mmHg)	1.03	0.94 – 1.12	0.569
Follow-up duration (years)	1.01	0.78 – 1.32	0.918
Mean IOP during follow-up (mmHg)	1.09	0.95 – 1.26	0.220
IOP fluctuation (mmHg)	1.17	0.98 – 1.39	0.091
AGIS approach with interaction term			
Age (years)	1.03	1.00-1.06	0.038
Gender (% male)	0.63	0.34-1.14	0.123
Cardiovascular disease (%)	1.50	0.81-2.78	0.197
HFA MD (% < -6 dB)	1.78	0.81-3.88	0.149
FDT MD (% < -6 dB)	1.53	0.72-3.24	0.269
GDx (The Number)	1.01	0.99-1.02	0.509
Baseline IOP (mmHg)	1.02	0.94-1.12	0.603
Follow-up duration (years)	1.02	0.79-1.32	0.878
Mean IOP during follow-up (mmHg)	1.04	0.85-1.27	0.696
IOP fluctuation (mmHg)	0.85	0.34-2.07	0.712
Mean IOP * IOP fluctuation	1.02	0.97-1.07	0.476
AGIS approach with stepwise selection			
Age (years)	1.03	1.01 - 1.06	0.010
HFA MD (% < -6 dB)	2.72	1.50 – 4.95	0.001
Mean IOP during follow-up (mmHg)	1.16	1.05 - 1.29	0.003
	Hazard ratio	**95% confidence interval**	***P* value**
EMGT approach			
Age (years)	1.03	1.01 - 1.05	0.006
FDT MD (% < -6 dB)	1.75	1.14 - 2.70	0.013
Baseline IOP (mmHg)	1.07	1.02 - 1.11	0.010
CGS approach			
Age (years)	1.03	1.01 - 1.05	0.006
FDT MD (% < -6 dB)	1.75	1.14 – 2.70	0.013
Baseline IOP (mmHg)	1.07	1.02 - 1.11	0.010

HFA = Humphrey Field Analyzer; MD = mean deviation; FDT = Frequency Doubling Technique perimeter; GDx = nerve fiber analyzer; IOP = intraocular pressure.

Table 4 Results of multiple linear regression analyses with rate of progression (mean deviation slope) as dependent variable

	Regression coefficient	**95% confidence interval**	***P* value**
(Intercept)	0.771	0.226 – 1.315	0.006
HFA MD (% < -6 dB)	-0.179	-0.324 – -0.034	0.016
Mean IOP during follow-up (mmHg)	-0.043	-0.067 – -0.019	<0.001
Age (years)	-0.004	-0.010 - 0.001	0.136

HFA = Humphrey Field Analyzer; MD = mean deviation; IOP = intraocular pressure.

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5

Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis

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ABSTRACT

Objective: To determine the association between myopia and open-angle glaucoma.

Design: Systematic review and meta-analysis of observational studies.

***Participants*:** Thirteen studies involving 48,161 individuals.

Methods: Articles published between 1994 and 2010 were identified in PubMed, Embase and reference lists. Study specific odds ratios were pooled using a random effects model.

Main Outcome Measures: Odds ratios with 95% confidence intervals of myopia as a risk factor for open-angle glaucoma.

Results: Data from 11 population-based cross-sectional studies were included in the main analyses. The pooled odds ratio of the association between myopia and glaucoma based on 11 risk estimates was 1.92 (95% confidence interval 1.54 to 2.38). Based on seven risk estimates, the pooled odds ratios of the associations between low myopia (myopia up to -3 dioptres) and glaucoma and high myopia (-3 dioptres and more myopic) and glaucoma were 1.65 (1.26 to 2.17) and 2.46 (1.93 to 3.15), respectively. There was considerable heterogeneity among studies that reported an association between any myopia and glaucoma (I^2=53%) and low myopia and glaucoma (I^2=29%), but not for high myopia and glaucoma (I^2=0%). After omitting the studies that contributed significantly to the heterogeneity, the pooled odds ratios were 1.88 (1.60 to 2.20) for any myopia and glaucoma and 1.77 (1.41 to 2.23) for low myopia and glaucoma.

Conclusions: Individuals with myopia have an increased risk of developing open-angle glaucoma.

INTRODUCTION

Myopia, or short-sightedness, affects about 1.6 billion people worldwide and the prevalence is expected to rise to 2.5 billion by the year 2020.[1-2] Myopia has long been identified as a risk factor for open-angle glaucoma (OAG).[3-6] OAG is an irreversible eye disease responsible for approximately 12% of global blindness, which is second to cataract.[7] It is largely unknown why myopia increases the risk of OAG. Myopic eyes have longer axial lengths and vitreous chamber depths,[8-9] and eyes with an increased axial length seem to have a greater deformability of the lamina cribrosa. This might contribute to a higher susceptibility to glaucomatous optic disc changes.[8,10]

There is conflicting evidence concerning the range of refractive error important for OAG. While some studies have reported an association with any myopia,[11-14] others have found the relationship only in individuals with high myopia.[15-18] A better understanding of the role of the magnitude of the refractive error is clinically important from the point of view of individualized risk management, amongst others.

The reported associations between myopia and OAG are predominantly based on the results of observational studies. However, to the best of our knowledge, a systematic approach to quantitatively combine the results of all available studies evaluating the association between myopia and OAG does not exist. The aim of this review is to examine the magnitude of the association between myopia and OAG by systematically identifying and quantitatively combining all available and relevant observational studies.

METHODS

Search strategy

Two of the authors (MMV and FGJM) independently conducted a systematic search of Pubmed and Embase up to 27 October 2010 in accordance with the MOOSE consensus statement.[19] The search terms used in PubMed included ((("myopia"[MeSH Terms] OR "myopia"[All Fields]) OR myopic[All Fields] OR ("refractive errors"[MeSH Terms] OR ("refractive"[All Fields] AND "errors"[All Fields]) OR "refractive errors"[All Fields] OR ("refractive"[All Fields] AND "error"[All Fields]) OR "refractive error"[All Fields])) AND (OAG[All Fields] OR POAG[All Fields] OR ("glaucoma"[MeSH Terms] OR "glaucoma"[All Fields])) AND (("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields]) OR ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields]) OR determinant[All Fields] OR determinants[All Fields] OR ("association"[MeSH Terms] OR "association"[All Fields]) OR associated[All Fields]). For Embase we used (myopia/exp OR myopia OR myopic OR refractive) AND (error/exp OR error) AND (OAG OR POAG OR glaucoma/exp OR glaucoma) AND (((((risk/exp OR risk) AND factor) OR risk/exp OR risk) AND factors) OR determinant OR determinants OR association/exp OR association OR associated).

Retrieved studies from both Pubmed and Embase were imported into Refworks (version 1.0; Refworks, Bethesda, Maryland, USA) where duplicate articles were manually deleted. Titles and abstracts of the remaining studies were independently scanned by two authors (MWM and MMV). The extracted studies were compared and inconsistencies were resolved by consensus. The full texts of the remaining studies were then read to determine if they met our inclusion criteria. In addition, the reference lists from all identified studies were examined.

Inclusion and exclusion criteria

Studies were included if they (i) reported myopia as covariate, (ii) had OAG as the outcome measure, and (iii) reported a measure of the association either as odds ratio (OR) or hazard ratio (HR) with 95% confidence interval (CI), or allowed for the calculation of it from the raw data presented in the article. We excluded (i) studies involving secondary glaucoma or angle-closure glaucoma, (ii) studies published in non-English language, and (iii) studies without a clear-cut definition of myopia and or detailed description of OAG assessment. When multiple publications from the same study population were available, we checked for duplicate analysis and included only the most recent publication.

Data extraction and quality assessment

For each study, the following characteristics were extracted: (i) last name of first author, (ii) year of publication, (iii) study design, (iv) race/ethnicity of the study population, (v) number of subjects in the analysis, (vi) age range of subjects included in the studies, (vii) case definition of OAG, (viii) definition of myopia, (ix) the effect estimate(s), and (x) which confounding factors was adjusted for. The study quality was assessed with the tool described by Sanderson et al.[20] The variables examined included the methods for selecting study participants, methods for measuring exposure (myopia) and outcome variable (OAG), design-specific sources of bias (excluding confounding), methods for controlling confounding, statistical methods (excluding control of confounding), and conflict of interest.

Statistical Analysis

The fully-adjusted study specific ORs were combined to estimate the pooled OR with 95% CI using the random effects model. The random effects model was chosen because it accounts for both within-study and between-study variability, and we expected significant heterogeneity among the included studies. For the Andhra Pradesh study,[21] that reported results for urban and rural cohorts separately, we combined the two ORs and subsequently included the pooled OR in the meta-analysis. Most of the studies included in our meta-analysis reported both an OR for any myopia and ORs after stratification. For studies that only reported stratified ORs, we pooled the ORs to obtain an overall estimate for any myopia. Following the stratification as used in the majority of the studies, myopia was stratified in low myopia, defined as myopia with a spherical equivalent refractive error up to -3 dioptres, and high myopia, defined as a spherical equivalent refractive error of -3 dioptres and more myopic.

Statistical heterogeneity among studies was evaluated using I^2 Statistic. I^2 is the percentage of the total variation across the studies that is due to heterogeneity.[22] Values of less than 24%, 25-49%, 50-74% and 75% or above denote no, low, moderate and high heterogeneity, respectively.[23] Heterogeneity due to study design was avoided by restricting the main analyses to population-based cross-sectional studies only. Furthermore, we performed a sensitivity analysis which investigates the contribution of each study to the heterogeneity by sequentially omitting one study and reanalysing the pooled estimate for the remaining studies.[24] Publication bias was evaluated with the use of Egger regression asymmetry test and the Begg's test.[25,26] All statistical analyses were performed with Stata version 11.1 (StataCorp, College Station, Texas, USA). A two-sided p value less than 0.05 was regarded as significant for all analyses.

RESULTS

Figure 1 shows the selection process. The literature search yielded 1176 articles; 527 from PubMed and 649 from Embase, of which 70 were reviewed in full text. After a thorough review, 13 studies met the inclusion criteria for this meta-analysis.[21,27-38] All studies were population based; 11 cross-sectional,[28-37] one case-control,[27] and one longitudinal cohort study.[38] Six studies were conducted in Asia,[21,32-36] two in North America,[31,37] two in Australia,[29-30] two in Europe,[27,38] and one in Barbados.[28] Table 1 (available at http://aaojournal.org) presents the characteristics of the included studies. The studies were published between 1994 and 2010 and comprised a total study population of 48,161 individuals. The definition of OAG and myopia varied across studies. Three studies included an increased IOP in their case definition of OAG,[27,30,31] one study included the family history of OAG,[30] and two studies included a history of glaucoma treatment.[27,31] Seven studies included the cup-disk ratio (a measure of optic nerve damage) with different cut-off values;[21,27,29-32,35] all studies included a visual field test.[21,27-38] Seven of the 13 included studies reported risk estimates for low and high myopia separately.[29,31-34,36,37]

The pooled OR for all 13 studies was 1.93 (95% CI 1.57 to 2.37; I^2=55%; P=0.01). To avoid heterogeneity due to study design, two studies (one case-control and one cohort study) were subsequently excluded from the analyses.[27,38] Figure 2 presents the multivariate ORs for each study separately and for the 11 cross-sectional studies combined. The pooled OR of the association between any myopia and OAG was 1.92 (95% CI 1.54 to 2.38). There was a statistically significant heterogeneity among the 11 cross-sectional studies (I^2=53%; P=0.02). Sensitivity analysis showed that the Andhra Pradesh study and the Beijing study substantially influenced the pooled OR. After excluding these two studies, the pooled OR was 1.88 (95% CI 1.60 to 2.20) with no evidence of heterogeneity (I^2=7%; P=0.38).

From the 11 included studies, seven studies reported risk estimates for both low and high myopia. Figure 3 shows the ORs of the association between low myopia and OAG. The pooled OR was 1.65 (95% CI 1.26 to 2.17) with a low heterogeneity (I^2=29%; P=0.21). Sensitivity analysis showed that the Beijing study substantially influenced the pooled OR. After excluding this single study, the pooled OR was 1.77 (95% CI 1.41 to 2.23) with no evidence of heterogeneity (I^2=0%; P=0.66). Figure 4 shows the ORs of the association between high myopia and OAG. The pooled OR was 2.46 (95% CI 1.93 to 3.15) with no heterogeneity (I^2=0%; P=0.45). There was no evidence of publication bias as indicated by a non-significant Egger test (P=0.25) and Beggs's test (P=0.13).

DISCUSSION

The findings from this meta-analysis indicate that individuals with myopia have a roughly doubled risk of developing OAG in comparison with individuals without myopia. The pooled ORs were 2.46 (95% CI 1.93 to 3.15) for high myopia and 1.77 (95% CI 1.41 to 2.23) for low myopia, with a cut-off value of -3 dioptres.

Although the point estimate of the pooled OR of high myopia was larger than that of low myopia, the difference was small. A more pronounced dose-response relationship would have reinforced the association between myopia and OAG. The apparent absence of a clear dose-response relationship might be the consequence of the population-based design of the included studies. Myopia beyond, for example, -10 dioptres is seen on a regular basis in a clinical setting. In a population-based sample, however, most participants with high myopia have a refractive error between -3 and -4 dioptres, and values beyond -5 dioptres are rare.[39-41]

The observed heterogeneity among the included cross-sectional studies was explained by the Andhra Pradesh study and the Beijing study. Although these studies, in contrast to the majority of the included studies, were conducted in Asia and included both urban and rural cohorts, the disparate results of these two studies in this meta-analysis remain unclear. Two studies, Ponte et al.[27] and Czudowska et al.[38] were omitted beforehand because of different study designs. In their case-control study, Ponte et al. reported an association between myopia (-1.5 dioptres and more myopic) and OAG with an OR of 5.56 (95% CI 1.85 to 16.67). In their population based cohort study, Czudowska et al. reported an association between high myopia and incident OAG with a HR of 2.31 (95% CI 1.19 to 4.49); the association between low myopia and incident OAG was not significant (HR 1.16; 95% CI 0.72 to 1.88). These studies confirm the presence of an association between myopia and OAG.

Strengths of this meta-analysis include the population-based design of the included studies and their high response rates, ranging from 78.7% to 97.3%. The population-based design is likely to minimize the possibility of selection bias. Even if myopes would be preferentially ascertained (because they might be more eager to participate in an eye study), this could bias the estimate of the prevalence of myopia, and thus of the prevalence of glaucoma, but not of the association between myopia and glaucoma. Selection bias may be present in clinical case-control studies, for example because individuals with myopia tend to visit an optician or ophthalmologist more often than individuals with emmetropia, and therefore are more likely to be diagnosed with OAG. An increased optician or ophthalmologist visit frequency amongst myopic subjects, however, may also introduce a bias in population-based studies: the treatment of a timely detected ocular hypertension may prevent or delay the development of OAG. By adjusting the analyses for the intraocular pressure, as is done in most studies (Table 1; last column; available at http://aaojournal.org), the effect of this bias should have been minimised as much as possible.

Moreover, if this bias would dominate the results, a protective effect of myopia would have been found. Residual or unknown confounding could be present in the included studies and thus in the pooled analysis. Inadequate control for confounding factors may bias the results towards both underestimation and overestimation of ORs.

The way patients were diagnosed with myopia and OAG differed between the included studies and therefore some diagnostic bias might be present. As can be seen in Table 1 (available at http://aaojournal.org), the cut-off point between low and high myopia varied between -3 and -4 dioptres (-3 dioptres in most studies); the cut-off point between emmetropia and (low) myopia varied between -0.01 and -1.5 dioptres (-0.5 or -1 dioptres in most studies). The OAG definition was based on a combination of glaucomatous visual field loss and optic disc abnormalities in most studies, with various criteria and cut-off points. Visual field defects as well as anomalous appearing optic discs have been reported in persons with myopia.[42-44] This could have resulted in either an over-classification or an under-classification of OAG in persons with myopia because of the difficulties in classifying the optic disc and the visual field in some myopic eyes. This misclassification of OAG may have biased the reported effect estimate of the association between myopia and OAG. Moreover, persons with myopia have – on average – slightly larger optic discs and, related to that, larger excavations.[43-45] As most OAG definitions relied on the size of the excavation without adjusting for the size of the optic disc, this may have resulted in an overestimation of the presence of OAG in participants with myopia. Such an overestimation could partially explain the reported increased risk. However, the fact that the only longitudinal study yielded roughly the same results suggests that all these potential sources of misclassification did not produce a substantial bias (compared to cross-sectional data, incident data should be less prone to misclassification of abnormal or large optic discs and myopic visual field loss).[38] Ponte et al.[27] required their controls to have very small optic disc excavations. This requirement may have resulted in an underrepresentation of myopia amongst the controls (see

above), and this might explain their large odds ratio. Their wide confidence interval, however, precludes firm conclusions.

Finally, the major setback of published studies and of meta-analyses of published studies in general is publication bias. Publication bias may be an issue because studies that report statistically significant results are more likely to get published than studies that report non-significant results and this could have distorted the findings of our meta-analyses.[46] However, Egger regression asymmetry test and the Begg's test suggested no evidence of publication bias in our study.

In conclusion, findings from this meta-analysis indicate that subjects with both low myopia and high myopia have an increased risk of developing OAG. This should be taken into account when it comes to individualized risk management in, for example, screening or treatment decisions. Future research is warranted to determine the association between myopia and OAG in severe myopia (which is rare in population-based samples) and to elucidate the pathophysiological mechanism underlying the association between myopia and OAG.

Table 1. Characteristics of the included studies

Source	Study design	Race / Ethnicity	Study population	Age	Definition of glaucoma	Definitions of myopia (SEq in dioptres)	Odds Ratio (95%CI)	Adjusted covariates
Ponte et al. *The Casteldaccia Eye Study (1994)*[27]	Population-based case-control study	White	264	≥40	Cases: IOP ≥24 mmHg, history of treated glaucoma, GVFL. Controls: IOP ≤20 mmHg, CD-ratio: 0-0.2, pink discs, no aphakia or pseudophakia, no history of (treated) glaucoma	<-1.5*	5.6(1.9-16.7)*	Age, gender, ocular steroids or antibiotics use, shallow anterior chamber, DM, hypertension, iris texture, myopic macular degeneration
Wu et al. *The Barbados Eye Study (1999)*[28]	Population-based cross-sectional	Black	4036	40-84	GVFL, optic disc abnormalities	<-0.5*	1.5(1.1-2.0)*	Age, gender, SES, lens opacity
Mitchell et al. *The Blue Mountains Eye Study (1999)*[29]	Population-based cross-sectional	White	3654	49-97	GVFL, CD-ratio ≥0.7 or asymmetry ≥0.3	≤-1.0* ≤-1.0 to >-3.0† ≤-3.0‡	2.4(1.5-4.0)* 2.3(1.3-4.1)† 3.3(1.7-6.4)‡	Age, gender, family history, DM, steroid use, typical migraine history, hypertension, pseudo-exfoliation
Weih et al. *Visual Impairment Project (2001)*[30]	Population-based cross-sectional	Diverse	4498	≥40	IOP ≥22mmHg, GVFL, CD-ratio ≥0.8 or asymmetry ≥0.4, family history of glaucoma	≤-0.5*	1.6(0.9-6.7)*	Age,rural residence and family history
Wong et al. *The Beaver Dam Eye Study (2003)*[31]	Population-based cross-sectional	White	4670	43-86	GVFL, IOP ≥22 mmHg, CD-ratio ≥0.8 or asymmetry ≥0.2, history of glaucoma treatment	≤-1.0* ≤-1.0 to >-3.0† ≤-3.0‡	1.6(1.1-2.3)* 1.6(1.1-2.4)† 1.5(0.8-2.6)‡	Age, gender
Ramakrishnan et al. *The Aravind Comprehensive Eye Survey (2003)*[32]	Population-based cross-sectional	Indian	5150	≥40	GVFL, CD-ratio ≥0.9 or asymmetry ≥0.3, optic disc abnormalities, normal gonioscopy	<-0.5* Mild Moderate Severe	2.8(1.7-4.6)*^ 2.9(1.3-6.9)† 2.1(1.0-4.6)‡ 3.9(1.6-9.5)‡	Age, gender, DM, hypertension, pseudo-exfoliation
Suzuki et al. *The Tajimi Study (2006)*[33]	Population-based cross-sectional	Japanese	2874	≥40	optic disc abnormalities, perimetric results, other ocular findings	<-1.0* <-1.0 to >-3.0† ≤-3.0‡	2.2(1.5-3.3)*^ 1.9(1.0-3.3)† 2.6(1.6-4.4)‡	Age, IOP
Xu et al. *The Beijing Eye Study (2007)*[34]	Population-based cross-sectional	Chinese	4319	≥40	optic disc abnormalities, GVFL	<-0.5* Low to moderate	3.8(2.1-6.7)*^ 0.6(0.3-1.5)†	Age, IOP

						Marked or high	4.7(1.8-12.5)‡	
Casson et al. *The Meiktila Eye Study (2007)*[35]	Population-based cross-sectional	Diverse	1997	≥40	CD-ratio ≥0.7 or ≥0.6 with asymmetry ≥0.3, reduced NRRW, GVFL, >90^0 of TM visible	<-0.5*	2.7(1.0-7.5)*	Age, IOP, AL
Garudadri et al. *The Andhra Pradesh Eye Disease Study (2010)*[21]	Population-based cross-sectional	Indian	3724	≥40	Asymmetrical CD-ratio, NRRW reduced to 0.1, GVFL	≤-0.5*	1.0(0.6-1.6)*^	Age, DM, gender, IOP, hypertension
Perera et al. *The Singapore Malay Eye Study (2010)*[36]	Population-based cross-sectional	Malay	3109	40-80	optic disc abnormalities, GVFL	<-0.5* <-0.5 to ≥-4.0† <-4.0‡	1.8(0.9-3.7)*^ 1.3(0.6-2.7)† 2.8(1.1-7.4)‡	Age, gender, IOP, education, height, CCT, hypertension, HbA_{1c}
Kuzin et al. *The Los Angeles Latino Eye Study (2010)*[37]	Population-based cross-sectional	Latino	5927	≥40	optic disc abnormalities, GVFL	≤-1.0* ≤-1.0 to >-3.0† ≤-3.0‡	1.8(1.2-2.8)* 1.6(0.9-2.6)† 2.0(1.1-3.7)‡	Age, IOP, DM, gender, family history, NO, CP
Czudowska et al. *The Rotterdam Study (2010)*[38]	Population-based cohort study	White	3939	≥55	Incident GVFL	≤-0.01* ≤-0.01 to >-4.0† ≤-4.0‡	1.5(1.1-2.0)*^# 1.2(0.7-1.9)†# 2.3(1.2-4.5)‡#	Age, gender, IOP, IOP treatment, family history, baseline GON

Abbreviations: SEq = spherical equivalent; CI= confidence interval; IOP = intraocular pressure; GVFL = glaucomatous visual field loss; CD = cup disk; DM = diabetes mellitus; SES = social economic status; NRRW = neuro retinal rim width; TM = trabecular meshwork; AL = axial length; CCT = central corneal thickness; HbA_{1c} = hemoglobin A1c; NO = nuclear opacification;CP = corneal power; GON = glaucomatous optic neuropathy; * = any myopia; † = low myopia; ‡ = high myopia; ^ = calculated from data contained in the article; # = hazard ratio.

Figure 1 Flow diagram showing the selection process for inclusion of studies in the meta-analysis

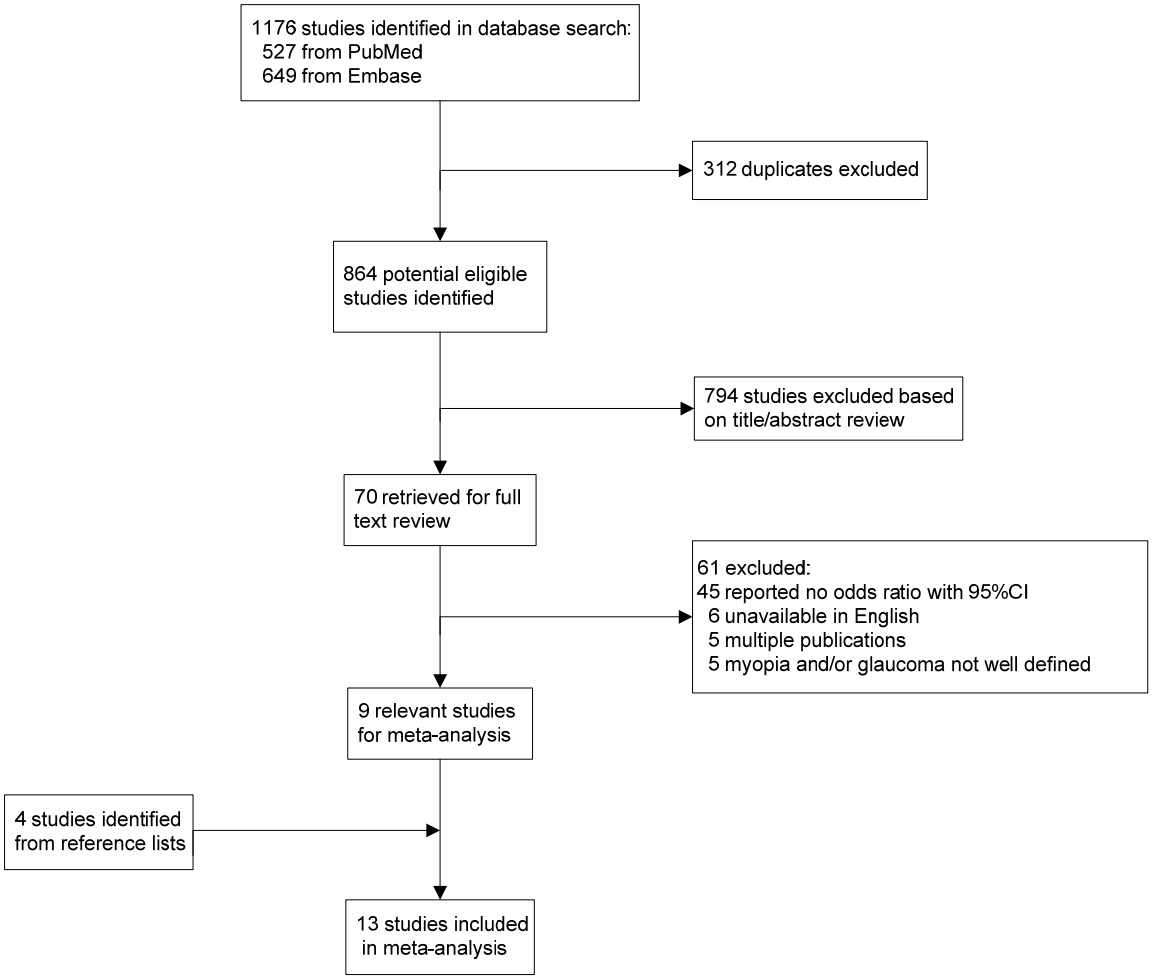


Figure 2 Forest plot of risk estimates of the association between myopia and open-angle glaucoma

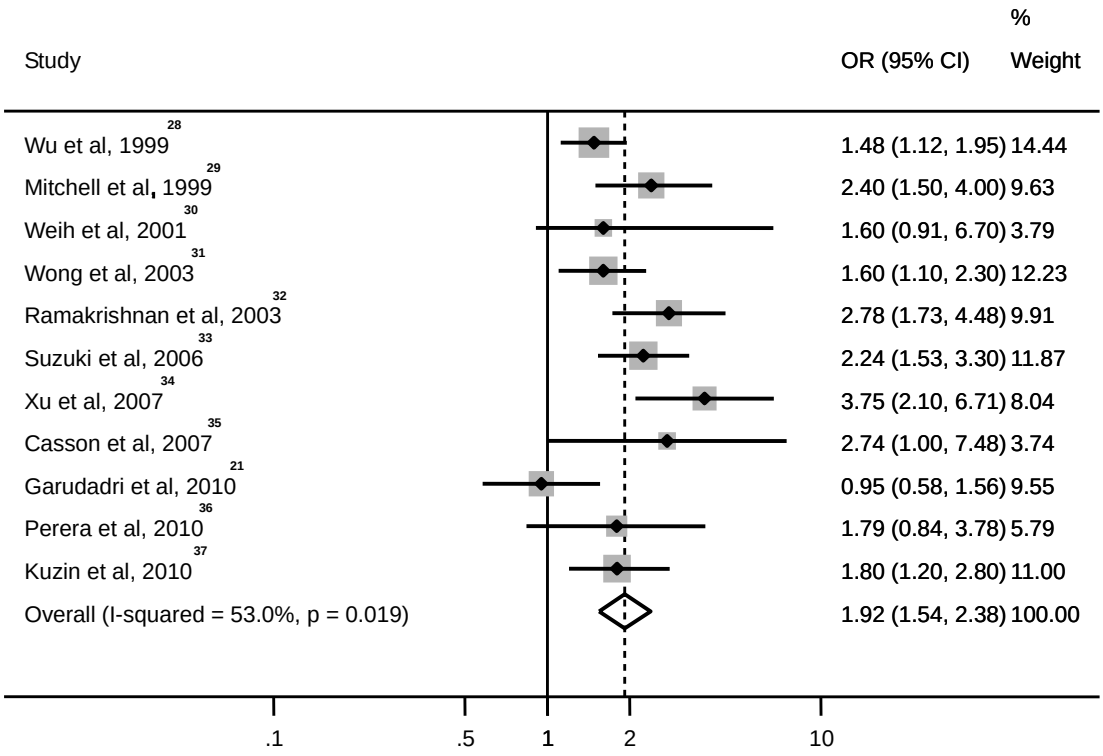


Figure 3 Forest plot of risk estimates of the association between low myopia myopia and open-angle glaucoma

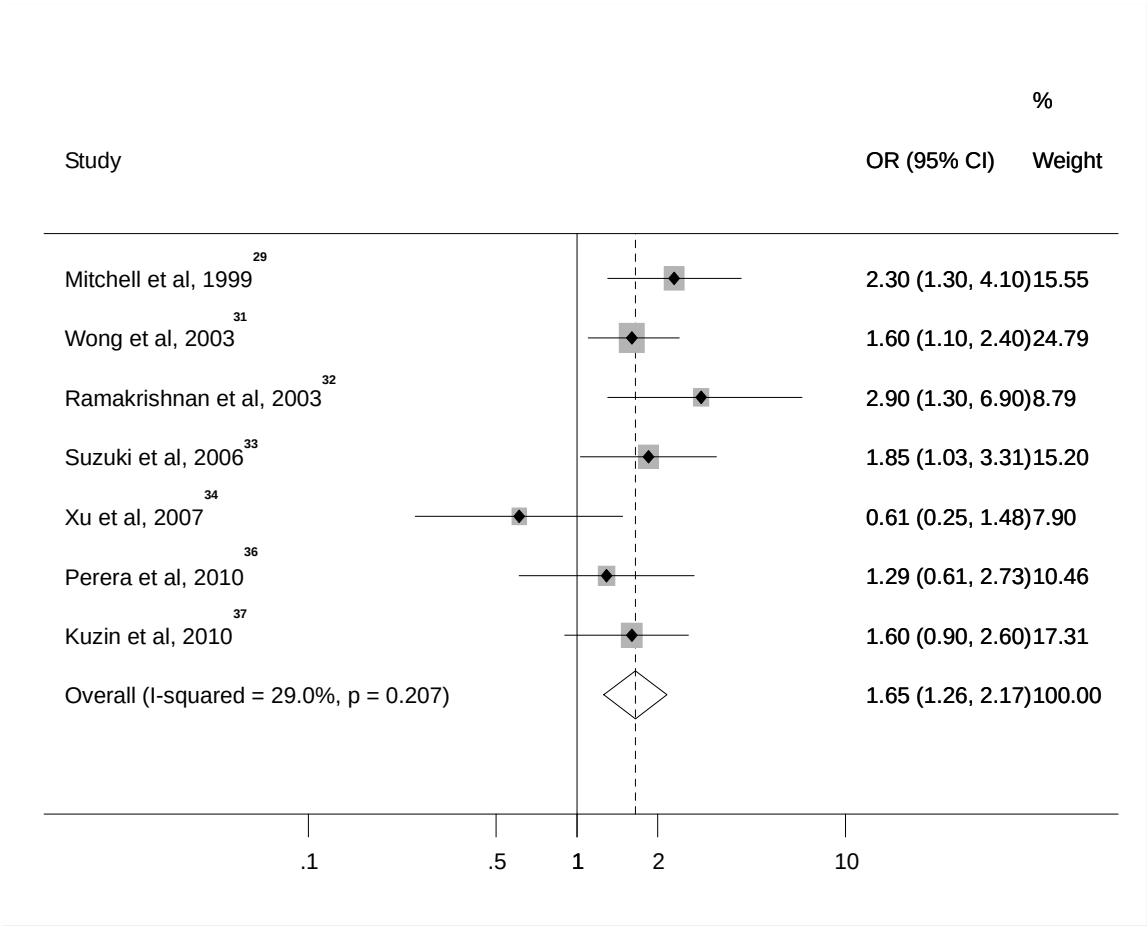
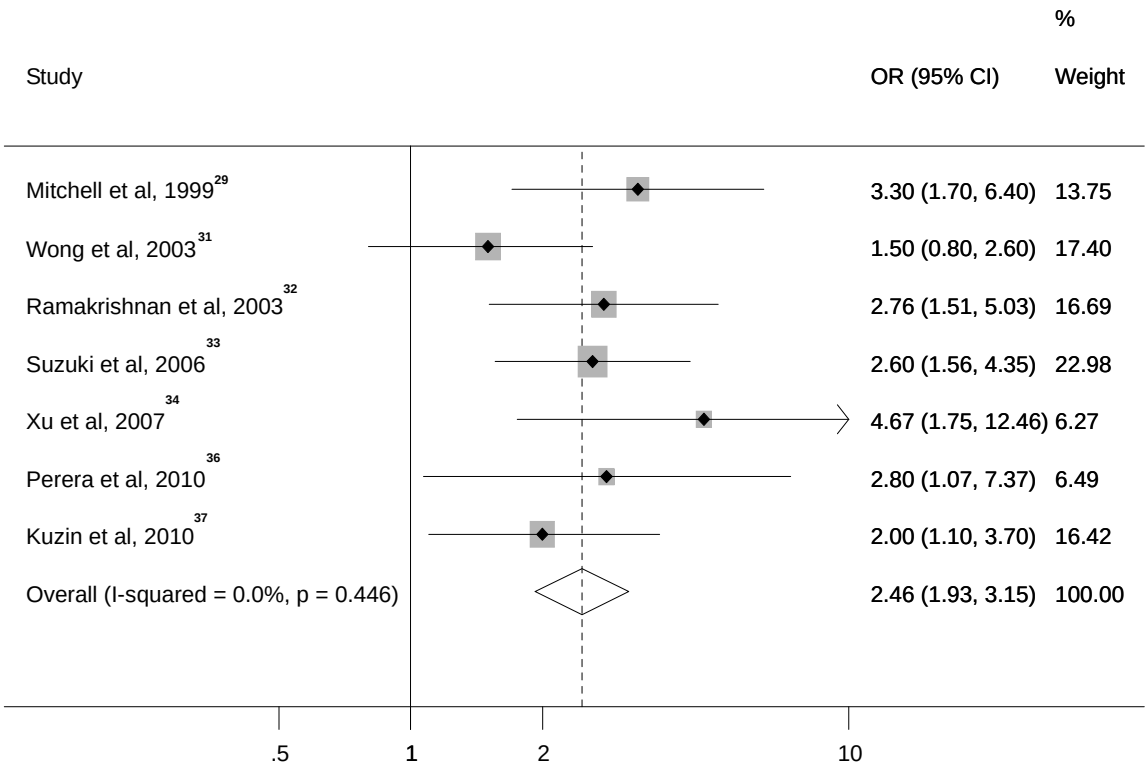


Figure 4 Forest plot of risk estimates of the association between high myopia myopia and open-angle glaucoma



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6

Systemic medications and open-angle glaucoma - a systematic review of the literature

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Abstract

Medications administered systemically can cause a substantial rise in the intraocular pressure (IOP) and thus induce open-angle glaucoma (OAG). Well-known and extensively studied medications with this side effect are corticosteroids. The anti-neoplastic agents docetaxel and paclitaxel have also been reported to have this side effect but this suspicion appeared to be based on a single case report. Other systemic medications are associated with a lowering of the IOP. Drugs that fall into this category include carbonic anhydrase inhibitors and cannabinoids. Several anti-hypertensive medication classes have been reported to be related to OAG, both in a protective and a harmful manner, and at least partially through IOP-independent mechanisms. Ginkgo biloba extract has been reported to increase ocular blood flow and cholesterol-lowering drugs appear to reduce the risk of OAG and slow down its progression – presumably through an IOP-independent mechanism. In addition, we will also report findings about the effect of antithrombotics and estrogens on OAG. The objective of this review is to present and evaluate the current state of knowledge of the effect of systemic medications on OAG.

Introduction

Although the beneficial effects of systemic medications are numerous, they can also trigger undesirable side effects. Undesirable side effects have been documented for almost all medications on various body tissues and organs including the eye.[1-7] Unwarranted ocular effects may progress and cause irreversible damage, resulting in visual impairment and blindness.[7,8] Corticosteroid-induced glaucoma is an example of such an adverse effect of medications in which patients develop an elevated intraocular pressure (IOP), optic neuropathy and visual field defects indistinguishable from open-angle glaucoma (OAG).[2,9] OAG, the eye disease targeted in this review, is responsible for approximately 12% of global blindness, which is second to cataract.[10]

Traditionally, the management of OAG is targeted towards the reduction of the IOP (the only modifiable risk factor) and systemic medications that cause an increase in IOP are the most obvious medications that have OAG as a side effect. The corticosteroids mentioned above are the most well-known example of medications that can cause a substantial rise in IOP and thus induce OAG.[11,12] Some patients develop OAG without a clearly elevated IOP. Here, individual variation of the susceptibility of the optic nerve may play a role. Also, some factors influence the course of the disease without altering the IOP, suggesting a vascular component or a role for neuroprotection.[13-16] An example is the IOP-independent protective effect of statins.[17]

Despite its public health relevance, reviews summarizing evidence-based information about OAG and its association with systemic medications mainly focus on steroid-induced OAG and angle closure glaucoma.[11,18-20] The objective of this systematic review is to present and evaluate the current state of knowledge of the effects of systemic medications on OAG.

Search strategy

Articles assessed for this review were identified by an electronic search of PubMed and Embase, for English language studies from the inception of the databases till March 2011. We reviewed all relevant articles related to glaucoma and systemic medications, glaucoma and systemic diseases, and glaucoma medications, by using in PubMed the search term ("glaucoma"[MeSH Terms] OR "glaucoma"[All Fields]) AND systemic[All Fields] AND ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medications"[All Fields]) AND ("glaucoma"[MeSH Terms] OR "glaucoma"[All Fields]) AND systemic[All Fields] AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "diseases"[All Fields]) AND ("glaucoma"[MeSH Terms] OR "glaucoma"[All Fields]) AND ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medications"[All Fields]) and in Embase systemic AND diseases AND glaucoma/exp AND medications. For those medications found with this strategy, a further systematic search was performed in the same databases. For example, the search term used for "cannabinoids" in Pubmed was (("cannabinoids"[MeSH Terms] OR "cannabinoids"[All Fields] OR "cannabinoid"[All Fields]) AND ("glaucoma"[MeSH Terms] OR "glaucoma"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang]) and in Embase 'cannabinoids'/exp AND 'glaucoma'/exp AND [humans]/lim AND [english]/lim AND [embase]/lim .In addition, the reference lists from all identified studies were examined. Duplicate studies and studies reporting on angle-closure glaucoma were excluded. Systemic mediactions identified with this strategy were corticosteroids, docetaxel and paclitaxel, anti-hypertensive medications, antithrombotics, carbonic anhydrase inhibitors, cannabinoids, Ginko biloba extract, cholesterol-lowering drugs, and estrogens.

Corticosteroids

Corticosteroids have widespread clinical application and their anti-inflammatory properties make them also highly potent agents for ocular diseases.[21] Since their introduction to ophthalmology in the 1950s,[22] various ocular adverse effects including corticosteroid-induced glaucoma[23] and cataract[24] have been reported related to the topical application of steroids. The mechanism by which corticosteroids elevate the IOP is thought to be due to the accumulation of undegraded extracellular matrix material in the trabecular meshwork, thus impeding the outflow channels and increasing the outflow resistance.[25,26] Individuals who develop an increase in IOP after steroid therapy are referred to as steroid responders.[27-29] Glaucoma with a clinical picture similar to that of primary OAG (POAG) may develop if the IOP elevation is of sufficient magnitude and duration: steroid-induced glaucoma. In the literature, several risk factors have been suggested for being a steroid responder. They include the presence of POAG or its family history, age, diabetes mellitus, high myopia and rheumatoid arthritis.[30-39] Of these factors, the positive family history, age and high myopia are established risk factors for POAG as well.[33,40,41] Thus far, evidence supporting connective tissue diseases such as rheumatoid arthritis to be a risk factor for steroid responsiveness was mainly reported in case studies and case series and the results were inconclusive. For example, Bernstein reported an elevated IOP in 48 patients taking oral steroids for rheumatoid arthritis or other collagen diseases when compared to age and sex matched controls not taking steroids.[42] Although they attributed this to the systemic steroids, none of the controls had rheumatoid arthritis or other collagen diseases. In contrast, Belousna reported a lower IOP in 60 patients taking systemic steroids for collagen diseases when compared to the normal individual.[43] However, there was no report on the IOP of patients with collagen diseases who were not on steroid therapy. Gaston et al reported a higher incidence of steroid responsiveness than would be expected in a normal population in 34 patients with connective tissue diseases who were on steroid therapy.[44] They suggested

that the damage to the trabecular meshwork as a possible mechanism of steroid responsiveness.

For ophthalmologists, the topical corticosteroids are the most commonly prescribed class of steroids, and presumably the class most clearly related to the steroid response and to steroid-induced glaucoma. The question is on how far other classes of steroids, being the oral, inhaled and nasal steroids, and the steroid ointments, may induce steroid-induced glaucoma as well. Till date, most information about corticosteroid-induced glaucoma has been based on case reports. In addition to these case reports, Garbe et al. published two studies evaluating the association between the use of oral, inhaled, and nasal steroids and the risk of ocular hypertension or OAG in a health insurance database.[45,46] In these large case control studies, the use of inhaled and nasal steroids was not associated with an increased risk of ocular hypertension or glaucoma. However, they found an association in a subgroup of subjects with a prolonged administration of high doses of inhaled steroids (odds ratio [OR] 1.44; 95% confidence interval [CI] 1.01-2.06).[45] Furthermore, the use of oral steroids was shown to increase the risk of ocular hypertension or OAG (OR 1.41; 95% CI 1.22-1.63).[46] Mitchell et al. evaluated the association between the use of ophthalmic steroids, oral steroid and inhaled steroids and the risk of an elevated IOP or OAG in a cross-sectional population based study.[47] In this study there was only an association between inhaled steroid use and the presence of either OAG or elevated IOP in persons with a positive family history of glaucoma (OR 2.6; 95%CI 1.2-5.8). The use of oral steroids or ophthalmic steroids was not associated with an elevated IOP or OAG. Haeck et al. evaluated the association between the use of topical corticosteroids and the development of glaucoma and cataract. This retrospective study included 88 atopic dermatitis patients of whom 37 used topical steroids on their eyelids and periorbitally for an average duration of 4.8 years. In this study, the application of topical corticosteroids was not associated with the development of glaucoma or cataract in their study population.[48]

In a prospective population-based cohort study, we recently evaluated the association between all classes of steroids, being ophthalmic, inhaled, oral and nasal steroids and steroid ointments, and the 10-year risk of OAG in 3939 participants aged 55 years and older.[49] In this study, the use of any class of steroids was not associated with the incidence of OAG. In addition, we performed a systematic review of the literature to identify all published case reports regarding steroid induced glaucoma. Table 1 summarizes the results.[50-90] The review yielded 41 publications together reporting 74 cases.[50-90] The median age of these cases was 32 years, with a range from 3 weeks to 80 years. In the 74 cases, the OAG was presumed to be caused by ophthalmic steroids in 38 cases,[51-55,59,65,66, 72,78-80,84-87,89,90] by inhaled steroids in one case,[71] by nasal steroids in two cases,[73] by oral steroids in nine cases,[52,56,69,76,81-83] and by steroid ointments in 31 cases.[57-64,67-70,74,77,86-88,90]. Myopia was reported as a risk factor in seven cases,[51,56,57,65,77,85,87] a positive family history of glaucoma in eight cases,[51-53,57,58,62,75,85] diabetes mellitus in two cases,[51,73] and hypertension in one case.[76]

In the systematic review of published case reports, the most obvious finding was that the median age was 32 years and 81% of the identified cases were younger than the youngest age of 55 years of our study cohort. OAG before the age of 55 years is relatively rare.[91] This might suggest that steroid-induced glaucoma is an entity mainly limited to younger age groups. However, Garbe et al. included only individuals 65 years and older in their study. The results of Garbe et al. seem to conflict with that of our cohort study. Possible explanations for this apparent discrepancy are power limitations in our study and selection bias in the study of Garbe et al. (Chapter 2). The age ranges were between 49 and 97 years in the study of Mitchell et al.[47] and 37.2 ± 14.3 years (mean ± standard deviation) in the study of Haeck et al.[48]

Docetaxel and Paclitaxel

Docetaxel and paclitaxel belong to the family of chemotherapeutic drugs called taxanes.[92] They are used for the treatment of various neoplastic diseases including breast cancer.[93-96] Taxane-induced glaucoma was first reported in 1999 by Fabre-Guillevin et al.[97] In their report, a 31-year-old woman with a history of breast carcinoma who was on docetaxel therapy and who also used corticosteroids as an adjunct therapy developed an elevated IOP of 44 mmHg (normal range 10-21 mmHg). Optic discs and visual fields were normal; the angle was wide open. Docetaxel was discontinued and a topical β-blocker was started, together yielding an IOP within the normal range. However, on follow-up treatment with paclitaxel and methylprednisone, the IOP increased again and cupping of the optic discs and visual field defects developed. The authors attributed these findings to taxane use despite the concurrent use of corticosteroids; they based this conclusion on the absence of visual complaints during earlier use of corticosteroids alone, before the use of taxane. De Giorgi et al.[98] reported a 56-year-old woman affected by breast cancer who developed bilateral visual field loss during treatment with paclitaxel. Unlike in the earlier case, this woman developed visual field loss without an increased IOP. This patient was part of a prospective study with 12 patients on paclitaxel therapy of whom two additional patients developed visual field loss. In all three cases, the visual field loss resolved within 6 months after the end of the therapy. The IOP was normal in all 12 patients. De Giorgi et al. also suggested that the visual field loss might be due to neurotoxicity.

The taxanes are recognized as evidenced-based essential components of therapy for metastatic breast cancer.[99] In 2008, 182.460 women were estimated to be diagnosed with breast cancer in the United States.[100]

Despite the fact that paclitaxel and docetaxel are considered as fundamental drugs in the treatment of breast cancer, only one case of taxane-induced has been published thus far,[97] and in that case corticosteroids might have attributed to the OAG as well. All this questions the paradigm of taxane-induced OAG.

Antihypertensive medications

Antihypertensive medications including calcium channel antagonists (CCAs), β-blockers, diuretics and angiotensin converting enzyme (ACE) inhibitors are widely used drugs for the therapeutic management of hypertension.[101] Hypertension is an important risk factor for cardiovascular disease and cardiovascular disease have been implicated in the impaired vascular perfusion of the optic nerve head.[102] Because hypertension is generally treated with antihypertensive medications, it is difficult to attribute a possible increased risk of OAG to hypertension or its treatment. Several population-based studies have consistently reported an association between blood pressure and IOP .[103-107] Because blood pressure is positively associated with IOP, systemic hypertension may indirectly increases the risk of OAG. However, the evidence of an association between hypertension and OAG is not strong and most of the reports are inconsistent.[108-111] Antihypertensive medications have different mechanisms of actions. We hereby summarize the effects on OAG of the commonly used anti-hypertensive medications CCAs, β-blockers, diuretics and ACE inhibitors.

Calcium channel antagonists

The usage of CCAs in clinical medicine is dated back to the 1960's.[112] CCAs mediate their actions through the inhibition of the influx of calcium ions in cells, which causes relaxation of the vascular smooth muscle cells, reduction of the vascular resistance and

elevation of the regional blood flow in several organs including the eye.[113-117] Earlier studies have reported conflicting results about the effect of CCAs on IOP in both humans and rabbits.[118,119] In contrast, later studies have reported an IOP reduction in experimental animals and humans.[120-123] A beneficial effect of CCAs on the visual field in patients with normal tension glaucoma (NTG) has been reported.[124-127] In the study of Kitazawa et al., 25 consecutive patients with NTG received oral nifedipine 30 mg/day for six months.[124] The visual field was tested with standard automated perimetry prior to and monthly during the period of nifedipine administration. Six patients showed an improvement of the visual field as expressed by an increase in mean sensitivity (MS). In this study, there was no control group and they did not control for IOP; any differences in IOP between the groups. Koseki et al. studied 52 patients (average age 57.7 years) with NTG who were randomly assigned to receive oral brovincamine (20 mg three times daily) or to an untreated control group.[125] The two groups were followed prospectively for 2 years with standard automated perimetry every 4 months. Changes in mean deviation (MD), corrected pattern standard deviation (CPSD), and total deviation (TD) at 74 test points were analyzed using regression analysis with a linear mixed model. They concluded that oral brovincamine seems to retard further visual field deterioration. Mean changes in MD (standard error) during the study period were -0.07 (0.20) and -0.78 (0.18) dB/year in the brovincamine and control groups, respectively. In CPSD the mean changes (standard error) were 0.004 (0.016) and 0.032 (0.015) dB/year in the brovincamine and control group, respectively. The TD values were significantly deteriorating in six of 74 test points in the control group, whereas no points showed a significant trend in the brovincamine group (no P-vales provided). The analyses were not adjusted for IOP, but the differences were very small (average IOP 13.1 mmHg and 13.2 mmHg in the brovincamine and control group, respectively). Sawada et al. followed a total of 28, age- and visual field-matched patients with NTG who were randomly allocated to either brovincamine or placebo for a minimum of 2.5 years.[126] Visual field examinations were carried out at least every 6 months.

The mean (SD) follow-up periods were 39.1 (8.7) months and 37.9 (10.1) months in the brovincamine group and the placebo group, respectively. Stepwise discriminant analyses were performed to separate the patients who showed improvement in their visual fields from those who failed to improve in the brovincamine treated group. Brovincamine seemed to have a favourable effect on visual field in some patients with NTG as indicated by visual field improvements of six patients in the brovincamine treated group compared to none in the placebo group (no P-value provided). Sawada et al. did not correct for IOP. In another study, Koseki et al. examined the 3-year effect of oral nilvadipine on the visual field (as assessed with standard automated perimetry) and ocular circulation as assessed with the laser speckle method at 0,3,6, 12,18,24,30,and 36 months in NTG patients with a randomized placebo-controlled, double-masked, single centre trial.[127] Thirty-three patients were included (17 assigned to nilvadipine and 16 assigned to placebo); 13 in each group completed the study. Nilvadipine (2 mg twice daily) slightly slowed the visual field progression over 3 years in patients with NTG; the MD rate of progression was -0.01 dB/year in the treated arm as compared to -0.27 dB/year in the controls (P=0.040). During the 3-year follow-up period, the average IOP was 12.6 mmHg in the nilvadipine group compared to 12.8 mmHg in the placebo group (P>0.1). In this study, Koseki et al. did not correct for IOP. However, this difference in IOP seems to be too small to explain their findings (the influence of IOP on the MD rate of progression is typically less than 0.1 dB/year per mmHg).[128] Netland et al. compared 56 patients with either high tension glaucoma (HTG) or NTG who were currently taking CCAs to similar groups not taking such medication.[129] In this study, NTG patients taking CCAs demonstrated no evidence of progressive optic nerve damage after a mean follow-up period of 3.4 years whereas patients with HTG showed no marked difference in the progression of cases compared to controls. Like in the previously described studies, Netland et al. did not correct for IOP; any differences in IOP were not mentioned. In contrast to these clinical studies, two epidemiological studies suggested a harmful effect of CCAs on OAG. Langman et al. performed a large case-control study using a general practitioner database.[130] In this

study, 27,080 glaucoma cases were matched with 27,080 controls for age and sex.Treatment with CCAs was a significant risk factor for OAG (OR 1.34; 95% CI 1.24-1.44). Their result was consistent with the result of a prospective population-based cohort study by Müskens et al.[131] In this study, 3842 participants were followed for 6.5 years. Participants using CCAs had an 1.8 fold (95% CI 1.04-3.2) higher risk of developing OAG during follow-up. Unlike the analysis by Langman et al, Müskens et al. adjusted for the IOP, suggesting that the harmful effect of CCAs on OAG is IOP independent. Müskens et al. argued that the difference between their study and the aforementioned studies may be attributed to patient selection. The epidemiological studies do not rule out that a small, selective group of NTG patients might benefit from CCAs. It might also be the case that age plays a role in the observed differences. In Müskens et al, the mean age of the cases and controls was 71.2 and 74.2 years, respectively. In the First study of Koseki, the average age of the included 52 patients was 57.7 years and in his second study mentioned that patients with OAG were younger than 65 years. Apparently, the relationship between CCAs and OAG is not yet completely solved.

Beta blockers

Beta-adrenegic blocking agents otherwise known as β-blockers are generally classified as selective or non-selective based on their affinity to block either β_1 or β_2 adrenergic receptors, or both.[132] The therapeutic ocular hypotensive effect of β-blockers in patients was first published in a paper by Phillips et al. in 1967, using propranolol.[133] The introduction of topical timolol, a non-selective β-blocker in the late 1970s has paved the way for β-blockers use as a therapy for glaucoma.[134,135] The mechanism of action is mediated through the inhibition of aqueous humour secretion and thus lowering IOP.[136,137]

In contrast to the indisputable beneficial effects of topical β-blockers on OAG, the effects of systemic β-blockers are less clear. Unlike in the era of CCAs, clinical trials with systemic β-blockers seem not to exist. Three epidemiological studies addressed the role of systemic β-blockers in OAG.

In a prospective population-based cohort study, Müskens et al.[131] reported that the use of β-blockers was associated with a non-significant risk reduction of OAG (OR 0.6; 95% CI 0.3-1.02). Their result was consistent with the abovementioned study by Langman et al. who reported a reduced risk of glaucoma in users of β-blockers (OR 0.77; 95% CI 0.73-0.83).[130] In addition, Owen et al. also reported that the systemic use of β-blockers was associated with a lower risk of glaucoma (OR 0.87; 95% CI 0.80-0.94).[138] Their study was a case-control study performed within a primary care database. According to the authors, a possible explanation for this finding may be attributed to more complex pharmacological properties, including neuroprotective effects, ocular penetration and influences on the haemodynamics including effects on ocular blood flow and perfusion pressure.[138] Hence, systemic β-blockers seem to slow down the development of OAG.

Diuretics

Diuretics have been the first line of treatment of hypertension for decades.[139] Their usage in ophthalmology can be traced back to Richard Middlemore who, in 1835, treated acute glaucoma by a mercury diuretic in the form of a blue pill.[140] Diuretics mediate their mechanism of action by diminishing sodium reabsorption at different sites in the nephron thereby increasing urinary sodium and water losses.[141,142] Several studies reported about the association between the use of diuretics and OAG. In a randomized, double masked, controlled clinical trial, Miglior et al.[143] reported that the use of systemic diuretics was associated with an increased risk of the development of OAG (Hazard ratio [HR] 2.41; 95% CI 1.12-5.19) whereas the presence of systemic hypertension was not. The authors

argued that the significance of diuretics may be explained by chance alone, by a idiopathic detrimental effects of diuretics on the retinal ganglion cells or by a possible decrease of ocular perfusion pressure induced by its pharmacological reduction of systemic blood pressure. In addition, they observed that diuretics were more often used in combination with other antihypertensive medications, especially among those who developed OAG. However, because they did not measure blood pressure in their study, it is difficult to unravel the effects of blood pressure, the use of other antihypertensive medications or, for example, more complex interactions between both.[143] Langman et al. reported a small but significant risk of the use of diuretics in current users (OR 1.08; 95% CI 1.03-1.14) and ever users (OR 1.13; 95% CI 1.08-1.18).[130] Also Owen et al reported a small increased risk in their case-control study performed within a primary care database (OR 1.13; 95% CI 1.04–1.23). In contrast, Müskens, in their prospective population-based cohort study did not find any significant effect for either low-ceiling (OR 0.8; 95% CI 0.4-1.4) or high-ceiling (OR 0.8; 95% CI 0.4-1.8) diuretics.[131] A small harmful effect of diuretics could possibly be explained by residual confounding as diuretics tend to be prescribed to elderly patients with hypertension,[144] and linear adjustment for age (the most common approach) might not completely address the effect of age on the prevalence or incidence of OAG.[40,145]

Angiotensin converting enzyme inhibitors

Apart from the therapeutic management of hypertension, ACE inhibitors have also been shown to lower IOP in patients with ocular hypertension or primary OAG.[146,147] Although the precise mechanism is not yet understood, the rennin enzymatic system (RAS), an enzymatic cascade that generate a wide range of angiotensin peptides with varying biological actions are thought to be involved in the regulation of aqueous outflow and IOP reduction.[148,149] The major component of RAS has been documented in the human eye.[150,151]

Genetic studies thus far provided inconclusive evidence about the effects of ACE inhibitors on OAG. Bunce et al. reported no consistent evidence between ACE genotype and ocular signs of POAG but found evidence of an association between ACE genotype and optic disc size.[152] Hirooka et al. reported that ACE inhibitors might have a favourable effect on the visual field in patients with normal tension glaucoma (NTG).[153] Their finding was based on a retrospective observational case series that reviewed 38 patients with NTG. Control subjects (n=13) had no previous history of hypertension and the NTG patients with hypertension were divided into two groups; those receiving ACE inhibitors (n=12) and those receiving other antihypertensive medications (n=13). The mean follow-up (standard error of measurement [SEM]) was 49.8 (3) months for the control group, 42.4 (2.2) months for the ACE-inhibitor group and 46.8 (2.8) months for those receiving other antihypertensive medications. The mean (SEM) MD change per year was 0.48 (0.19) dB in the ACE inhibitor-treated group, -0.38 (0.23) dB in control subjects and -0.50 (0.39) dB in the anti-hypertensive drug-treated group (P=0.04). There was no difference between the maximum and minimum IOP measured for the control group, ACE-inhibitor group and those receiving other antihypertensive medications (P=0.24 and P=0.62, respectively). Langman et al in their large case-control study reported that the use of ACE inhibitors was associated with an increased risk of glaucoma (OR 1.34; 95% CI 1.24-1.44).[130] They suggested that the observed association might be attributed to the failure of ACE inhibitors to protect against a commonly associated disease rather than an increased risk caused by treatment, a suggestion based on the fact that the ORs were virtually identical in known current users of ACE inhibitors (OR 1.34; 95% CI 1.24-1.44) and ever uses of the drug (OR 1.30; 95% CI 1.21-1.38). Müskens et al. reported no significant effect of ACE inhibitors on OAG (OR 0.9; 95% CI 0.5-1.7).[131] Apparently, the relationship between ACE inhibitors and OAG is not yet completely solved.

Antithrombotics

Antithrombotic drugs are frequently used prophylaxis against impaired blood flow.[154] Although the exact pathogenesis of OAG is yet to be unravelled, impaired blood flow has been postulated to be involved in the retinal ganglion cell death as seen in OAG.[155] We investigated the association between the use of these drugs and the development of OAG in 3939 participants aged 55 years and older from the prospective population-based Rotterdam study.[156] The use of anticoagulants and platelet aggregation inhibitors was monitored continuously during follow-up. During a mean follow-up of 9.8 years, 108 (2.7%) of 3939 eligible participants developed OAG. The hazard ratio (HR) for anticoagulant use was 0.95 (95% CI 0.58 to 1.54; P=0.818) and for platelet aggregation inhibitors 0.80 (0.53 to 1.20; P=0.281). There was no significant trend towards a reduced risk of incident OAG with prolonged anticoagulant use (HR 0.80, 95% CI 0.44-1.44, P=0.45 and HR 0.76, 95% CI 0.41-1.39, P=0.37) and platelet aggregation inhibitors use (HR 1.17, 95% CI 0.57-2.43, P=0.67 and HR 0.81, 95% CI 0.51-1.28, P=0.37) for usage during two years or less and during more than two years, respectively.[156] Our study suggests that the use of anticoagulants and platelet aggregation inhibitors seems not to be associated with OAG. Thus far, apparently no other studies addressed this relationship.

Carbonic Anhydrase Inhibitors

The usage of carbonic anhydrase inhibitors (CAIs) in ophthalmology can be traced back to Becker,[157] who used acetazolamide in the management of glaucoma, in 1954. Since then, CAIs have been used widely for controlling IOP in glaucoma.[158] The mechanism of action of CAIs is to block carbonic anhydrase, which catalyses the conversion of carbon dioxide to bicarbonate.[159,160] The inhibition of carbonic anhydrase results in the decrease

of aqueous humour production in the ciliary processes and thus lowers the IOP.[161] Until recently, CAIs were only available for oral use and – due to numerous side effects - its use was essentially limited to the treatment of acute high intraocular pressures.[162-165] Nowadays, topical CAIs are available with fewer systemic side effects.[166,167] The IOP lowering effect of two commonly prescribed CAI have been documented in a meta-analysis of randomized clinical trials.[168] In this meta-analysis, dorzolamide and brinzolamide had a mean IOP lowering effect of -4.5 to -5.9 mmHg and -4.4 to -4.5 mmHg, respectively. As these pressure-lowering effects are somewhat smaller than that of oral CAIs, the oral CAIs remain very useful in special cases.[169]

Apart from their IOP lowering effect, CAIs have also been reported to improve the regulation of ocular perfusion, although evidence is limited.[170] Flammer and Drance reported a case of a 28-year-old woman with early glaucoma. Automatic perimetry showed reproducible improvement of the differential threshold responses in the visual field following 12 hours of acetazolamide therapy.[171] On the first occasion, the patient took three 250 mg tablets of acetazolamide over a 12-hour period and reported subjective improvement. Five months later, the patient again received three 250-mg tablets of acetazolamide over a 12-hour period, then underwent perimetry again and also reported improvement in her vision. Altogether, five visual field tests were performed.

Cannabinoids

Marijuana is the crude drug derived from dried leaves and flowering parts of the hemp plant Cannabis sativa.[172,173] It has a long history of use in medicine and recreation and contains more than sixty group of compounds known as cannabinoids with Δ^9-tetrahydrocannabinol (THC) being the most pharmacologically active component.[174-176] Hepler and Frank were the first to report a decrease in IOP after smoking marihuana.

In 1971, they observed that smoking marijuana could lower IOP by up to 45% in normal subjects.[177] Since then, several other studies have reported ocular hypotensive effects of different cannabinoids.[178-182] The mechanism of action by which cannabinoids lower the IOP is not fully understood.[183-185] Recent studies have also reported neuroprotective, anti-oxidative and vasorelaxant properties of cannabinoids.[186-191] Hence, cannabinoids might modify the risk of glaucoma – apart from via their IOP-lowering effect - by (1) inhibiting neuronal cell death, (2) scavenging toxic reactive oxygen species and (3) increasing the ocular blood flow. However, the clinical usefulness of cannabinoids has been limited by the development of tolerance and systemic side effects.[192]

Ginkgo biloba extract

Ginko biloba extract (GBE) is a Chinese traditional medicine obtained from the leaves of the *Ginko biloba* tree. Reports from early manuscripts shows that GBE has been used since 3000 BC.[193,194] They have been reported to ameliorate numerous disorders including peripheral vascular disease, cerebral insufficiency, dementia and Alzheimer.[195-198]

GBE has been reported to increase ocular blood flow but not IOP in a phase 1 cross-over trial of GBE with placebo control in 11 healthy volunteers (8 women, 3 men) aged 34 (standard deviation 3) years.[199] In this study, subjects were administered 40 mg GBE or placebo three times daily for 2 days. Color doppler imaging was used to measure ocular blood flow before and after treatment. GBE significantly increased end-diastolic velocity in the ophthalmic artery (baseline versus GBE-treatment [mean with standard deviation between brackets]: 6.5 (0.5) versus 7.7 (0.5) cm/s; P=0.023) with no changes seen in placebo (baseline versus placebo: 7.2 (0.6) versus 7.1 (0.5) cm/s; P=0.892). GBE did not show any significant effect on IOP (baseline versus GBE-treatment: 13.5 (0.9) versus

14.0 (1.0) mmHg; P=0.716) with no changes seen in placebo (baseline versus placebo: 14.6 (0.8) versus 14.0 (1.0) mmHg; P=0.290).[199] In another study, Quaranta et al. evaluated the effect of GBE on pre-existing visual field damage in patients with NTG. In this prospective, randomized, placebo-controlled, double-masked cross-over trial, GBE significantly improved visual field damage in 27 patients with normal tension glaucoma without altering the IOP.[200] Patients were administered 40 mg GBE, three times daily for 4 weeks followed by a wash-out period of 8 weeks, then 4 weeks of placebo. Other patients were first administered the placebo and then GBE. Visual field tests were performed at baseline and at the end of each phase of the study using Humphrey field analyser [HFA]. After GBE treatment, a significant improvement in visual fields indices was recorded; MD at baseline versus MD after GBE treatment was -11.4 (3.3) dB versus -8.8 (2.6) dB (p=0.0001). The improvement was not maintained after 8 weeks of washout. No significant changes were found in IOP. An explanation for this observation as suggested by the authors was the ability of GBE to increase cerebral blood flow and thus improving ocular blood flow and invariably improving retinal sensitivity as well as concentration and alertness.[199] Other properties of GBE reported in the literature include neuroprotection, platelet activating factor inhibitory activity, nitric oxide inhibition, antioxidation, inhibition of apoptosis and excitotoxicity.[201-206]

Cholesterol-lowering drugs

The quest to discover microbial metabolites that would inhibit 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase lead to the discovery of a potent reductase inhibitor mevastatin in the 1970's.[207] Since then, other mevastatin analogues have been developed in the 1980s and 1990s.[208,209] Nowadays, statins are recognized as potent cholesterol-lowering drugs.[210] Several studies have reported various beneficial effects of statins on stroke, Alzheimer's disease, and a variety of eye diseases such as

age related maculopathy, cataract and diabetic retinopathy.[211-218] A few studies have explored the association between cholesterol-lowering drugs and OAG.[219-221]

McGwin et al. performed a large nested case-control study using an administrative clinical database. Cases were all male patients aged 50 years and older with a new diagnosis of glaucoma. Ten controls subjects were matched to each case according to age within a year. In this study, 667 cases were matched with 6667 controls and prescription files were assessed for statin use as well as additional medications to lower cholesterol levels. Long-term use of statin was associated with a lower risk of OAG (OR 0.60; 95% CI 0.39-0.92). Non-statin cholesterol-lowering agents were also associated with a reduced risk of having OAG (OR 0.59; 95% CI 0.37-0.97).[219] In contrast, Owen et al. found no evidence for a protective effect of statins (OR 0.97; 95% CI 0.88-1.06) in another case control study nested within a computerized primary care database of 177 general practices across the UK. In this study, 8778 cases diagnosed and/or treated for glaucoma were matched with 8778 glaucoma free controls for age, gender and practice.[138]

Recently, we reported that the use of statins was associated with a reduced risk of OAG (Hazard ratio [HR] 0.56; 95%CI 0.32 to 0.97), in a prospective population-based cohort study.[17] However, unlike McGwin et al, the use of non-statin cholesterol-lowering drugs (NSCLDs) was not associated with a reduced risk of OAG (HR 1.82; 0.71-4.66). The lack of association between NSCLDs and OAG might be attributed to the low number of users of NSCLDS in our study.[17] Furthermore, De Castro et al. reported that the use of statins was associated with a slower progression of glaucomatous optic nerve atrophy.[221] To determine the effect of statins on the rate of progression of optic nerve parameters in OAG, as defined by confocal scanning laser ophthalmoscopy (CSLO), they conducted a retrospective chart review. Their study included 149 eyes from 76 patients considered suspect for glaucoma based on cup-to-disc ratio >0.5, but with normal IOP and visual

fields. Cases included glaucoma suspects who took statin drugs for more than 23 months and the control group were glaucoma suspects who never used statins. All patients underwent optic nerve head imaging using the Heidelberg Retinal Tomograph [HRT] and visual field testing with HFA. Comparing controls with the statin group there were significant differences in the progression of multiple CSLO parameters, including rim volume, retinal nerve fibre layer cross-sectional area, and mean global retinal nerve fibre layer thickness, with adjustment for age, gender, race, IOP, CCT, refractive error and multiple systemic morbidities.

The mechanism by which cholesterol-lowering drugs might reduce the risk of OAG is yet to be elucidated. McGwin et al. suggested that the mechanism might be IOP mediated whereas Marcus et al. attributed the mechanism to anti-inflammatory and neuro-protective properties of statins on neuronal cells – per exclusion - because the observed protective effect was IOP-independent.[222-226] Likewise, De Castro et al. corrected for IOP in their model and attributed their findings to optic nerve head changes suggestive of a neuroprotective effect of statins against glaucoma progression.

Estrogens

Estrogens, the female sex hormone, are steroid hormones that play an important role in the growth and development of various tissues throughout the body.[227] Their presence have also been reported in various ocular tissues.[228] Estrogens exert their effect by binding to two estrogen receptors.[229] Various studies have reported a higher incidence and prevalence of OAG in men.[230-232] This observation was also confirmed in a meta-analysis in which men were 1.37 (95% credible interval 1.22 to 1.53) times more likely than women to have OAG.[233] Earlier studies have reported higher IOP among postmenopausal woman than in premenopausal women and in men of similar age.[234-236]

In addition, a study has reported an increased risk of OAG in early menopausal women and female sex has been reported to be a risk factor in normal tension glaucoma.[237,238] Except for the latter study, these observations might suggest a protective role of estrogen in the era of OAG. Studies performed in women on hormone replacement therapy have reported significant decreases in IOP and significant increases in tear break-up time and schirmer test.[239-242] The decrease of IOP as a result of the systemic hormone replacement has been attributed to estrogen.[243] Furthermore, estrogen has been applied as topical drop with promising result in patients with keratoconjuctivitis sicca.[244] Ozcura et al. therefore proposed that topical estrogen drops may be a new alternative in the treatment of glaucoma.[245] This, however, has been questioned by others.[246]

Conclusion

Several systemic drugs have been related to IOP and/or OAG but the reported effects are unequivocal for a limited number of these drugs only. Table 2 summarizes the findings from this review. The role of steroids and CAI is already part of the clinician's armamentarium. There seems to be no basis for a universal avoidance or recommendation of the use of any class of antihypertensive drugs if needed for an adequate regulation of the blood pressure. However, clinicians should be aware of possible effects on OAG in individual patients. Of the other systemic drugs listed in Table 2, the statins seem to be closest to a potential clinical application in the management of OAG - given our current state of knowledge that the use of supplementary treatment that protects retinal ganglion cell death independent of an IOP lowering is warranted.

Table 1 Age distribution of case studies and case series reporting an association between steroid use and open-angle glaucoma

Sources	Age (years)	Types ofsteroid used	Estimated duration of use	Other risk factors
Francois J, 1954[50]	35	Ophthalmic	3 years	NA
Goldmann H, 1962[51]	31	Ophthalmic	Months	Myopia
	43	Ophthalmic	Years	DM
	57	Ophthalmic	Months	-
	9.5	Ophthalmic	Years	-
	34	Ophthalmic	2 years	FH, myopia
Bernstein HN, 1963[52]	25	Oral, Ophthalmic	1 year	FH
Armaly MF, 1963[53,54]	32	Ophthalmic	4 weeks	FH
	42	Ophthalmic	3 months	-
	44	Ophthalmic	Months	-
Mills DW, 1965[55]	17	Ophthalmic	Years	NA
Long WF, 1977[56]	20	Oral	Days	Myopia
Michaeli-Cohen	35	Ointment	Years	FH, myopia
A,1998[57]	45	Ointment	Years	-
Garrott HM, 2004[58]	40	Ointment	-	-
	71	Ointment	Weeks	FH
	55	Ointment	6-9 months	FH
van Boxtel LA, 2005[59]	20	Ophthalmic, Ointment	Years	NA
	28	Ophthalmic, Ointment	Years	NA
	32	Ophthalmic, Ointment	Years	NA
Eisenlohr JE, 1983[60]	33	Ointment	4 years	-
Ross JJ, 2004[61]	42	Ointment	2 years	NA
Sahni D, 2004[62]	29	Ointment	Years	FH
Zugerman C, 1977[63]	30	Ointment	Years	-
Nielson NV, 1978[64]	68	Ointment	2 years	DM
	80	Ointment	3 years	NA
Park JJ, 2002[65]	6.5*	Ophthalmic	>6 weeks	Myopia
Butcher JM, 1994[66]	47	Ophthalmic	3 years	-
McLean CJ, 1995[67]	30	Ointment	5 Years	-
Cubey RB, 1976[68]	22	Ointment	7 years	-
Vie R, 1980[69]	29	Ointment	Years	-
Aggerwal RK et al.	24	Ointment	>2 years	NA
1993[70]	23	Ointment	>11 years	NA
	25	Ointment	>3 years	NA
Dreyer EB, 1993[71]	57	inhaled	6 months	-
Woods AC, 1950[72]	17	Ophthalmic	10 days	-
Opatowsky I, 1995[73]	71	Nasal	5 months	DM
	61	Nasal	Months	
Brubaker R, 1975[74]	18	Ointment	Years	-
Covell LL, 1958[75]	58	Oral	>1 year	Arthritis
	59	Oral	Years	FH, Arthritis
	65	Oral	Years	HT, Arthritis
Stern JJ, 1953[76]	59	Oral	Days	-
thoe Schwartzenberg	26	Ointment	7 years	Myopia
GW 1999[77]	22	Ointment	>9 years	JG
Hutcheson KA, 2007[78]	3+	Ophthalmic	1 week	-

Sasaki R, 2003[79]	29	Ophthalmic	6 months	-
Wax M, 1998[80]	17	Ophthalmic	4 months	-
Perkins ES, 1965[81]	31	oral	Months	-
Tham cc, 2004[82]	9	Oral	Weeks	-
Al-Shahwan S, 2006[83]	9*	0ral	Months	-
Phillips RP et al. 1990[84]	37	Ophthalmic	Months	NA
	16	Ophthalmic	> 1 year	NA
Burde RM, 1970[85]	17	Ophthalmic	Years	FH
	20	Ophthalmic	Years	Myopia
Hales RH, 1973[86]	19	Ophthalmic, Ointment	3 years	NA
	16	Ointment	3 years	NA
Baratz KH et al. 1999[87]	31	Ointment	4 years	Myopia
	56	Ophthalmic	6 months	History of glaucoma
Al-Samarrai AR, 1993[88]	47	Ointment		NA
	43	Ointment		NA
	56	Ointment		NA
Kim JH, 1969[89]	30	Ophthalmic	9 years	NA
	32	Ophthalmic	1 year	NA
	35	Ophthalmic	3 years	NA
	23	Ophthalmic	1 year	NA
	38	Ophthalmic	1 year	NA
	40	Ophthalmic	10years	NA
Spaeth GL, 1977[90]	15	Ointment, Ophthalmic	5 years	NA
	43	Ophthalmic	3 years	NA
	16	Ophthalmic	1 year	NA
	45	Ophthalmic	Months	NA
	31	Ointment, Ophthalmi	2 Weeks	NA
	43	Ophthalmic	5 weeks	NA

Abbreviations: NA=not available; - =unknown; FH=family history of glaucoma; JG=Juvenile glaucoma; DM=diabetes mellitus; HT=Hypertension; *=Age in months;+=Age in weeks.

Table 2 Summary

Medications	Effect on IOP	Effect on OAG	Presumed mechanisms	Additional remarks
Corticosteroids	Increase	Harmful	Effect on IOP caused by changes in the trabecular meshwork; effect on OAG through effect on IOP	Steroid responders at higher risk of developing OAG
Docetaxel & Paclitaxel	Harmful/ Conflicting	Harmful/ conflicting	Unknown	Based on a single case study
Calcium antagonists	Conflicting (possible decrease)	Conflicting	Elevation of ocular blood flow	Contradicting results from human and animal studies (IOP); contradicting results from clinical studies in NTG patients and epidemiological studies (OAG)
Beta-blockers	Decrease	Protective	Inhibition of aqueous humor secretion	Evidence form three epidemiology studies; no clinical studies available
Diuretics	None	Conflicting (possible small harmful effect)	Unknown	
ACE-inhibitors	Decrease	No clear effect	Regulation of aqueous outflow via RAS	
Antithrombotics	None	None	NA	Evidence from a single population- based study
CAI	Decrease	No clear effect	Decrease in aqueous production by inhibition of carbonic anhydrase	Side effects have limited usage of systemic CAI
Cannabinoids	Decrease	Unknown (no studies with a sufficiently long follow-up available)	Unknown	Therapeutic use limited by the development of tolerance and systemic side effects
GBE	None	None (only short-term improvement of visual field)	Elevation of ocular blood flow	Short-term effect
Cholesterol-lowering drugs	None	Protective	Neuroprotection	
Estrogens	Decrease	Protective	Unknown	Effect on OAG only form indirect evidence (male/female differences and effects of menopause)

Abbreviations: IOP=Intraocular pressure; OAG=Open-angle glaucoma; NTG=Normal tension glaucoma; ACE=Angiotensin converting enzyme; NA= Not available; CAI=Carbonic Anhydrase Inhibitors; GBE=Ginkgo biloba extract.

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Summary

Glaucoma is a heterogeneous group of disease characterized by optic neuropathy and progressive visual field defects. An elevated intraocular pressure (IOP) is regarded as the major risk factor and the therapeutic management of OAG is currently targeted exclusively towards the lowering of IOP. The prevalence of glaucoma is expected to increase sharply in the coming decades with the current pace of population ageing. According to the World health organization, glaucoma accounts for the loss of nearly 6 million disability-adjusted life years (DALYs) per year. Because OAG is the most common form of glaucoma, the economic and social burden of this disease is also expected to increase. In order to ameliorate the economic and social burden of OAG a better understanding of the risk factors is expedient. On the basis of previously proposed risk factors and the current state of knowledge, we sought to evaluate the effect of some systemic medications and other risk factors of OAG. Chapters one, two and three are based on the prospective population-based Rotterdam Study initiated in 1990-1993 in 7,983 individuals aged 55 years and older living in the Ommoord district of Rotterdam, the Netherlands. For this study, data from a subset of 3939 participants who did not have OAG at baseline and who completed at least one follow-up examination was used. We had detailed information on prescriptions of all investigated medications from the local pharmacy records from January 1, 1991, and during complete follow-up.

Previous studies have reported beneficial effects of statins on a variety of eye diseases such as age-related maculopathy, cataract and diabetic retinopathy. However, there is conflicting evidence regarding the effects of statins and non-statin cholesterol-lowering drugs (NSCLDs) on OAG. In **Chapter 1** we showed that long-term use of statins was associated with a reduced risk of OAG and the observed effect was IOP independent. Our observation corroborates the results of earlier studies in favor of a beneficial effect of statin on OAG. However, we found no significant benefit effects of NSCLDs on OAG.

Evidence mainly from case reports and case series has suggested that corticosteroids can cause a substantial rise in IOP and thus induce OAG. However, it is largely unknown if this adverse effect of corticosteroids is limited to a few susceptible individuals or contributes to the burden of OAG in the population. **Chapter 2** describes the associations between the use of corticosteroids and incident OAG in the Rotterdam Study. We found that the use of any class of corticosteroids seems not to be associated with the incidence of OAG at the population level in the elderly. The majority of the previously published steroid-induced glaucoma cases were amply younger than the youngest age of our study cohort.

Although the exact pathogenesis of OAG is yet to be unravelled, impaired blood flow has been postulated to be involved in the retinal ganglion cell death as seen in OAG. Antithrombotic drugs such as anticoagulants and platelet aggregation inhibitors are frequently used prophylaxis against impaired blood flow**.** In **Chapter 3** we investigated the association between the use of antithrombotic drugs and the development of OAG in the Rotterdam Study. This is the first study to investigate the association between the use of anticoagulants and OAG; we found no significant beneficial effect of the use of antithrombotic drugs on the risk of OAG. The major limitation of this study is the small number of glaucoma cases and the small number of users of some classes of antithrombotic drugs which prohibits us from carrying out secondary analysis.

There is mounting evidence in the literature about risk factors for the progression of OAG. IOP has been established as a risk factor the progression of OAG. Despite several well-executed clinical trials, other risk factors remain controversial. In **Chapter 4** we used several statistical approaches to identify the risk factors associated with visual field progression in OAG and determined the influence of these statistical approaches in the Groningen Longitudinal Glaucoma Study (GLGS), a prospective cohort study in a clinical setting.

We included 221 eyes of 221 patients from GLGS. On average 7.2 reliable fields were available after a mean follow-up of 5.4 years and 89 eyes progressed. We found that IOP, disease stage and age were robust independent risk factors for visual field progression in OAG.

Chapter 5 addresses an important clinical question: is myopia a risk factor of OAG? Myopia has long been identified as a risk factor for OAG. However, there is conflicting evidence concerning the range of refractive error important for OAG. While some studies have reported an association with any myopia, others have found the relationship only in individuals with high myopia. In order to reconcile this controversy we carried out a systematic review and meta-analysis. Thirteen studies involving 48,161 individuals met the inclusion criteria; data from 11 population-based cross-sectional studies were included in the main analyses. The pooled relative risk of the association between myopia and glaucoma based on 11 risk estimates was 1.92 (95% confidence interval 1.54 to 2.38). Based on seven risk estimates, the pooled relative risks of the associations between low myopia (myopia up to -3 dioptres) and glaucoma and high myopia (-3 dioptres and more myopic) and glaucoma were 1.65 (1.26 to 2.17) and 2.46 (1.93 to 3.15), respectively. After omitting studies that contributed significantly to heterogeneity, the pooled relative risk was 1.88 (1.60 to 2.20) for any myopia and glaucoma and 1.77 (1.41 to 2.23) for low myopia and glaucoma. Therefore, we could conclude that individuals with myopia have an increased risk of developing OAG.

In **Chapter 6** the current state of knowledge of systemic medications and OAG is reviewed. Medications administered systemically within the body can cause a substantial rise in IOP and thus induce OAG. Corticosteroids are the most well-known and extensively studied medications with such property. Anti-neoplastic agents such as docetaxel and paclitaxel and anti-hypertensive medication such as calcium channel antagonists have also been reported with such effects.

In contrast, medications like carbonic anhydrase inhibitors, beta blockers, cannabinoids, ginkgo biloba extract and cholesterol-lowering drugs have been reported to diminish the risk and thus seem to have protective effect independent of IOP probably mediated via neuroprotective property. This presents an opportunity for clinical applicable treatment of OAG other than by means of lowering IOP but additional evidence is deemed appropriate. In addition, many studies have suggested a protective role of estrogens on the risk of OAG but more research are need to confirm this effect and in our study population, the use of anticoagulants and platelet aggregation inhibitors seems not to be associated with glaucoma.

Samenvatting

Glaucoom is een heterogene groep van aandoeningen van de oogzenuw die gekenmerkt wordt door een versnelde beschadiging van de oogzenuw gevolgd door gezichtsveldverlies. Een hoge oogdruk is de belangrijkste risicofactor en tevens het belangrijkste aangrijpingspunt voor de behandeling van glaucoom. Wereldwijd is glaucoom de op één na belangrijkste oorzaak van blindheid.

De vergrijzing van de wereldbevolking zal de prevalentie van glaucoom doen toenemen in de komende decennia. Volgens de Wereldgezondheidsorganisatie is glaucoom verantwoordelijk voor het verlies van bijna 6 miljoen “disability-adjusted life years” (DALY's) per jaar. In de westerse wereld is openkamerhoekglaucoom (OKG) de meest voorkomende vorm van glaucoom. Te verwachten is dat de economische en sociale lasten van deze ziekte toenemen. Met het oog op een verbetering van de economische en sociale lasten van OKG is een beter begrip van de risicofactoren nuttig. Het onderzoek beschreven in dit proefschrift beschrijft de invloed van een aantal veelgebruikte medicamenten en andere risico factoren op OKG. De hoofdstukken 1, 2 en 3 zijn gebaseerd op het in 1990-1993 gestarte prospectieve Erasmus Rotterdam Gezondheid Onderzoek (ERGO/ Rotterdam study) onder 7983 mannen en vrouwen van 55 jaar en ouder, woonachtig in de Rotterdamse wijk Ommoord. Voor deze studies werden de gegevens van 3939 personen zonder glaucomateus gezichtsveldverlies bij aanvang van de studie gebruikt. We hadden gedetailleerde geautomatiseerde informatie tot onze beschikking over voorschriften van alle onderzochte medicijnen van de plaatselijke apotheekadministratie vanaf 1 januari 1991, en tijdens de volledige follow-up.

Eerdere studies hebben gunstige effecten van statines op verschillende oogziekten zoals leeftijdsgebonden maculopathie, cataract en diabetische retinopathie gerapporteerd.

Echter, er is tegenstrijdig bewijs over de effecten van statines en overige cholesterolverlagende medicijnen (NSCLDs) op OKG. In Hoofdstuk 1 toonden we aan dat langdurig gebruik van statines was geassocieerd met een verlaagd risico van OKG en het waargenomen effect was onafhankelijk van de intraoculaire druk (oogdruk). Onze waarneming bevestigt de resultaten van eerdere studies in het voordeel van een gunstig effect van statines op OKG. We vonden geen significante effecten van de overige cholesterolverlagende medicijnen op OKG.

Case reports en case series hebben laten zien dat corticosteroïden een aanzienlijke stijging van de oogdruk kunnen veroorzaken en dus steroïdgeïnduceerd glaucoom. Het is echter grotendeels onbekend of dit nadelige effect van corticosteroïden beperkt is tot een paar voor steroiden gevoelige personen of bijdraagt aan de last van OKG op populatie niveau. Hoofdstuk 2 beschrijft de associaties tussen het gebruik van corticosteroïden en de incidentie van OKG in de ERGO studie. We vonden voor geen van de toedieningsvormen van corticosteroïden dat het gebruik geassocieerd lijkt te zijn met de incidentie van OKG op populatieniveau bij ouderen. De meerderheid van de eerder gepubliceerde steroïdgeïnduceerde glaucoomgevallen waren ruimschoots jonger dan de jongste leeftijdsgroep van ons studiecohort.

Hoewel de exacte pathogenese van OKG nog niet ontrafeld is, heeft men verondersteld dat een verminderde bloedtoevoer van invloed is op de celdood van de retinale ganglion zoals die te zien is in OKG. Antitrombotische geneesmiddelen zoals trombocytenaggregatieremmers en anticoagulantia worden vaak gebruikt als profylaxe tegen een verminderde doorbloeding. In hoofdstuk 3 onderzochten we de associatie tussen het gebruik van antitrombotica en de ontwikkeling van OKG in de ERGO Studie. In deze studie, de eerste die naar het verband tussen anticoalgulantia en OKG keek, vonden we geen significant gunstig effect van het gebruik van trombocytenaggregatieremmers of anticoagulantia op het risico van OKG.

De belangrijkste beperking van deze studie is het geringe aantal gevallen van OKG en het kleine aantal gebruikers van een aantal klassen van anthitrombotica die ons niet toelaat om eventuele kleine effecten in subgroepen te vinden.

Er zijn steeds meer aanwijzingen in de literatuur over risicofactoren voor de progressie van OKG. De oogdruk is de meest bekende risicofactor van de progressie van OKG. Ondanks enkele goed uitgevoerde klinische studies blijven andere risicofactoren controversieel. In Hoofdstuk 4 hebben we gebruik gemaakt van verschillende statistische benaderingen om de risicofactoren die verband hebben met gezichtsveldprogressie in OKG te identificeren en bepaalden we de invloed van deze verschillende statistische benaderingen in de Groningen Longitudinal Glaucoma Study (GLGS), een prospectieve cohort studie in een klinische setting. We includeerden 221 ogen van 221 patiënten uit GLGS. Gemiddeld 7,2 betrouwbare gezichtsvelden waren beschikbaar na een gemiddelde follow-up van 5,4 jaar. Negenentachtig ogen vertoonden progressie. We vonden dat oogdruk, ziektestadium en leeftijd robuuste onafhankelijke risicofactoren waren voor progressie van gezichtsveldafwijkingen in OKG.

Hoofdstuk 5 gaat in op een belangrijke klinische vraag: is bijziendheid (myopie) een risicofactor voor OKG? Myopie is al lange tijd geïdentificeerd als een risicofactor voor OKG maar er is onduidelijkheid met betrekking tot het bereik van de refractieve fout: hoewel sommige studies een associatie tussen OKG en zowel lage als hoge bijziendheid hebben gerapporteerd, hebben andere studies deze associatie alleen bij personen met hoge bijziendheid gevonden. Met als doel deze controverse op te lossen hebben wij een systematische review en meta-analyse uitgevoerd. Dertien studies met 48.161 personen voldeden aan de inclusie criteria; gegevens van 11 transversale populatiestudies werden opgenomen in de analyses. Het gepoolde relatieve risico van de associatie tussen myopie en glaucoom gebaseerd op 11 studies was 1,92 (95% CI 1,54 tot 2,38).

Gebaseerd op zeven studies waren de gepoolde relatieve risico's van het verband tussen lage myopie (bijziendheid tot -3 dioptrie) en glaucoom en hoge myopie (-3 dioptrieën en meer bijziend) en glaucoom respectievelijk 1,65 (1,26-2,17) en 2,46 (1,93 tot en met 3.15). Na het weglaten van studies die in belangrijke mate bijdragen aan de heterogeniteit, was het gepoolde relatieve risico 1,88 (1.60 tot 2.20) voor alle myopie en glaucoom en 1,77 (1,41 tot 2,23) voor lage myopie en glaucoom. Mensen met myopie hebben dus een verhoogd risico op het ontwikkelen van glaucoom, zelfs al bij lage myopie.

In hoofdstuk 6 wordt de huidige stand van de kennis van de effecten van systemische medicatie op OKG beschreven. Systemische toediening van medicijnen binnen het lichaam kunnen een aanzienlijke stijging van de oogdruk veroorzaken en dus OKG. Corticosteroïden zijn de meest bekende en uitvoerig bestudeerde medicijnen met dergelijke kenmerken. Van anti-neoplastische middelen zoals docetaxel en paclitaxel is ook een oogdrukverhogend effect gerapporteerd. Andere medicijnen zoals koolzuuranhydraseremmers, bètablokkers, cannabinoïden en ginkgo biloba-extract verlagen de oogdruk en cholesterol-verlagende middelen lijken een beschermend effect te hebben bij OKG zonder de oogdruk te beïnvloeden – mogelijk hebben deze middelen dus een neuroprotectief effect bij OKG. Hier ligt een mogelijkheid voor de eerste klinsch-toepasbare behandeling van OKG anders dan door middel van oogdrukverlaging, maar aanvullend bewijs lijkt aangewezen. Daarnaast hebben veel studies gesuggereerd dat oestrogenen een beschermende rol hebben bij OKG, maar meer onderzoek is nodig om dit effect te bevestigen. Het gebruik van trombocytenaggregatieremmers en anticoagulantia lijkt tot dusver niet geassocieerd te zijn met OKG.

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About the author

Michael Marcus grew up in Lagos, Nigeria. After completing his secondary school education, he studied chemistry at the University of Ibadan in Nigeria for a year and medicine at Obafemi Awolowo University in Nigeria for two years. In 1996, he relocated to the Netherlands and studied biomedical sciences at the Free University in Amsterdam and graduated in 2004. In 2005, he started a research masters at the University of Utrecht with a major in (clinical) epidemiology and obtained his master's degree in 2007. In 2008, he started his PhD project presented in this thesis at the department of ophthalmology, University Medical Center Groningen under the supervision of Dr. Nomdo Jansonius in collaboration with the ophthalmic-epidemiology (Prof. Hans Vingerling) and the pharmaco-epidemiology (Prof. Bruno Stricker) group at the Department of Epidemiology, Erasmus Medical Center Rotterdam. From March 2012, Michael will commence his recently secured appointment as a postdoctoral research associate in statistics and epidemiology at the Roy Castle Lung Cancer Research, The University of Liverpool Cancer Research Centre, Liverpool, United Kingdom.