Classification and quantification of risk factors and treatment strategies for ocular hypertension and primary open-angle glaucoma

Qëndresë, Daka

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

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DISSERTATION

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This study was performed at the Department of Pharmacology of School of Medicine, University of Zagreb and University Clinical Centre of Kosova, Medical Faculty, University of Prishtina.

Mentor: Prof. Vladimir Trkulja, MD, PhD.

In memory of my uncle Arbër Krasniqi

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CONTENTS

ABBREVIATIONS

AAO	American Academy of Ophthalmology
ACG	Angle Closed Glaucoma
AE	Adverse Events
AH	Aqueous Humor
AMSTAR	Assessment of Multiple Systematic Reviews
APOE	Apolipoprotein E Gene
ASB10	Ankyrin Repeat and SOCS Box Containing 10 Gene
ATOH7	Atonal Homolog 7 Gene
BET	Betaxolol
BCVA	Best Corrected Visual Acuity
BID	Twice a Day
BMI	Body Mass Index
BIMA	Bimatoprost
BRINZ	Brinzolamide
BRIM	Brimonidine
CAIs	Carbonic Anhydrase Inhibitors
CAV1/CAV2	Caveolin 1 Gene /Caveolin 2 Gene
CCT	Central Corneal Thickness
CDC7	Cell Division Cycle 7 Gene
CDKN2B	Cyclin-Dependent Kinase Inhibitor 2B Gene
C/D Ratio	Cup/Disc Ratio
CDSR	Cochrane Database of Systematic Reviews
CH	Corneal Hysteresis
CHOLINOMIMETICS	Acetylcholine Receptor Agonists
CODA	Cavitary Optic Disk Anomalies
CSLT	Confocal Scanning Laser Tomography
CYP1B1	Cytochrome P450, Family 1,Subfamily B, Polypeptide 1 Gene
DARE	Database of Abstracts of Reviews of Effects
DB	Double blind
DCLK1	Doublecortin-Like Kinase 1 Gene
DM	Diabetes Mellitus
DORZ	Dorzolamide

EED	NHS Economic Evaluation
EGS	European Glaucoma Society
ERG	Electroretinography
F	Female
GAS7	Growth Arrest-Specific 7 Gene
GAT	Goldmann Applanation Tonometry
CHEK2	Checkpoint Kinase 2 Gene
GLC1A	Glaucoma/Primary Open Angle Genetic Loci
GON	Glaucoma Optic Neuropathy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSTM1, *GSTT1*, *GSTP1*	Glutathione S Transferase Polymorphisms
GVFD	Glaucomatous Visual Field Defects
GWAS	Genome-Wide Association Study
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
HTA	Health Technology Assessment
HTG	High Tension Glaucoma
HWE	Hardy-Weinberg Equilibrium
ICD	International Classification of Diseases
IOP	Intraocular Pressure
ITT	Intention –To –Treat
IR	Incidence Rate
IRR	Incidence Rate Ratio
JOAG	Juvenile Open Angle Glaucoma
LAT	Latanoprost
LOCF	Last Observation Carried-Forward
LOXL1	Lysyl Oxidase-Like 1Gene
M	Male
MeSH	Medical Subject Headings
METAREG	Meta-regression analysis
MOOSE	Meta-analysis of Observational Studies in Epidemiology

MTC	Mixed Treatment Comparison (Network Meta-Analysis)
MTHFR	Methylenetetrahydrofolate Reductase Gene
MYOC	Myocilin Gene
NCKAP5	NCK-Associated Protein 5 Gene
NICE	National Institute for Clinical Excellence
NNTB	Number Needed to Treat to Benefit
NNTH	Number Needed to Treat to Harm
NoS	Newcastle-Ottawa Scale
NTF4	Neurotrophin 4 Gene
NTG	Normal Tension Glaucoma
NRR	Neuro Retinal Rim
OAG	Open Angle Glaucoma
OBF	Ocular Blood Flow
OCT	Optical Coherence Tomography
OHT	Ocular Hypertension
OHTS	The Ocular Hypertension Treatment Study
ONH	Optic Nerve Head
OPA1	Optic Atrophy 1 Gene
OPTN	Optineurin Gene
OR	Odds Ratios
PCG	Primary Congenital Glaucoma
PGAs	Prostaglandin Analogues
PDG	Pigment Dispersion Glaucoma
PLXDC2	Plexin Domain Containing 2 Gene
POAG	Primary Open Angle Glaucoma
PP	Per-Protocol
PRISMA	Preferred Reporting Items for Systematic review and MetaAnalyses
PT	Publication Type
PXFG	Pseudoexfoliation Glaucoma
QD	Once a Day
RCTs	Randomized Controlled Clinical Trials
RGCs	Retinal Ganglion Cells
RNFL	Retinal Nerve Fibre Layer

RR	Relative Risk
RRI	Relative Risk of Incidence
SALL1	Spalt-Like Transcription Factor 1Gene
SB	Single Blind
SCYL1	SCY1-Like 1Gene
SIX1/SIX6	SIX Homeobox 1Gene / SIX Homeobox 6 Gene
SLP	Scanning Laser Polarimetry
SNP	Single Nucleotide Polymorphism
SRBD1	S1 RNA Binding Domain 1 Gene
tHcy	Total Homocysteine
TGF β2	Transforming growth factor-beta 2 Gene
TGFBR3	Transforming Growth Factor, Beta Receptor III Gene
TID	Three Times a Day
TIM	Timolol
TMCO1	Transmembrane and Coiled-Coil Domains 1Gene
TMTC2	Transmembrane and Tetratricopeptide Repeat Containing 2 Gene
TNF-α	Tumor Necrosis Factor α Gene
TP53	Tumor Protein 53 Gene
TRAV	Travoprost
UBM	Ultrasound Biomicroscopy
UC	Unfixed Combinations
VEP	Visually Evoked Potential
VF	Visual Field
WDR 36	WD Repeat Domain 36 Gene
WHO	World Health Organization
ZP4	Zona Pellucida Glycoprotein 4 Gene
α-agonists	Alpha-Adrenoceptor Agonists
β-blockers	Beta-Adrenoceptor Antagonists

1. INTRODUCTION

1.1. Glaucoma

1.1.1. Definition

Glaucoma was first mentioned in ancient Greece; the word "*Glaucosis*" in Hippocratic writings described a blinding disease. The concept of glaucoma was refined over the years, where it has evolved from a disease of eye pressure to a disease of optic nerve neuropathy. Currently, glaucoma describes a family of multifactorial optical neuropathies characterized by a progressive loss of retinal ganglion cells (RGCs) leading to typical optic nerve head (ONH) damage and distinctive visual field (VF) defects (1). It can permanently damage vision in the affected eye and lead to blindness if left untreated. Glaucoma may present with a variety of signs and symptoms, depending upon type and severity, such as: excavation of the optic disk, hardness of the eyeball, corneal anaesthesia, reduced visual acuity, seeing of coloured halos around lights, disturbed dark adaptation, VF defects and headaches (2).

1.1.2. Classification and prevalence

Glaucoma is classified by different authors according to cause, the age of onset, initial pathological event or mechanism. Glaucoma may be congenital or acquired. According to the mechanism by which aqueous outflow is impaired with respect to the anterior chamber angle configuration, glaucoma is classified as open-angle or angle-closure glaucoma. It can also be classified as primary glaucoma or secondary glaucoma, depending on the presence or absence of ocular or systemic disorders that may contribute to pressure rise (3).
Classification of primary glaucoma is depicted in Table 1, whereas classification of secondary glaucoma is depicted in Table 2.

Table 1. Classification of primary glaucoma (3).

Open Angle Glaucoma (OAG)	Angle Closure Glaucoma (ACG)	Congenital Glaucoma
Primary Open Angle Glaucoma (POAG)	Primary Angle Closure Suspect	True Congenital
Normal Tension Glaucoma (NTG)	Primary Angle Closure	Infantile Glaucoma
High Tension Glaucoma (HTG)	Primary Angle Closure Glaucoma	Juvenile Glaucoma

Table 2. Classification of secondary glaucoma (3).

	Site of aqueous outflow obstruction	Conditions that contribute to rise IOP
OAG	Pre-trabecular	Membrane overgrowth: fibrovascular, endothelial or epithelial proliferation.
	Trabecular	Obstruction: meshwork structure alteration, red cell, ghost cell, phacolytic, hypertensive, uveitic, pseudoexfoliation or pigment dispersion.
	Post-trabecular	Impair of aqueous outflow: occlusion of the Schlem's canal, elevated episcleral venous pressure.
ACG	Pupil block	Pupil seclusion, lens subluxation, anterior chamber lens implant without iridotomy, adhesive capsular block, aphakic pupil block, or phacomorphic.
	Without pupil block	Capsular block syndrome without adhesions, iris, ciliary body or posterior segment cyst/tumour, contract of retrolenticular fibrovascular tissue, ciliochoroidal effusion, malignant or late neovascularization.

OAG = Open Angle Glaucoma; ACG = Angle Closed Glaucoma; IOP = Intraocular Pressure.

Glaucoma is the leading cause of irreversible blindness worldwide (4-8), with OAG being the most common form (5, 6). It is the second most common cause of blindness after cataracts (4, 6-7). It was estimated that by year 2010, 45 million people around the world will suffer from OAG and 16 million from ACG. This number will be increased to 79.6 million by 2020, and of these, 74% will have OAG. The total number with OAG in 2020 will be 58.6 million, with the highest number among people of European descent. Bilateral blindness will be raised to 5.9 million people in 2020 (6).

Several large population-based studies have been carried out to determine the prevalence of glaucoma. Studies in developed countries suggest that more than 50% of the prevalent OAG is undetected (8), and this estimate is likely to be higher in developing countries (5).

In a recent meta-analysis of POAG prevalence that included 46 studies conducted in different countries, authors concluded that prevalence increases more rapidly in Caucasian than in black and Asian populations, but at all ages black populations have the highest prevalence estimates. Data from this study suggests that OAG prevalence in men is approximately 1.4 times that in women (9).

1.1.3. Primary open angle glaucoma (POAG)

Over the years, there has been a lack of consistent definition of POAG. Since 1980s, different definitions and descriptions have been published, based on optic disc, specific VF and intraocular pressure (IOP) criteria (10).

American Academy of Ophthalmology (AAO) defines POAG as a progressive, chronic optic neuropathy in adults where IOP and other unknown factors contribute to damage and in which, in the absence of other identifiable causes, there is a characteristic acquired atrophy of the optic nerve and loss of RGCs and their axons. This condition is associated with an anterior chamber angle that is open by gonioscopic appearance (11).

Today, IOP is not the key part of the definition for POAG. Diagnosis is based on the presence of the optic nerve damage, manifested either by optic disc or VF abnormalities (12). Indeed, the European Glaucoma Society (EGS) definition of POAG has been arbitrarily subdivided into High Tension (HTG) and Normal Tension (NTG) disease according to IOP levels, even though they may represent a spectrum of optic neuropathies variably sensitive to IOP (13).

1.1.3.1. Primary open angle glaucoma/ High tension glaucoma (HTG)

Although HTG and NTG may represent two distinct clinical entities, there is an amount of conflicting literature. Studies have identified similarities and differences regarding the appearance of the ONH and VF that raised questions about different mechanisms and aetiologies of optic nerve damage, making it difficult to draw any clear conclusions (14-16).

In general, HTG is characterized by elevated IOP without treatment. It is generally bilateral but not always symmetrical and presents typically from 35 years of age onward. Clinically, it is characterised by an excavation of the optic nerve, referred to as glaucomatous optic neuropathy (GON) and a glaucomatous visual field defect (GVFD). Anterior chamber angles are open and normal.

1.1.3.2. Primary open angle glaucoma/ Normal tension glaucoma (NTG)

Historically, NTG was referred to as "low tension glaucoma". Recently, it has been shown that OAG is a disease in which the aetiology extends from being predominantly IOP dependent at one end (pure HTG), to predominantly IOP independent at the other end (pure NTG). Involvement of vascular factors in OAG increases as the predominance of IOP decreases (17). Today, it is generally thought that physiological variation of Central Corneal Thickness (CCT) is important only for the IOP measurement but not related to any particular

type of glaucoma. So, related to NTG, it could be that IOP is falsely lower as an error of measurement – that it is actually HTG, but with a thin cornea.
Two studies showed that the risk of glaucoma increases by 40% and 30% for every 40 micrometers thinner cornea (18, 19). Except VF defects, that in NTG typically appear deeper, steeper and closer to the fixation and GON, there are characteristic disc haemorrhages.

1.1.4. Primary open angle glaucoma suspect

The term POAG suspect is used to define individuals where not all the criteria that define POAG are presented. It refers to an individual with clinical findings or risk factors that indicate an increased likelihood of developing POAG.
POAG suspects may have one of the clinical findings in at least one eye with open anterior chamber: appearance of the ONH or retinal nerve fibre layer (RNFL) that is suspicious for glaucomatous damage; a VF suspicious for glaucomatous damage in the absence of clinical signs of other optic neuropathies; or consistently elevated IOP associated with normal appearance of the ONH and RNFL and with normal VF test results. The definition excludes known secondary causes for OAG (13, 20). An overlap exists between findings in people with early POAG and in those who are glaucoma suspect and without the disease.
The diagnosis of POAG is usually supported if two or more of the findings are present.

1.1.5. Ocular hypertension (OHT)

The word "*preglaucoma*" was used to define individuals with an elevated IOP and without detectable glaucomatous damage in the standard clinical eye and VF examination, although the majority of them never developed POAG. Diagnosis between ocular hypertension (OHT) and early POAG is often difficult (21).
In a review published in 1998, authors found that 20% of the papers published in the last 15 years used raised IOP as the only criteria to diagnose glaucoma (22). Today, the OHT term is widely used for research and classification purposes for individuals with IOP higher than 21 mmHg but without any VF, ONH and RNFL changes.
EGS in its classification states that the term OHT should be only used to indicate that the IOP is consistently outside two or three standard deviations from the normal mean, with all other ocular findings within normal limits.

1.2. Risk factors and pathophysiology

The exact cause and pathophysiology of the POAG remains unknown and still relatively poorly understood despite numerous research in this area. Furthermore, for many years authors have suggested that HTG and NTG represent clinical entities with different pathogenesis and risk factor implications.
According to data from newer studies, NTG and HTG represent a continuum disease in which elevated IOP is the predominant risk factor, while additional independent factors take increasing importance in NTG (13, 14, 17, 23). This definition links different risk factors into the pathogenesis of POAG, although there are a number of studies that do not support this theory (16, 24).

1.2.1. Risk factors

In epidemiology, a risk factor is a variable that represents an inherited characteristic, environmental exposure, or an aspect of personal behaviour that influences the probability of an individual to develop the disease. Risk factors can be divided into various categories. The distinction between causal and associated risk factors but also modifiable and non-modifiable risk factors is important to understand the pathogenesis, the diagnosing process and to plan the management of the disease (25).
The identification of risk factors has a preventive and therapeutic implication in POAG. The most studied risk factor that influences POAG is elevated IOP. IOP is causal and changeable, and is the main clinically treatable risk factor that can help prevent POAG (25, 26). Multiple theories exist about the role of IOP in the pathogenesis of GON, whereas causal role is demonstrated by a number of experimental, clinical and epidemiological studies.
In humans, IOP has a non-Gaussian distribution with a mean of 16 mmHg and two standard deviations on either side that gives a range of normal IOP from 11-21mmHg. In elderly people, the deviation is greater than in younger individuals, particularly in women, that may range up to 24 mmHg (3, 19, 27). In general, it is noticed that, the higher the IOP, the greater the likelihood of glaucoma, although, many eyes with IOP above the average range do not develop glaucoma and others within normal range of IOP develop it.
In addition to the level of IOP, it seems that of relevance is also circadian and day to day IOP fluctuation (27, 28).

Some POAG risk factors are not changeable, however, they are studied because of their importance in identification of individuals that are indicated for close ophthalmic supervision. General risk factors that may contribute to POAG are summarized in Table 3, whereas ocular and systemic risk factors are summarized in Table 4.

Several ocular, systemic and general risk factors have been proposed to play a role in the POAG pathogenesis and conversion of OHT to POAG but the most studied and with the growing body of evidence are: age, race, ethnicity, family history, genetics, vascular factors, diabetes mellitus, myopia, corneal thickness, and ONH. Some books also mention lifestyle, socioeconomic status, alcohol consumption or smoking as possible risk factors.

Table 3. General risk factors that may contribute in POAG

General risk factors	Description	References
AGE	Age appears to be an important risk factor. Prevalence studies demonstrate that it is unusual to see the disease before the age of 40, and more than three times higher after the age of 65. It is believed that damage progresses faster in older people.	3, 21, 25, 28
RACE	It is not clear whether race is directly affiliated as a risk factor, or if there are other associated factors that increase the prevalence in a certain race. Prevalence studies state that POAG prevalence in black people is higher, develops earlier and is more severe while NTG occurs more in Japan.	3, 11, 21, 29
FAMILY HISTORY	The exact risk of family history cannot be estimated, the disease develops in older individuals and long term follow-up is required. Responsible genes can show incomplete penetrance and variable expressivity in some families. IOP, facility of aqueous outflow and optic disc size are also genetically determined. First-degree relatives of patients with POAG are at an increased risk.	3, 11, 21, 29
GENETICS	Genetic studies detected different mutation in loci of the human genome associated with POAG like: *MYOC, OPTN, WDR36, OPA1* and the *NTF4* gene.	3, 11, 25
GENDER	Gender is not listed in the risk factors in the majority of glaucoma books. Studies did not find a clear-cut evidence of gender as a risk factor, although some studies have found a higher prevalence of NTG in females.	3, 25

POAG = Primary Open Angle Glaucoma; NTG = Normal Tension Glaucoma; IOP = Intraocular Pressure; *MYOC* = Myocilin; *OPTN* = Optineurin; *NTF4* = Neurotrophin; 4; *WDR36* = WD Repeat Domain 36; *OPA1*= Optic Atrophy 1.

Table 4. Ocular and systemic risk factors that may contribute in POAG

Ocular risk factors	Description	References
ONH	ONH characteristics are now part of the definition of POAG, and in many protocols are not listed in risk factors. For many years enlarged ONH was considered as a risk factor. Recently, cup/disc ratio, cup/disc ratio asymmetry and pattern standard deviation are described in literature as additional risk factors.	28, 30
CCT	CCT is lower in NTG patients and higher in people with OHT. This relationship led to the idea that CCT may also be an independent risk factor. Indeed CCT, curvature of the cornea, cornea biomechanics can all affect the measurement of IOP. There is also an opposing thought on whether CCT contributes to the conversion of OHT in POAG.	11, 19, 28, 30
MYOPIA	Supporting evidence is not strong but, it is thought that myopic eyes maybe at increased risk for POAG. This relationship remains controversial. People with myopia are more likely to seek eye care and thus have a higher probability of having glaucoma detected early, disc evaluation is complicated, retinal changes and high refractive errors can cause visual field abnormalities.	11, 21, 25, 29
Systemic risk factors		
VASCULAR DISEASES	Relationship between POAG and vascular diseases is difficult to prove and still remains controversial. The higher probability of involvement of vascular factors is when POAG occurs or progresses at lower IOPs. A range of vascular diseases is thought to be associated with the development and progression of some POAG cases like: systemic hypertension, systemic hypotension cardiovascular diseases, migraine, and vasospasms.	21, 28, 31
DIABETES MELLITUS	Linkage between POAG and diabetes mellitus (DM) has been proposed due to vascular deregulation in diabetes. There are some studies that show a correlation between diabetes mellitus and POAG, but it still remains controversial if diabetes is an independent risk factor.	3, 21

ONH = Optic Nerve Heat; OHT=Ocular Hypertension; CCT = Central Corneal Thickness; IOP = Intraocular pressure; POAG = Primary Open Angle Glaucoma; NTG = Normal Tension Glaucoma.

1.2.2. Pathophysiology

A definitive description of processes that causes the characteristic atrophy of the optic nerve and loss of RGCs and their axons in POAG still needs to be established.
RGC death in POAG occurs predominantly through apoptosis rather than necrosis, where the pre terminal event is calcium ion influx into the cell body and increase of intracellular nitric oxide (3). An excessive release of the excitatory neurotransmitters in the extracellular environment after the axon death may trigger the death of the neighbouring neuron cells (26). It is demonstrated that after initial injury, progressive pathological changes result also with changes in RGC bodies, photoreceptors, *lateral geniculate nuclei*, visual cortex and *lamina cribrosa* (32-36).
On a histological level, it is characterized by loss of axons, blood vessels and glial cells that seem to start at the level of *lamina cribrosa* (21). These alternations cause tissue remodelling, leading to the enlargement or the asymmetrical deep of the optic cup, optic disc haemorrhage, peripapillary atrophy, neuroretinal rim (NRR) and RNFL thinning that is unique for GON (37, 38).
Several theories describe the occurrence of optic neuropathy in POAG, but most widely studied are the mechanical and vascular theory. However, it is generally recognized that POAG can be caused by a mixture of both mechanisms (39, 40). These mechanisms may include axoplasmic flow reduction, interference in the delivery of nutrients or removal of metabolic products, neuronal growth factors deprivation, oxidative stress and the initiation of immune-mediated damage.
The precise mechanism is still a hot topic on glaucoma research, and the theories will be discussed only because of their historical importance.

1.2.2.1. Mechanical theory

The mechanical theory of POAG is based on the mechanical force that causes elevated IOP in *lamina cribrosa, glia* and axons of ONH (41).
Elevated IOP is caused due to the altered rate between aqueous secretion and outflow resistance in the presence of open anterior chamber angle. The increase of outflow resistance is supposed to be caused by structural alternation of trabecular meshwork. There is a histopathological and biochemical evidence of several factors contributing to these mechanisms, however they are not well understood (29).

In the context of mechanical theory of POAG, it is believed that pressure gradient is more important around the ONH rather than the absolute IOP (3). According to this theory, direct compression of axons and the deformation of the pores and channels of the *lamina cribrosa* disrupts axoplasmic flow and leads to RGCs death (26).
Most studies support the theory that the level and duration of increased IOP is important for the development of POAG, however, some authors state that factors such as scleral rigidity (42) are of primary interest.
Furthermore, affection of ONH in NTG beside the normal IOP level, and absence of glaucomatous damage in OHT despite the elevated IOP leads to idea that in individuals alternative or additional causative factors contribute to the development of GON.

1.2.2.2. Vascular theory

The vascular theory of POAG is based on the instability of blood flow in the microvasculature that supplies ONH (43, 44).
Blood flow instability contributes to GON development through ischemic and hypoxic insult of the ONH tissues, including: the RGC axons, astrocytes, glial cells, pericytes and the central retinal vessels (43).
Possible mechanisms that cause GON may extend from: losing of capillaries, reductions in blood flow, failure of vascular regulation, interference with delivery of nutrients or removal of metabolic products from axons, and increases in vessel rigidity at both levels (3, 28).
Evidence of decreased blood flow in OHN is demonstrated by histopathology, fundus fluorescein angiography, and Doppler measurements (45-47). Some studies demonstrated impairment of normal autoregulation of retinal vessels or atrophy of peripapillary capillaries that supply the RNFL in POAG patients (46-48).
A lot of research has been conducted to explore the role of ocular and systemic vascular factors in the pathophysiology of POAG, but still they are not well understood and remain controversial.

1. 3. Diagnosis and prognosis

For the proper management of POAG, comprehensive evaluation of the eye is important. It can reveal the diagnosis, severity and the progression of the disease. All components of the eye evaluation should be performed and more than one visit is required (11, 49).
POAG identification may require a variety of modalities for the clinical examination, but some are particularly important. Examination includes: anamnesis; refraction evaluation; pupil, and slit-lamp examination of the anterior segment; tonometry; pachymetry; gonioscopy; fundus, ONH and RNFL evaluation; VF assessment and electrophysiology.

1.3.1. Anamnesis

POAG has a painless and insidious nature, and patients usually do not report symptoms during the early phase (26). Very rarely, patients with elevated IOP will note brow arch and haloes around lights. Visual acuity alternation occurs only in advanced disease or when *scotoma* is close to fixation, and VF defects are not consciously perceived by patients (2, 28, 29). In a recent study of moderate glaucoma patients with a range of GVFD, it was found that VF filed is not perceived as a black tunnel or as black patches masking the field (50). Some patients may suffer from loss of chromatic or achromatic sensitivity, reduced contrast sensitivity and increased blur.
Since POAG patients lack symptoms, the initial examination history should contain: ocular history, family history, and systemic risk factors that can be associated with POAG.
An assessment of the impact of patient's visual function in relation to hobbies, employment, and daily living should be performed (27).

1.3.2. Clinical examination

Evaluation of refraction to obtain the best corrected visual acuity (BCVA) is crucial for accurate VF testing, but also to exclude clinical confusion of disc morphologies that can be due to early myopia (21).
Pupils should be examined for reactivity and afferent pupil defect that may be present in eyes with advanced optic nerve damage in highly asymmetric cases of glaucoma (51).
Examination of the anterior segment in slit-lamp is done to exclude other forms of glaucoma or ocular pathologies. In POAG the anterior segment is without any pathology.

1.3.3. Tonometry

Diagnosis of POAG cannot be made according to the IOP level; however tonometry is always performed before gonioscopy and pupil dilatation. Beside diagnosis, tonometry is used to evaluate the effect of glaucoma treatment on the IOP.
IOP can fluctuate by the influence of numerous factors like: time of day, heartbeat, respiration, exercise, fluid intake, topical and systemic medications. In POAG patients, IOP fluctuates well beyond that is seen in normal populations and tonometry measurements should be recorded at different hours of the day or on different days (3, 11, 21). This way of measurement is important to: establish the diagnosis of NTG, stop the progression of POAG due to unrecognized fluctuations, and evaluate the ability of anti-glaucoma therapies to lower the IOP throughout the 24h day (52-54).
A number of tonometers utilizing different techniques have been produced. Goldman applanation tonometer remains the preferred one and relatively accurate, whereas non-contact tonometers used more for screening purposes are less precise. Accuracy of any types of tonometers can be affected by different factors, the most important are CCT and corneal biomechanical properties (corneal hysteresis and corneal resistance factor) (25).

1.3.4. Pachymetry

Measurement of CCT is recommended as it influences Goldman aplanation tonometry (GAT) readings. However, there is no agreement as to whether there is a validated correction algorithm for GAT and CCT (25, 55). Normal CCT is 540+/-30μm, whereas each glaucoma cabinet has tables for correction of IOP in respect to pachymetry findings.
It remains unclear whether CCT represents a risk factor due to its effect on IOP measurement or whether CCT is a risk factor itself.

1.3.5. Corneal hysteresis

Corneal hysteresis (CH) measurement reflects the viscoelastic properties of the cornea and gives an indication of its biomechanical integrity.
CH does not show any significant variations throughout the day (25), and has greater impact than CCT and corneal curvature in the IOP measurement errors (56).
Low CH value is a risk factor for underestimation of the IOP and a high CH value for overestimation, however, CCT and CH are independently associated with IOP (57).

1.3.6. Gonioscopy

POAG diagnosis requires careful evaluation of the anterior chamber angle to exclude secondary causes of IOP elevation. Indirect and direct gonioscopy techniques are used for this examination and a number of lens constructed based on these techniques.
In the office, most applicable is indirect gonioscopy (58). Beyond gonioscopy, that is a subjective technique, available imaging techniques for evaluation of the anterior chamber angle are: ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (OCT). These two techniques are non-invasive, but do not replace the goniosocpy and are used just as complements (25, 27).

1.3.7. Optic nerve head and retinal nerve fibre layer examination

In POAG diagnosis and management the most critical part is evaluation of ONH and RNFL. Alternations in ONH and RNFL are the most typical for POAG, and often occur before VF defects (26, 29, 59). It is important to notice: NRR thickness, disc asymmetry, pallor of the disc, disc haemorrhages, peripapillary atrophy, blood vessel changes, visibility and loss of RNFL (21). Relevant variables that can be extracted are: horizontal and vertical cup-to-disc ratio, volume of cup and rim, and average RNFL thickness. Data of these parameters should be collected in drawings or visualisation techniques, and quantitative measurements by instruments should be performed.
Evaluation techniques for these structures involve: subjective techniques (direct and indirect ophthalmoscopy), stereoscopic fundus photography and imaging techniques. Currently, the most common used imaging techniques are: scanning laser polarimetry (SLP), confocal scanning laser tomography (CSLT), time domain and spectral domain OCT.

1.3.8. Visual Field Function

Except ONH and RNFL evaluation, VF test is crucial for POAG diagnosing and management. This psychophysical test remains the primary visual function test performed in POAG. It reflects characteristic changes of the RNFL anatomy and determines the impact of VF on a patient's quality of life and activities of daily living (60, 61). Interpretation of VF test should be very careful as the results can be affected by: ability of patient and examiner, fixation, luminance, stimulus, refraction, pupil size and opacities of eye media (3).

In POAG, defects in VF occur at 30°, models include: *paracentral* and *arcuate* or *Bjerrum's scotoma*, nasal step, altitudinal or temporal wedge defects and less characteristic changes like general depression. In early stages of the disease defects are located in the periphery of the visual field (3, 21, 27, 29). Different devices that use different techniques and programs have been constructed for VF testing. Some are better for identification and others for following the progression, however, all of them have weaknesses. Currently, most preferable for assessment is the automated static perimtery. Suprathreshold static perimetry is suited for rapid screening, while manual perimetry remains helpful in documenting defects outside the central 30° and in monitoring end-stage VF loss (11, 29). Sensitive assessment of POAG progression can be performed by independent programs that calculate and compare VFs (62).

1.3.9. Electrophysiology

Electrophysiological examination techniques provide localised information of RGCs functions (63, 64). In POAG, RCGs are lost before the appearance of subjective VF defects (65), however, electroretinography (ERG) and visually evoked potential (VEP) examinations are not routinely performed. They are a part of the objective testing when patients are not able to perform perimetry.

1.3.10. Genetic Testing

Association of the genes with POAG does not have the specificity required for a gene-based diagnostic or screening test, although they may be helpful to screen individuals in risk and to decide for therapy. These tests can be carried out only in some specialised laboratories and are not performed routinely (25).

1.3.11. Ocular Blood Flow Measurement

Measurement of ocular blood flow (OBF) in POAG diagnosis is based on the possible influence of vascular risk factors of the disease, but this assessment is not supported by evidence. Furthermore, information is practically useless for clinicians. Only few guidelines recommend treatment of POAG patients in regard to reduced OBF (25, 66). Different techniques and instruments are available, but the ideal test to measure comprehensive OBF of patients is yet to be developed.

1.4. Treatment

The aim of therapy in POAG is to prevent functional impairment of vision by slowing the apoptosis of RGCs within a patient's lifetime. Elevated IOP, which is the main factor implicated in mechanisms that are thought to precipitate RCGs apoptosis in POAG, is currently the only treatable factor approved by many guidelines (11,13).
Many studies demonstrate that decreasing IOP prevents both conversion of OHT to POAG and progression of POAG (67-69), however, it remains unclear which modality of the IOP-lowering therapy is the most effective, with the fewest adverse effects and lowest cost.
Non-IOP lowering therapy toward factors that may play a role in POAG pathogenesis are being investigated (70-72), but until now neither proved enough evidence.

1.4.1. Conservative therapy

Medical therapy has an important role in POAG treatment, especially during the last years that the pharmaceutical market has presented a variety of IOP lowering drugs and different combinations. Drugs are considered as the first line of treatment, and in most patients they can control the disease alone.
Medications reduce elevated IOP either by reducing aqueous production or by increasing aqueous outflow through the conventional or the unconventional pathway (73, 74). Table 5 summarizes five major classes of IOP-lowering drugs: direct and indirect acetylcholine receptor agonists (cholinomimetics); alpha-adrenoceptor agonists (α-agonists); carbonic anhydrase inhibitors (CAIs); beta-adrenoceptor antagonists (β-blockers); and prostaglandin analogues (PGAs) (75, 76). Each group comprises of several individual drugs, whereas fixed combinations are also available. Some drugs are not used anymore as the new drugs from the same group, which have greater effect and less adverse effects became available.

1.4.2. Laser and surgical therapy

Indications for laser and surgical therapy changed with the introduction of new generations of lasers and novel surgery devices with low morbidity for surgical intervention but, still remain the second line of treatment.

Table 5. Five major classes of IOP-lowering drugs

α-agonists	*β*-blockers	CAIs	PGAs	Cholinomimetics
Dipivefrin	Timolol	Acetazolamide	Travaprost	Pilocarpine
Brimonidine	Levobunolol	Methazolamide	Latanaprost	Carbachol
Apraclonidine	Betaxolol	Dorzolamide	Brimatoprost	Physostigmine
Epinephrine	Carteolol	Brinzolamide	Tafluprost	Echothiopate
Clonidine	Metipranolol	Diclorphenamide	Unoprostone	Demecarium
	Pindolol			Aceclidine
	Befunolol			Achetylcoline

α-agonists = Alpha-Adrenoreceptor Agonists; *β*-blockers = Beta-Adrenoreceptor Antagonists;
CAIs = Carbonic Anhydrase Inhibitors; PGAs = Prostaglandin Analogues;
Cholinomimetics = Direct and Indirect Acetylcholine Receptor Agonists.

Lasers can be considered as a first line therapy in some patients, usually adjunct to medical therapy or with attempt to gradually withdraw medical therapy, although the reduction of medication is a secondary consideration (3, 21). Laser procedures used to lower IOP include: trabeculoplasty, iridotomy, iridoplasty and cycloablation.
Laser trabeculoplasty is a procedure most commonly used in case of POAG. It lowers IOP by targeting trabecular meshwork by argon, diode and selective laser or alternative lasers like continuous wave length lasers of red and infrared wavelengths (28).

In POAG patients, surgery is considered when maximal drug therapy is not effective, although it can reduce the number of patient visits to the doctor and can achieve a lower IOP without additional medications.
Commonly performed surgery is a partial thickness procedure called guarded trabeculectomy. Different modifications of trabeculectomy evolved to prevent failure of filtration with the use of anti-metabolites agents and aqueous shunts (13, 21). Several newer non penetrating surgeries with lower morbidity have been presented recently, however these options are not much studied (27, 77). Combined surgeries of glaucoma and cataracts are also performed lately as prevalence of glaucoma and cataracts in the eye increases with age (25, 78).

Special skills and expensive instruments are required to perform laser and surgical procedures, and therefore they are not in the aim of this thesis.

1.5. Public health consequences

In POAG the optical nerve destruction is usually slow, however, visual loss cannot be reversed. VF loss normally starts by affecting the peripheral vision, therefore remains unrecognized for a long time. Late detection with a consequent delayed treatment commencement is a major risk factor for blindness.

The incidence of blindness from POAG has been variously reported. It was estimated that 20 years into the diagnosis and treatment of POAG, incidence of blindness was 27% unilateral and 9% bilateral, with 15 patients legally blind at least in one eye at the time of diagnosis (79). Many issues related to blindness from POAG are linked to poverty and incidence maybe higher in developing countries where the diagnosis and treatment are delayed. However, if diagnosed and treated in time, most POAG patients will retain useful vision for their entire lives. This is especially problematic in developing countries with limited public health resources for diagnosis, treatment and reimbursement of POAG patients.

The International Classification of Diseases (ICD), the standard diagnostic tool for epidemiology, health management and clinical purposes of the World Health Organization (WHO) defines blindness as visual acuity of less than 20/400 (6/120) or VF loss to less than 10° in the better eye with the BCVA. By this tool low vision is defined as visual acuity equal to 20/200 (6/60) or VF loss to less than 20° in the better eye with the BCVA (80). WHO Member States use this tool for national mortality and morbidity statistics, but also for reimbursement and resource allocation decision.

While in many parts of the world sophistication and efficacy of diagnostic and therapeutic methods rely on expensive equipment and drugs, and research is focused in etiological issues, in developing countries the primary goal is adequate preventive and therapeutic care related to their limited budget (81). First step to achieve this is identifying people with a higher risk of developing POAG, and to approve a public health strategy of treatment with the lowest-cost intervention.

Although the economic evaluation for POAG is in its infancy, practical adaptation of data analysis of risk factors and treatment modalities is highly important for these countries, because physicians and regulations often adopt non cost-effective strategies enhancing the perception of findings (81, 82).

1.6. The problem

As illustrated already by its classification, glaucoma in general is a very complex and multifaceted condition. The current understanding is that the two major classes – open angle (OAG) and angle closed (ACG) glaucoma – are actually different diseases with different pathophysiology and different risk/causative factors. OAG is by far more prevalent (~75% of all glaucoma cases) and its primary form, i.e., primary open angle glaucoma, POAG, bears the major part of the overall healthcare burden of glaucoma.

Although not without controversy, the definition, features and clinical characteristics of POAG are nowadays well defined, but the primary cause(s) that triggers the cascade of events resulting in POAG is less clear and is in the focus of the current research.
Elevated IOP is the only clearly defined major risk factor for development of POAG, although this relationship is not a "perfect" one. There is also a growing body of evidence suggesting that other factors may play a role in pathogenesis of POAG, but the contribution of these multiple factors is uncertain and different etiological theories on POAG have been proposed. In the attempts to improve the public health strategies for coping with the overall burden of the disease, systematic evaluation of the existing evidence on potential relevant other (apart from IOP) risk factors is warranted.

Reduction of IOP prevents both conversion of OHT to POAG and progression of POAG, i.e., progression the optic neuropathy and impairment of vision. Different treatment modalities targeting factor that may play a role in POAG pathogenesis are being investigated, but for the time-being the only modality recommended by the professional guidelines is IOP-lowering treatment (11, 13, 8). Reduction of IOP can be achieved by medications, laser and surgical therapy. Topical drug therapy is a standard initial treatment, whereas the latter two options are implemented mainly when conservative therapy is not effective, not tolerated or not utilized by the patient. According to the guidelines, IOP-lowering treatment should start with a mono-compound therapy and should aim to reduce IOP by 20-30%. A rational first line mono-compound drug is the one installed as infrequently as possible for the therapeutic effect and with the fewest side-effects. If the first line medication is not effective or not tolerated it could be substituted, another drug may be added (unfixed combination) or a patient could be switched to a fixed combination of different compounds (9, 11, 13).

A recent comprehensive evaluation (83, 84) demonstrated a high level of evidence of efficacy in IOP reduction of various topical pharmacological treatments but with some uncertainty regarding their mutual relationship in this respect. The latter was in part due to inconsistent results of some studies and to the complexity of the setting (e.g., different forms of OAG, treatment-naïve/previously unsuccessfully treated patients) and treatment modalities (mono-compounds, fixed/unfixed combinations) (83, 84). It is therefore of interest to evaluate the existing evidence on relative efficacy, tolerability and cost-effectiveness profile of mono-compound topical medications specifically in POAG and OHT, the most common conditions requiring IOP-reducing therapy.

2. HYPOTHESIS AND AIMS OF THE STUDY

The present study was motivated by three hypotheses related to POAG/OHT:

I. There might be other, apart from increased IOP, factors with relevant individual contributions to the risk of POAG.

II. There might be practically relevant differences between IOP-lowering treatments regarding efficacy and safety in POAG/OHT.

III. There might be relevant differences between IOP-lowering treatments regarding cost-effectiveness profile in POAG/OHT.

By the year 2010, there were already 112 systematic reviews/meta-analyses in the field of glaucoma (85, 86) embracing a variable number of primary studies addressing different aspects of the disease. Considering the continuous research interest in these topics, it is reasonable to assume that the body of data has further increased over the past few years. Under such circumstances, a systematic synthesis of the existing research appears to be an appropriate methodological approach to achieve the aim of improved overall management (preventive and curative) of glaucoma, more specifically, of POAG and OHT.

In this respect, the present study aims to answer specific research questions:

1. What is the existing evidence on factors other than the increased IOP that are potentially modifiable or could be used for timely identification of people at an increased risk of POAG?

2. What is the existing evidence on relative efficacy and safety of mono-compound topical IOP-lowering medications in treatment of POAG/OHT?

3. What is the existing evidence on relative cost-effectiveness of the mono-compound topical IOP-lowering medications in treatment of POAG/OHT?

3. MATERIALS AND METHODS

In the context of evidence-based medicine, systematic reviews/meta-analyses are generally considered to provide the highest level of evidence based on filtered data. Considering the reports indicating existence of a large number of such studies related to glaucoma (85, 86), the present study was conceived as an overview of systematic reviews: a method of identification, qualitative and quantitative evaluation and synthesis of the available clinical evidence about the posed research questions. Primary studies were considered only in case of out-dated or incomplete (missed studies, non-evaluated endpoints) systemtic reviews.
Although related to the same topic, the questions conceptually differed: one addressed "prognostic relationships" and was to be based on evaluation of observational data (systematic reviews/meta-analyses of observational studies); the other addressed "therapeutic relationships" and was to be based on interventional studies (systematic reviews/meta-analyses of interventions).
Since the nature and methodology of the observational and interventional primary studies differ, the methodological characteristics of systematic reviews of such studies also differ. Consequently, an overview of reviews has certain methodological features that depend on whether it deals with prognostic or therapeutic issues. However, most of the methodological steps are common to all overviews of reviews. The present study followed the format and methods for an overview of systematic reviews as proposed by the current Cochrane Handbook for Systematic Reviews (version 5.1.0., 2011) (87).
This section first depicts the common methodological characteristics of both parts ("prognostic" and "therapeutic") of the present study, followed by methodological particulars for the each part. The common elements are: literature search; selection of studies; data collection; assessment of study quality; data synthesis and evaluation of quality of evidence.

3.1. Literature search

All performed literature searches included searches of electronic databases of published studies, as well as hand searches – reference lists of identified relevant publications. Unpublished material was considered to be irrelevant therefore no attempts were made to identify. Common search strategies [(separately for prognostic and interventional studies) (Tables 8, 9)] were defined by me and mentor and then searches were performed by each one individually. Assistance of a professional librarian was used in this step. Direct search terms

and control terms were adapted to each database. All searches were conceived to be sensitive not specific, hence no restrictions were set in respect to the journal, publication date, geographical location or language. Literature searches on both topics were repeated on two occasions during 2013, and final searches were concluded by the end of February 2014.

3.2. Selction of studies (reviews)

The inclusion of studies (reviews) in the present overviews was based on predefined criteria formulated in collaboration with mentor (study selection protocols 3.6.2 and 3.7.2). Study (review) selection was carried-out independently by me and mentor, but a consensus had to be reached at two steps in the selection process. The entire process consisted of the following steps:

a. identification and removal of duplicate publications from the body of records identified by the initial search;

b. screening of non-duplicates based on titles and abstracts for potential eligibility for inclusion. At this step, the selections made by me and mentor were compared and discrepancies were resolved by a consensus;

c. retrieval and full text evaluation of the selected studies for final assessment of eligibility for inclusion. At this step, the selections were again compared and discrepancies resolved through a consensus.

3.3. Data collection

Data collection forms were defined in a collaboration with mentor in order to collect:

a. descriptive data on included reviews (e.g., author name, publication year, the number and type of included primary studies [e.g., case-control or cohort observational studies for prognostic factors; randomized or non-randomized controlled trials of interventions], number of patients, evaluated questions [i.e., risk factors, treatments]);

b. data relevant for quality assessment of the included reviews which differed for those dealing with observational and those dealing with interventional studies (see below);

c. effect measures provided by the reviews (i.e., end results of the pooled analysis of primary studies).

The data collection process was performed independently by me and mentor, extraction forms were compared and discrepancies resolved by a consensus.

3.4. Assessment of study (review) quality

Each included review was assessed for quality independently by me and mentor. The final results were compared and discrepancies were resolved by a consensus. The process of assessment of quality is outlined in Figure 1:

a. there are two elements of quality of systematic reviews: (i) reporting quality and (ii) "technical quality". The latter depends on methods used to assess the level of various biases in primary studies; methods to protect the systematic review from publication bias; methods undertaken at the systematic review level to reduce biases arising from individual studies (e.g., sensitivity analyses); and data pooling techniques;

b. these elements were assessed using validated tools: recommended check-lists were used to evaluate reporting quality and Cochrane Handbook for Systematic Reviews (87) was consulted to evaluate methodology. Figure 1 depicts the two check-lists used that are described in more detail in subsections 3.6.3 and 3.7.3, on overview of reviews of observational studies (MOOSE) (88) and on overview of reviews of interventional studies (PRISMA)(89);

c. finally, a quality grade was assigned to each included review using the AMSTAR tool (90) (Figure 1).

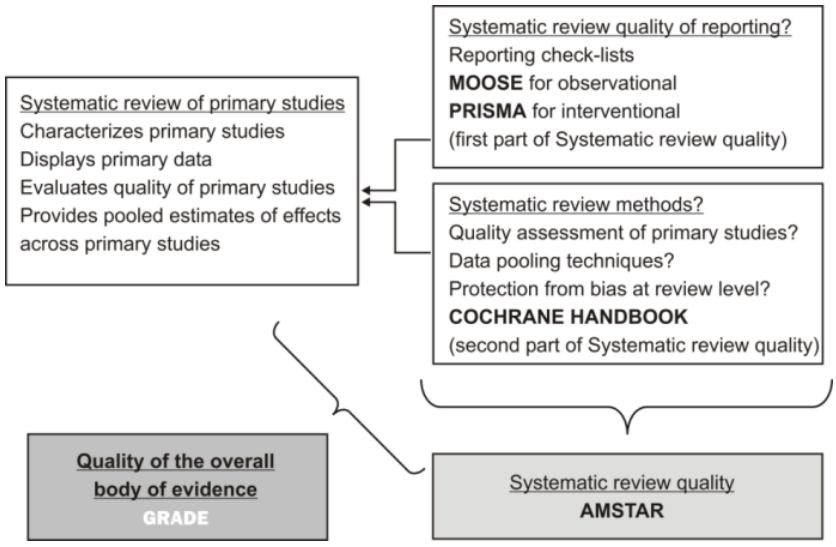

Figure 1. Schematic representation of the assessment of quality of included reviews and of definition of the level of quality of the body of evidence.

MOOSE (88) = **M**eta-analysis **O**f **O**bservational **S**tudies in **E**pidemiology;

PRISMA (89) = **P**referred **R**eporting **I**tems for **S**ystematic Review and **M**eta-**A**nalyses;

AMSTAR (90) = Tool for **A**ssessment of **M**ultiple **S**ys**T**em**A**tic **R**eviews;

GRADE (91) = **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation.

AMSTAR (**A**ssessment of **M**ultiple **S**ys**T**em**A**tic **R**eviews) is a validated tool (face and construct validity, inter-rater agreement) (90, 92) for grading quality of systematic reviews (regardless of whether they deal with observational or interventional primary studies). It is depicted in Table 6.

Table 6. The AMSTAR tool for grading quality of systematic reviews in healthcare (93).

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

AMSTAR poses 11 questions related to methodological quality of a systematic review and offers four possible answers: “Yes”, “No”, “Can’t answer (?)” and “Not applicable”. Only a “Yes” assigns a point to a review. The maximum score is 11. There are, however, no defined cut-off values of the AMSTAR score that would categorize reviews by quality: simply, 1 is the lowest and 11 is the highest level of quality of an individual review (93).

3.5. Data synthesis/Quality of evidence

In the final step, the present overview(s) evaluated the quality of the total body of evidence relevant for the posed research questions. This process was also conducted separately by me and mentor and disagreements were resolved through a consensus.

For this purpose, the GRADE (**G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation) system of evaluation of quality of evidence was used. The GRADE system (94 - 102) is a complex and comprehensive system of assessing quality of evidence in healthcare and is recommended for this purpose by the Cochrane Collaboration.

The GRADE system can be applied to a single study, e.g., observational (epidemiological) study or an interventional trial, or to systematic reviews embracing more such studies.

As a final result, the GRADE assigns one of the 4 categories of “quality” to the “body of evidence” (i.e., one study, more studies, a systematic review or a number of systematic reviews – depending on what represents the “body of evidence”), as depicted in Table 7.

In the case of systematic reviews, i.e., the body of evidence consisting of a systematic review, the GRADE quality rating process is broader and goes beyond what is assessed by the AMSTAR tool: it does not consider only the methodological quality of the systematic review *per se*, but considers also elements like: (i) total number of included studies; (ii) the number of patients per study and overall; (iii) quality of individual studies and the quality of the systematic review; (iv) precision of the (pooled) estimates; (v) level of heterogeneity; (vi) outcome measures in individual studies and the systematic review and their practical relevance; (vii) the data synthesis method, i.e., not only its technical correctness, but also its logic, e.g., only direct vs. mixed or indirect comparisons.

Hence, the level of quality of the body of evidence assessed by the GRADE process subsumes the results of AMSTAR, but adds additional elements.

Table 7. The GRADE system categorization of "quality of the body of evidence" (pertaining to a particular research question) in healthcare.

Level of quality	Marked as	Description/definition
• **High**	4 pluses (⊕⊕⊕⊕)	We are very confident that the true effect lies close to that of the estimate of the effect.
• **Moderate**	3 pluses (⊕⊕⊕F)	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
• **Low**	2 pluses (⊕⊕FF)	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
• **Very low**	1 plus (⊕FFF)	We have very little confident in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

To reach the final grade (of quality), the GRADE process evaluates 5 domains:

Limitations/bias – Depending on what represents a body of evidence (a single study, several studies, a systematic review; a randomized controlled trial, an observational study), this domain has certain specificities. Assessment requires knowledge about appropriate methods for each of the types of studies and recognition of potential methodological limitations and inadequate protection from bias – i.e., flaws in design and conduct. For example, in interventional studies limitations/biases arise from: non-randomization, inadequate allocation concealment, small single-center trials, non-blinding, inadequate subject evaluation methods, inadequate (for the aim) patient selection, etc. In observational/epidemiological studies, limitations arise from not accounting for confounders, inadequate definition of the sample (of the population) etc. In systematic reviews, limitations/biases can be generated at both the primary study level and the meta-analytical level. Inadequate statistical analysis is a common source of limitation/bias in any type of study.

Inconsistency – This is a typical item for evaluation in systematic reviews/meta-analyses and pertains to high heterogeneity (as detected in formal assessment or as apparent discrepancy in the results of individual studies) as a potential obstacle for data pooling. In individual studies it may refer to, e.g., inconsistent results in intent-to-treat and per-protocol data sets, or inconsistency between primary and secondary endpoints.

Indirectness – This item pertains to several different characteristics. Evidence (a single study, a systematic review) can be only indirectly related to the posed research question if: a) it was gathered in population (sample) or system that differs from that to which the research question is addressed; b) it was gathered with an intervention that is not exactly the one at

which the research question aimed; or if an inadequate comparator is used; c) it assessed surrogate outcomes. Indirectness results in poor generalizability of the results. In meta-analyses, indirectness has one additional potential source – indirect comparison, e.g., in network meta-analysis.

Imprecision – This item pertains to imprecise estimates (e.g., wide confidence intervals) in a study (or a systematic review) and is typically due to small samples.

Publication bias – This item pertains primarily to systematic reviews.

The process of grading starts with an "a priori" grade that could then be either reduced or increased. In the case of evidence related to interventions, randomized controlled clinical trials (RCTs) and systematic reviews have a "high quality" starting point. Subsequently, each of the above 5 domains is assessed and the starting grade is either unchanged (by item), or it is reduced by 1 or 2 steps ("downgrading by 1", i.e., -1; "downgrading by 2", i.e., -2). Downgrading by -1 is implemented when body of evidence is seriously flawed at a certain item, and downgrading by -2 is implemented when it is very seriously flawed.

For observational studies, the starting "a priori" grade is "low quality", however, it could be upgraded in the assessment process based on the following: a) a large effect is detected that is likely not biased; b) there is a "dose-dependent" trend (e.g., in epidemiology – more extensive exposure results in a greater effect of a risk factor); c) all plausible residual confounding (effects not accounted for in data analysis that could have affected the outcome) would (i) reduce the demonstrated effect or (ii) would increase the effect, but none is shown. Hence, observational studies could also attain "high quality". Theoretically, RCTs/systematic reviews downgraded for some reason could be also upgraded by the presented criteria.

All systematic reviews included in the presented overviews were assigned the GRADE quality of evidence score and those that attained at least the "moderate quality" level were then used to derive answers to the posed research questions.

In case of out-dated or incomplete data, data from high quality primary studies were pooled. In this case priority was given to random effects estimates rather than to the fixed effects estimates. Results of pooled estimation were presented numerically and graphically. Sensitivity analyses were performed in order to attain unbiased estimates and explore heterogenity. Comprehensive Meta-Analysis softaware version 2.2.064 2011 (Biostat Inc., Englewood, NJ, USA) and SAS for Windows 9.2 (SAS Institute Inc., Cary, NC, USA) (macros for multiple modifier meta-regression) were used for data analyses.

3.6. Risk factors for POAG – protocol for observational studies

3.6.1. Search strategy

We searched the following electronic databases: MEDLINE using both, free interface of PUBMED and Ovid platform; all EBM reviews databases (Cochrane DSR, ACP Journal Club, HTA, DARE) accessible on OVID platform; and SCOPUS. In PUBMED, "clinical queries" and "related articles" functions were used to broaden the search. Search terms used were: "systematic review", "meta-analysis", "case-control", "prospective cohort" to identify the study design; "glaucoma", "open angle glaucoma" to identify the condition; "intraocular pressure", ocular hypertension", "age", "myopia", "race", "gene" and a number of others to identify risk factors. The search strategy is depicted in Table 8.

3.6.2. Study selection

The overview included systematic reviews/meta-analyses meeting the following criteria:

a. primary studies were prospective cohort or case-control studies;
b. POAG disease, as defined by AAO. Both HTG and NTG variants were considered since there is no clear distinction between the two conditions apart from the values of IOP;
c. assessed any (one or more) possible risk factor.

The overview did not include:

a. individual studies (just in case of out-dated or incomplete data from systematic reviews);
b. other forms of reviews and reviews reported only in the abstract form;
c. reviews dealing with secondary OAG or ACG.

3.6.3. Data extraction and quality assessment

Quality assessment of the included reviews followed the general scheme depicted in Figure 1 and under 3.4. The specificity was the use of the MOOSE (88) checklist regarding the quality of reporting, designed specifically to meet the needs characteristic for observational (epidemiological) studies and systematic reviews dealing with such studies. Hence, MOOSE includes items that are common to any systematic review (e.g., reporting on definition of the research question, search strategy, funding sources, publication bias, characteristics of primary studies etc.), however, in comparison to systematic review on interventional studies it lacks items such as: blinding, randomization, allocation concealment and similar. Finally, it includes certain items specific for the methodology of epidemiological studies, in particular

accounting for confounding. For quality assessment of primary studies, the tool developed by the National Institute for Clinical Excellence (NICE) (103) was considered.

3.6.4. Data synthesis/Quality of evidence

Assessment of the quality of evidence was performed as described under 3.5. An adaptation of GRADE for reviews of prognostic (observational) studies that has been developed (104), was consulted in assigning the quality level to evidence arising from observational studies and systematic reviews of observational studies.

SAS 9.2 software (SAS Institute Inc., Cary, NC, USA) was used to perform multivariate meta-analysis of adjusted relative risk of POAG associated with different "smoking dose" and for regression analysis of adjusted relative risk on "smoking dose". Comprehensive Meta-Analysis softaware version 2.2.064 2011 (Biostat Inc., Englewood, NJ, USA) was used to perform random-effects meta-analysis of studies assessing DM as a risk factor for incident POAG and subgroup analysis, whereas SAS 9.2 software for meta-regression analysis.

Table 8. Search strategy for systematic reviews/meta-analyses on POAG risk factors.

1. Meta-analysis [pt]	28. Retinal diseases [All Fields]
2 .Meta-analysis [All Fields]	29. Risk factors [MeSH Terms]
3. Systematic review [All Fields]	30. Risk factors [All Fields]
4. 1 OR 2 OR 3	31. Risk [All Fields]
5. POAG [All fields]	32. Hypertension [All Fields]
6. Primary open angle glaucoma [All Fields]	33. Ocular hypertension [MeSH Terms]
7. Open angle glaucoma [All Fields]	34. Ocular hypertension [All Fields]
8. Open angle [All Fields]	35. Hypothyroidism [All Fileds]
9. Glaucoma [All Fields]	36. Obesity [MeSH Terms]
10. Glaucoma, open angle [MeSH Terms]	37. Genetic [All Fields]
11. 8 AND 9	38. Cup-disc ratio[All Fields]
12. 5 OR 6 OR 7 OR 10 OR 11	39. Cup-to-disc ratio [All Fields]
13. 4 AND 12	40. Optic Disk [MeSH Terms]
14. Age [All Fields]	41. Optic nerve head [All Fields]
15. Race [All Fields]	42. Central corneal thickness [All Fields]
16. Continental population groups [MeSH Terms]	43. CCT [All Fields]
17. Family history [All Fields]	44. Corneal hysteresis [All Fields]
18. Diabetes mellitus [All Fields]	45. Smoking [All Fields]
19. Diabetes mellitus [MeSH Terms]	46. Smoking [MeSH Terms]
20. Diabetes [All Fields]	47. Alcohols [MeSH Terms]
21. Vascular diseases [MeSH Terms]	48. Alcohol [All Fields]
22. Vascular diseases [All Fields]	49. Socioeconomic status [All Fields]
23. Myopia [MeSH Terms]	50. 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49
24. Myopia [All Fields]	
25. Refractive errors [MeSH Terms]	
26. Refractive errors [All Fields]	51. 13 AND 50
27. Retinal diseases [MeSH Terms]	

MeSH = Medical Subject Headings; pt = Publication Type.

3.7. Mono-compound IOP-lowering drugs in POAG/OHT – protocol for interventional studies

3.7.1. Search strategy

We searched MEDLINE (by free interface of PUBMED), COCHRANE (CDSR, DARE, HTA, NHS EED) and SCOPUS electronic database. The same strategy was used to search studies for efficacy, safety and cost-effectiveness profile of mono-compound topical IOP-lowering drugs. Search terms used were: "systematic review", "meta-analysis", "RCT", to identify the study design; "glaucoma", "open angle glaucoma", "ocular hypertension" to identify the condition; and "therapy", "treatment", "intervention", "drug" and all individual names of known IOP-lowering compounds to identify interventions. The search strategy is depicted in Table 9.

3.7.2. Study selection

The overview included systematic reviews/meta-analyses meeting the following criteria:

a. embraced randomized controlled trials (RCTs) of any design;
b. POAG/OHT conditions, as defined by AAO/EGS. At least 85% of patients included in individual trials, or across all included primary trials suffered from POAG/OHT;
c. the efficacy outcome was IOP, i.e., end-of-treatment IOP or IOP reduction; safety outcome was incidence of (any) adverse event or withdrawal due to adverse events;
d. evaluated cost-effectiveness profile of individual treatments or comparative evaluations.

The overview did not include:

a. individual studies (just in case of outdated or incomplete data from systematic reviews);
b. other forms of reviews and reviews reported only in the abstract form;
c. reviews dealing with secondary OAG or ACG.

3.7.3. Data extraction and quality assessment

Quality assessment of the included reviews followed the general scheme depicted in Figure 1 and under 3.4. The specificity was the use of the PRISMA (89) checklist regarding the quality of reporting, designed specifically to meet the needs characteristic for RCTs. Hence, PRISMA includes items that are common to any systematic review, but also items typical for the RCT methodology: e.g., blinding, randomization, allocation concealment, intention-to-treat (ITT) analysis.

3.7.4. Data synthesis/Quality of evidence

Assessment of the quality of evidence was performed as described under 3.5. Random-effects pooling methods were used to recalculate data from studies in which major flaws were related to methods of data pooling.

To quantify mono-compound IOP-lowering drugs, separate and combined relationship analyses for efficacy and tolerability/safety were performed.

Drugs could not been ranked based on their cost-effectiveness profile as no studies were found.

Table 9. Search strategy for systematic reviews/meta-analyses on efficacy and safety of topical mono-compound treatments in POAG/OHT.

1. Meta-analysis [pt]	36. Prostanglandins, Synthetic [All fields]
2. Systematic review [pt]	37. Latanoprost [All fields, MeSH terms]
3. 1 OR 2	38. Travoprost [All fields, MeSH terms]
4. Randomized controlled trials [pt]	39. Bimatoprost [All fields, MeSH terms]
5. Clinical trial [pt]	40 .Unoprostone [All fields, MeSH terms]
6. 4 OR 5	41. Tafluprost [All fields, MeSH terms]
7. 3 AND 6	42. Adrenergic alpha-agonists [All fields, MeSH terms]
8 . Placebo [All fields, MeSH terms]	
9. Experimental design [All fields]	43. Apraclonidine [All fields, MeSH terms]
10. Crossover studies [All fields, MeSH terms]	44. Brimonidine [All fields, MeSH terms]
11. Control groups [All fields, MeSH terms]	45. Epinephrine [All fields, MeSH terms]
12. 8 OR 11	46. Dipivefrin [All fields, MeSH terms]
13. 7 AND 12	47. Clonidine [All fields, MeSH terms]
14. POAG [All Fields]	48. Cholinomimetics [MeSH terms]
15. OHT [All fields]	49. Cholinergic agonists [All fields, MeSH terms]
16. Ocular hypertension [All fields, MeSH terms]	50. Pilocarpine [All fields, MeSH terms]
17. Primary open angle glaucoma [All Fields]	51. Carbachol [All fields, MeSH terms]
18. Glaucoma, Open Angle [All Fields, MeSH Terms]	52. Physostigmine [All fields, MeSH terms]
19. 14 OR 18	53. Echothiophate [All fields, MeSH terms]
20. Adrenergic beta-antagonists [All fields, MeSH terms]	54. Demecarium [All fields, MeSH terms]
21. Beta adrenergic receptor blocking agent [All fields]	55. Aceclidine [All fields, MeSH terms]
22. Timolol [All field, MeSH terms]	56. Acetylcoline [All fields, MeSH terms]
23. Metipranolol [All fields, MeSH terms]	57. Treatment [All fields]
24. Carteolol [All fields, MeSH terms]	58.Therapy [All fields, MeSH terms]
25. Levobunolol [All fields, MeSH terms]	59. Pharmacological Intervention [All fields]
26. Betaxolol [All fields, MeSH Terms]	60. Drug [All fields, MeSH terms]
27. Pindolol [All fields, MeSH terms]	61. 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60
28. Befunolol [All fields, MeSH Terms]	
29. Carbonic Anhydrase Inhibitors [All fields]	
30. Carbonate dehydratase inhibitors [All fields]	
31. Acetazolamide [All fields, MeSH terms]	
32. Brinzolamide [All fields, MeSH terms]	
33. Dorzolamide [All fields, MeSH terms]	62. 19 AND 61
34. Dichlorphenamide [All fields, MeSH terms]	63. 13 AND 62
35. Methazolamide [All fields, MeSH terms]	

MeSH = Medical Subject Headings; pt = Publication Type.

4. RESULTS

4.1. Risk factors for POAG

4.1.1. Eligible studies

The flow of study selection is depicted in Figure 2. The initial search retrieved 3606 records. All were screened by titles and abstracts and duplicate publications were removed. The remaining 3261 records were once again screened by titles and abstracts and 38 articles were retrieved in full text for the final evaluation of eligibility. At this step, 13 articles (105-117) were excluded (Table 10) and the remaining 25 (119-123, 136-150) were included for quality assessment and data synthesis. No relevant article was identified through the hand search.

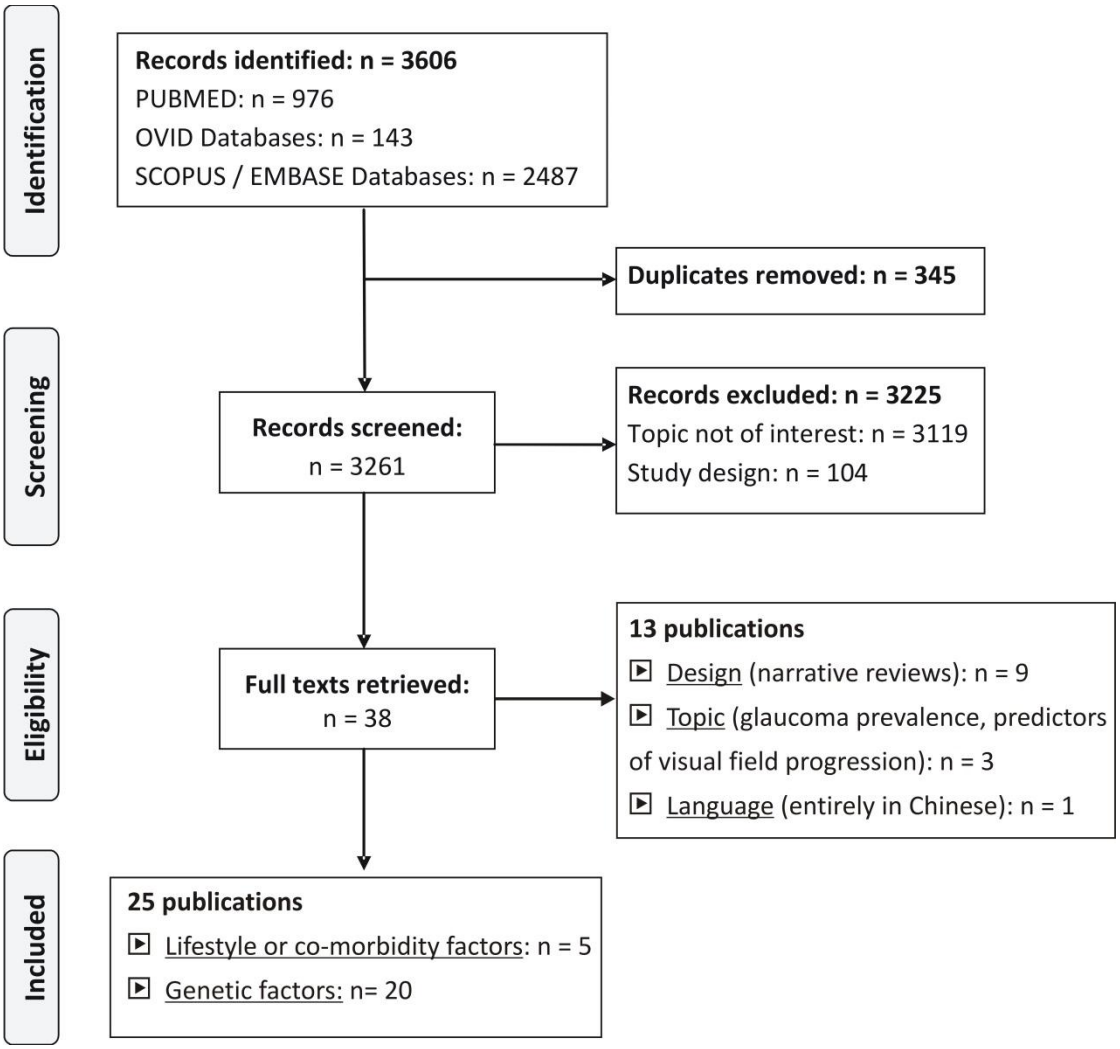

Figure 2. PRISMA flow-chart of study selection process.

As depicted in Figure 2, 5 of the included systematic reviews addressed either lifestyle factors (which are potentially modifiable) or co-morbidity factors (which, if present, could "signal" a potentially increased risk of glaucoma), whereas 20 addressed genetic factors, i.e., associations between occurrence of POAG and presence of certain genetic markers. Considering conceptual differences between the two groups of targeted "risk factors", the 5 "non-genetic" and 20 "genetic" systematic reviews are addressed separately.

Table 10. Records excluded after full text reading.

Article	Reason for exclusion
Stewart WC. The effect of lifestyle on the relative risk to develop open-angle glaucoma. Curr Opin Ophthalmol 1995;6:3-9.	A narrative review.
Sommer A. Glaucoma risk factors observed in the Baltimore Eye Survey. Curr Opin Ophthalmol 1996;7:93-8.	A narrative review.
Friedman DS, Wilson MR, Liebmann JM, Fechtner RD, Weinreb RN. An evidence-based assessment of risk factors for the progression of ocular hypertension and glaucoma. Am J Ophthalmol 2004;138:S19-31.	A narrative review.
Boland MV, Quigley HA. Risk factors and open-angle glaucoma: classification and application. J Glaucoma 2007;16:406-18.	A narrative review.
Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. Surv Ophthalmol 2008;53:S3-10.	A narrative review.
Bron A, Chaine G, Villain M, Colin J, Nordmann JP, Renard JP, Rouland JF. Risk factors for primary open-angle glaucoma. J Fr Ophtalmol 2008;31:435-44.	A narrative review.
Pasquale L, Kang JH. Lifestyle, nutrition and glaucoma. J Glaucoma 2009;18:423-428.	A narrative review.
Guedes G, Tsai JC, Loewen NA. Glaucoma and aging. Curr Aging Sci 2011;4:110-7.	A narrative review.
Worley A, Grimmer-Somers K. Risk factors for glaucoma: what do they really mean? Aust J Prim Health 2011;17:233-9.	A narrative review.
Rudnicka AR, Mt-Isa S, Owen CG, Cook DG, Ashby D. Variations in primary open-angle glaucoma prevalence by age, gender, and race: a Bayesian meta-analysis. Invest Ophthalmol Vis Sci 2006;47:4254-61.	A review of glaucoma prevalence (not of interest).
Dueker DK, Singh K, Lin SC, Fechtner RD, Minckler DS, Samples JR, Schuman JS.Corneal thickness measurement in the management of primary open-angle glaucoma: a report by the American Academy of Ophthalmology. Ophthalmology 2007;114:1779-87.	Corneal thickness as an indicator of POAG management (not of interest).
Ernest PJ, Schouten JS, Beckers HJ, Hendrikse F, Prins MH, Webers CA. An evidence-based review of prognostic factors for glaucomatous visual filed progression. Ophthalmology 2013;120:512-19.	Factors predicting POAG progression (not of interest).
Liu T, He XG. Meta-analysis on the association of Myocilin Q368X mutation and primary open angle glaucoma. Zhonghua Yan Ke Za Zhi 2007;43:361-6.	Manuscript entirely in Chinese.

4.1.2. Systematic reviews addressing lifestyle and co-morbidity characteristics as potential risk factors for POAG

The present work was pre-defined as an overview of reviews, hence it addressed only those (potential) risk factors for POAG that have been assessed through systematic reviews with quantitative (meta-analysis) or at least semi-quantitative (e.g., provide quantitative data but no meta-analysis) approach.

Many more risk factors have been tackled over the years, some depicted already in the Introduction section. For example, narrative reviews not included in the present overview (due to the fact that they were purely narrative) (Table 10) addressed relationships between POAG and a variety of demographic (i.e., age, sex, race/nationality, family history of the disease), lifestyle (e.g., physical activity, diet, habits), environmental and co-morbidity factors (ocular and non-ocular).

The quest for factors influencing POAG occurrence has been particularly focused on potentially modifiable factors. Recent narrative reviews (111, 113) and a large prospective cohort study (118) addressed several potentially modifiable variables as potential risk factors for POAG. As depicted in Table 11, data from individual primary studies (cross-sectional and case-control studies provide lower level of evidence, and prospective cohort studies provide a higher level of evidence), suggest:

a. for some factors that may affect IOP, there is no relevant epidemiological data that would allow conclusions about their relationship to POAG (e.g., physical exercise, yoga);

b. for some factors, there are quality data that most likely exclude them as factors affecting the risk of POAG (e.g., antioxidant dietary intake, tobacco smoking);

c. for some factors, there are quality data indicating some, but minor and apparently not particularly relevant effect on the risk of POAG (e.g., moderate alcohol drinking, dietary fat intake, hormone replacement therapy in postmenopausal women);

d. there is a quality but limited data suggesting excessive coffee drinking as a risk factor for incident POAG.

Table 11. Several potentially modifiable lifestyle characteristics as potential risk factors for POAG as assessed in recent narrative reviews (111,113) and a prospective cohort study (118).

Characteristic	Data	Conclusions on risk of POAG
Activities that transiently increase IOP e.g., weight-lifting, certain yoga positions	Although effects on IOP reproducible in separate studies, no data on the potential effect on POAG.	Unknown.
Activities that transiently reduce IOP	Aerobic training reproducibly reduces IOP in, but no data on the effect on POAG.	Unknown.
Drinking coffee (caffeinated)	Several studies indicated association of excessive coffee drinking and higher IOP; a large prospective cohort study indicated a greater risk of POAG with ≥5 cups/day (adjusted RR 1.6).	Excessive coffee intake likely increases the risk of POAG; association stronger with high-tension POAG.
Drinking alcohol	Case-control & prevalence studies conflicting (no, positive or negative association); a large prospective cohort indicated a small independent decrease in incident POAG with ≥2 drinks/day.	Moderate alcohol consumption might contribute to a lower risk of POAG.
Smoking (tobacco)	Case-control and cross-sectional studies conflicting; prospective cohorts found no evidence for association with POAG.	Smoking does not seem to affect the risk of POAG.
Hormone replacement therapy	Several large prospective cohort studies indicated a greater risk of POAG with earlier menopause and a weak inverse effect of HRT.	HRT (estrogen+ gestagene) might slightly reduce the risk of POAG in post-menopausal women.
Dietary antioxidant intake	In a large prospective cohort study with a detailed evaluation, carotenoids, vitamin C or E or specific fruits and vegetables high in antioxidants showed no independent association with the risk of POAG.	Dietary antioxidant intake does not seem to affect the risk of POAG.
Dietary fat intake	In a large prospective cohort study, a diet characterized with a higher omega 6/omega 3 fatty acids was independently associated with a slightly lower risk of POAG.	Dietary fat intake might modify the risk of POAG.
Indices of obesity	Higher BMI repeatedly associated with higher IOP; but prospective cohorts found independent association of higher BMI and lower risk of POAG women (not in men); waist-to-hip – no association.	In women, higher BMI is associated with a lower risk of POAG.

IOP = Intraocular Pressure; POAG = Primary Open Angle Glaucoma;

RR = Relative Risk; HRT = Hormone Replacement Therapy; BMI= Body Mass Index.

Characteristics of the 5 included systematic reviews are summarized in Table 12. Two reviews addressed cigarette smoking (119, 121), one addressed diabetes mellitus (120), one addressed myopia (122) and one (123) addressed circulating levels of homocysteine, folic acid, vitamin B12 and vitamin B6, as well as a single nucleotide polymorphism (SNP) in the gene encoding methylenetetrahydrofolate reductase (*MTHFR*) as potential risk factors for POAG.

The AMSTAR check-list assessing elements of each of these systematic reviews is depicted in Table 13. Two reviews were assigned "N" for "comprehensive search" of the literature, (119, 120) since it was not performed. Two reviews were assigned "?" considering the listing of both included and excluded studies (122, 123). Data pooling method was inappropriate in one meta-analysis (119), unclear in one (120) and not performed in one systematic review (121). In one review (121) publication bias was not assessed, whereas one review (119) did not asses the scientific quality of the included studies and was not used appropriately in formulating conclusions.

To assess quality of the body of evidence provided by these systematic reviews, we implemented the GRADE system modified for the purpose of prognostic studies (104).
In this system, primary prospective cohort studies not only assessing associations but also possible mechanisms of risk factors are considered "phase 3 studies", whereas prospective cohorts assessing associations are considered "phase 2 studies". Systematic reviews of such studies have an *a priori* GRADE level of "high quality" (⊕⊕⊕⊕). Primary case-control studies are considered "phase 1 studies" and systematic reviews on such studies have an *a priori* GRADE level of "moderate quality" (⊕⊕⊕).
The level of evidence can be downgraded based on limitations/biases (individual studies), imprecision, inconsistency or publication bias, and up-graded on the account of a large effect or dose-effect (104). Cross-sectional studies are not considered relevant, since they "capture" prevalence and cannot serve for estimation of risk.
Table 14 summarizes GRADE quality of evidence level for the 5 included systematic reviews. Table 15 summarizes main reasons for the assigned GRADE quality score.

Table 12. Main characteristics of included reviews (in chronological order).

Ref.	Objective	Criteria for primary studies	Studies (k), patients(n)	Primary study assessments
Bonovas 2004a (119)	Cigarette smoking as a risk factor for POAG.	Case-control, cohort or cross-sectional; English language.	Cross-sectional k=4; n=9960. Case-control k=3; n=814.	Quality: not assessed. Analysis: separate for current and past smoking. Fixed-effect pooling, all studies combined.
Bonovas 2004b (120)	Diabetes as a risk factor for POAG.	Case–control, cohort or cross-sectional; English language.	Cross-sectional k=7; n=23000. Case-control k=5; n=2290.	Quality: confounding, case ascertainment & response rates. Analysis: by study type; sensitivity by quality; random-effects.
Edwards 2008 (121)	Cigarette smoking as a risk factor for POAG.	Case-control, cohort; outcomes: incidence or progression of POAG.	Case-control k=9, n= not clear. Cohort k=2, n=172000.	Quality: 5-6 key methodological elements by study type. Analysis: no pooling, numerical data presented.
Marcus 2011 (122)	Myopia as a risk factor for OAG.	Any observational study; English language, OAG as an outcome.	Cross-sectional k=11, n=35000. Cohort k=1, n=3684.	Quality: Sanderson tool. Analysis: random-effects pooling, sensitivity.
Xu 2012 (123)	Plasma tHcy levels; serum vit B12, folic acid or vit B6 levels or SNP C677T in the *MTHFR* gene as risk factors for POAG.	Any observational study.	All studies were case-control. tHyc k=12, n=546/535. Folic acid, B6 k=6, n=222/252. B3 k=3, n=109/115. *MTHFR* k=10, n=1406/1216.	Quality: not assessed. Analysis: fixed or random-effects pooling; sensitivity "leave-one out" and by sample size.

POAG = Primary Open Angle Glaucoma; OAG =Open Angle Glaucoma;

tHcy = Total Homocysteine; SNP = Single Nucleotide Polymorphism; *MTHFR* = Methylenetetrahydrofolate Reductase.

Table 13. AMSTAR checklist scores for the included studies.

Ref.	Bonovas 2004a (119)	Bonovas 2004b (120)	Edwards 2008 (121)	Marcus 2011 (122)	Xu 2012 (123)
Design "a priori"?	Y	Y	Y	Y	Y
Duplicate selection/extraction?	Y	Y	Y	Y	Y
Comprehensive search?	N	N	Y	Y	Y
Publication status clear?	Y	Y	Y	Y	Y
List included/excluded provided?*	Y	Y	Y	?	?
Study characteristics provided?	Y	Y	Y	Y	Y
Quality of studies assessed?	N	Y	Y	Y	Y
Quality accounted for conclusions?	N	Y	Y	Y	Y
Appropriate method for pooling?	N	?	?	Y	Y
Publication bias assessed?	Y	Y	N	Y	Y
Conflict of interest declared?	Y	Y	Y	Y	Y
AMSTAR score	7	9	9	10	10

*All studies provided lists of included studies, but not also of excluded studies (marked by "?" – "can't tell").

Table 14. The GRADE system quality of evidence provided by the included systematic reviews.

Ref.	N° studies	Cohort studies	Univariate			Multivariate			Phase	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate or large effect	Dose effect	Quality of evidence*
			+	⊗	!	+	⊗	!									
Bonovas 2004a (119)	7	0	1	2	0	1	3	0	1	Ψ (-1)	Ψ (-1)	Y	Y (minor)	Ψ (-1)	Ψ	Ψ	⊕ Very low
Bonovas 2004b (120)	12	0	1	1	0	4	6	0	1	Ψ (-1)	Y	Y	Y	Ψ (-1)	Ψ	Ψ	⊕ Very low
Edwards 2008 (121)	11	2	0	1	0	2	8	0	1, 2	Ψ (-1)	Y	Y	Y	Y	Ψ	Ψ	⊕⊕⊕ Moderate
Marcus 2011 (122)	11	0	0	0	0	8	3	0	--*	Ψ	Y	Y	Y	Y	Ψ	Ψ	⊕ Very low
Xu 2012 (123)	tHCy 12	0	7	5	0	0	0	0	1	Ψ (-2)	Ψ (-1)	Y	Y	Y	Ψ	Ψ	⊕ Very low
	Folic acid 6	0	0	6	0	0	0	0	1	Ψ (-2)	Y	Y	Y	Y	Ψ	Ψ	⊕ Very low
	Vit B12 6	0	0	6	0	0	0	0	1	Ψ (-2)	Y	Y	Y	Y	Ψ	Ψ	⊕ Very low
	Vit B6 3	0	1	2	0	0	0	0	1	Ψ (-2)	Ψ (-1)	Y	Y	Y	Ψ	Ψ	⊕ Very low
	MTHFR 10	0	0	10	0	0	0	0	1	Ψ (-1)	Y	Y	Y	Y	Ψ	Ψ	⊕⊕ Low

*All primary studies were cross-sectional, i.e., "below phase 1".

(+) = positive association; (⊗) = no association; (**!**) = negative association.

Ψ = the review is flawed in this respect; Y = the review is not flawed in this respect.

tHcy = Total Homocysteine; *MTHFR* = Methylenetetrahydrofolate Reductase.

Table 15. Main reasons for the AMSTAR and GRADE scores.

Bonovas 2004a (119)	1. No prospective cohort study. Case-control studies could be considered "phase 1" and cross-sectional should be excluded. With only "phase 1" studies, the *a priori* GRADE score is "moderate quality" (⊕⊕⊕). 2. However, many limitations: a) only 3 small case-control studies with apparently prevalent cases (not incident); b) Only 1 employed adjustments other than age and sex (or body mass index); c) Fixed-effect pooling inappropriate - we found I^2 of 43% across all studies (a random-effects meta-analysis across all studies indicated ***no association*** between "current smoking" and POAG: pooled OR=1.40, 0.92-2.13; p=0.133) (in contrast to report); d) Pooling case-control and cross-sectional studies not appropriate. A re-analysis indicated no association in cross-sectional and a mild association (based on 1 out of 3 studies) in case control-studies illustrating inconsistency. 3. Only Medline was searched. 4. No large effect, no dose-effect.
Bonovas 2004b (120)	1. No prospective cohort study. Case-control studies could be considered "phase 1" and cross-sectional should be excluded. With only "phase 1" studies, the *a priori* GRADE score is "moderate quality" (⊕⊕⊕). 2. However, several limitations: a) cases likely prevalent (not incident); b) 4/5 studies DM established only as "medical history; c) 1/5 no covariate adjustment, 2/5 only age & sex or body mass index; d) the overall estimate indicating association of DM and POAG (OR=1.5, p<0.05) pooled across the subgroups by study type. But, cross-sectional studies should be disregarded – the 5 case-control studies yield (random-effects) OR=1.45, 0.85-2.46, p=0.173, I^2=49.5%. 3. Regardless of the "publication bias evaluation" – only one electronic database searched, hence possible omission of relevant data.
Edwards 2008 (121)	1. Systematic review but without meta-analysis. 9 smaller case-control studies of poor quality, 2 prospective cohort studies, of which one is a pooled analysis of 2 separate cohorts, judged as "high quality", that would correspond to "phase 2" studies. Hence, the a priori GRADE score is "high quality" (⊕⊕⊕⊕). 2. Data from all cohort studies consistent, however one cohort study provided no numerical data, just a conclusion of "no effect". Therefore, the limited number of numerical data (pooled analysis of two cohorts) is a limitation.
Marcus 2011 (122)	1. The 11 studies used to estimate myopia as a risk factor for OAG were all cross-sectional: cross-sectional studies measure prevalence, not incidence, hence cannot quantify "risk". 2. The only prospective cohort study actually assessed myopia as a risk factor for incident glaucomatous visual field loss.
Xu 2012 (123)	1. No prospective cohort study. Case-control studies could be considered "phase 1" and the *a priori* GRADE score is "moderate quality" (⊕⊕⊕). 2. However, several limitations: a) cases likely prevalent (not incident); b) There were no covariate adjustment in any of the primary studies. This introduced bias because (i) many factors may affect plasma/serum levels homocysteine or measured vitamins and (ii) many other factors may affect the risk of POAG. Hence, limitations were particularly "severe" when potential "predictors" were measure metabolite levels, and somewhat less severe when potential predictor was single nucleotide polymorphism. 3. Some pooled estimates were reported with extremely high heterogeneity (I^2 almost 100%).

POAG = Primary Open Angle Glaucoma; OAG= Open Angle Glaucoma; DM = Diabetes mellitus;

GRADE = Grading of Recommendations Assessment, Development and Evaluation; OR = Odds Ratios.

4.1.2.1. Cigarette (tobacco) smoking

Two systematic reviews addressed cigarette smoking as a risk factor for POAG. One review provided very low quality of evidence (Bonovas et al. 2004) (119) based only on cross-sectional and case-control studies and due to a number of methodological flaws at the systematic review level (Tables 14, 15); and the other one (Edwards et al. 2008) (121) provided evidence of moderate quality (Tables 14, 15).
In fact, relevant evidence in Edwards et al. 2008 (121) comes from 2 publications addressing prospective cohort studies, of which one (a pooled analysis of two primary studies) provided numerical data. This latter report (124) was a joint analysis of data from two large prospective nation-wide epidemiological cohort studies in USA: the Nurses' Health Study, embracing exclusively women (98% White); and Health Professionals Follow-up study, embracing exclusively men (98% White). We identified another similar prospective nation-wide epidemiological cohort study in USA that addressed cigarette smoking as a risk factor for POAG – the Black Women's Healthy Study (125).

In terms of quality and considering the tool developed by the National Institute for Clinical Excellence (NICE) (103), each of these 3 studies should be considered to be of "high quality", i.e., meeting the criteria of "low risk of bias" since they:

- included representative samples ("sampling bias" low);
- adequately addressed non-participation and loss to follow-up ("attrition" and "non-respondent" bias low);
- smoking/non-smoking and the extent of exposure reliably assessed ("misclassification" bias low);
- the outcome [incident POAG] adequately verified ("observer"/"detection" bias low);
- important confounders reliably detected and accounted for in the analysis.

None of the studies found any association between smoking and the risk of POAG:
a. as "current smoking " vs. never;
b. as "former smoking" vs. never;
c. as a "dose" of current or former smoking in terms of the number of cigarettes/day or as "pack-years" of smoking.

Data for this latter measure of dose-exposure are summarized in Table 16. We used them to perform multivariate meta-analysis (accounting for correlation of estimates from the same study) of adjusted relative risk of POAG associated with different "smoking dose". Results are depicted at the bottom of Table 16 and demonstrate that smoking is not a risk factor for POAG.

Table 16. Evidence base for assessment of cigarette smoking as a risk factor for POAG: smoking dose (as "pack-years" of smoking) and incident POAG cases (124, 125) and summary results of a multivariate meta-analysis of adjusted relative risks. Estimates are given with 95% confidence intervals.

Population (ref.)	Never smoked	1-9	10-19	20-29	30 +
White women (124)					
Person-years	360348	154718	106384	80467	88579
Incident POAG (cases)	150	49	28	22	37
Adjusted relative risk*	1.00 (ref)	0.86 (0.62-1.20)	0.69 (0.46-1.04)	0.75 (0.47-1.18)	0.76 (0.53-1.10)
White men (124)					
Person-years	117802	57 913	50 175	15125	3716
Incident POAG (cases)	71	51	27	12	3
Adjusted relative risk*	1.00 (ref)	1.49 (1.02-2.17)	0.76 (0.48-1.21)	1.10 (0.58-2.06)	1.01 (0.31-3.32)
Black women (125)					
Person-years	272257	80139	21172	13715	28888
Incident POAG (cases)	201	65	18	22	55
Adjusted relative risk*	1.00 (ref)	0.94 (0.71-1.25)	0.72 (0.44-1.16)	0.93 (0.59-1.46)	1.08 (0.79-1.47)
TOTAL					
Person-years	750397	292770	177731	109307	121183
Incident POAG (cases)	422	165	73	56	95
Pooled adjusted RRI	**1.00 (ref)**	**1.06 (0.83-1.36)**	**0.72 (0.56-0.93)**	**0.91 (0.71-1.17)**	**0.96 (0.74-1.24)**
Across all exposures	**1.00 (ref)**	**0.91 (0.73-1.12)**			

POAG= Primary Open Angle Glaucoma; RRI= Relative Risk of Incidence.

*In the analysis by Kang (124), the effect of smoking was assessed with adjustment for age, body mass index, hypertension, diabetes mellitus, African-American descent, amount of daily alcohol intake.

In the study by Wise (125), adjustments were for age, period of follow-up, education, amount of daily alcohol intake, hypertension, physical activity, energy intake, diabetes and body mass index.

We performed multivariate meta-analysis of adjusted relative risks from the three cohorts: each study provided 4 estimates, one for each "smoking dose". We considered "smoking dose" as a categorical covariate and accounted for the correlation between estimates from the same study (cohort). We used SAS software (proc mixed) to fit the model (126).

We used the data also to perform a dose-response meta-analysis depicted in Figure 3. No "dose-dependent" trend in the adjusted relative risk of incident POAG was observed related to smoking.

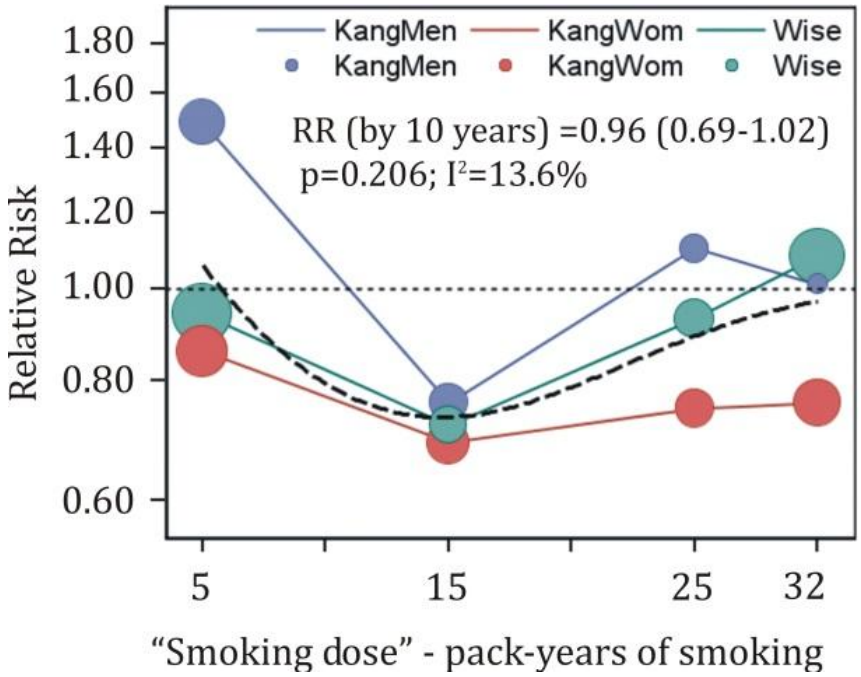

Figure 3. "Dose-response" meta-analysis for smoking as a risk factor for POAG.

Regression of adjusted relative risk on ""smoking dose" from the 3 cohort studies (size of the bubbles corresponds to weight assigned to each observation).

Black dashed line presents the trend of the pooled adjusted relative risk (RR).

Dotted line at RR=1 represents "no effect" (risk in non-smokers).

RR (by 10 years) = change in risk of POAG by increase in "smoking dose" by 10 pack-years (with 95% confidence intervals).

I^2 value indicates no heterogeneity between regression coefficients in the three studies.

We used SAS software (metadose macro) to fit the model (127).

In the light of the GRADE system modified for quality assessment of evidence in the prognostic setting (104), all these studies belong into the category of "phase 2" studies- they do not "explore prognostic pathways", but "aim to confirm/refute independent associations" between the presumed prognostic factor and the outcome.

Since each (as already depicted) individual study is of high quality, it is safe to conclude that there is a ***high quality*** body of evidence (GRADE ⊕⊕⊕⊕) that supports a conclusion that smoking is not a relevant risk factor for POAG.

4.1.2.2. Diabetes mellitus (DM)

Only one systematic review (Bonovas et al. 2004) (120) addressed DM as a risk factor for POAG. As elaborated, it provided evidence of low quality (Tables 14, 15) and is therefore not a basis for sound conclusions.
We have identified, however, several large cohort studies that, among other results, provided evidence about the relationship between DM and incident POAG and have not been included in any of the systematic reviews. Their particulars are depicted in Table 17.

In terms of quality (103), each of these studies should be considered to be of "high quality", i.e., meeting the criteria of "low risk of bias" since they:

- included representative samples ("sampling bias" low);
- adequately addressed non-participation and loss to follow-up ("attrition" and "non-respondent" bias low);
- DM (exposure, prognostic factor) and "non-DM" (non-exposure) were adequately ascertained and followed-up (the risk of "misclassification" bias is low);
- the outcome [incident POAG] was adequately verified ("observer"/"detection" bias low);
- important confounders reliably detected and accounted for in the analysis.

In the light of the GRADE system modified for quality assessment of evidence in the prognostic setting (104), all these studies belong into the category of "phase 2" studies – they do not "explore prognostic pathways", but "aim to confirm/refuse independent associations" between the presumed prognostic factor and the outcome.
Furthermore, each one provides consistent results that are reasonably precise, in a direct comparison (DM vs. non-DM), using a "direct measure".
Hence, each one individually provides high-quality evidence: there are no reasons for "downgrading" the quality level, but also, no reasons to "up-grade", since the observed effects are modest and no "exposure-gradient" response was observed.

Table 17. DM as a risk factor for incident POAG in prospective cohort studies (by year).

Ref.	Description	DM and incident POAG
Ellis 2000 (128)	A retrospective cohort based on validated administrative databases, population-based (White, Scotland, M&F). Inclusion: age >40 years; medically verified absence of glaucoma/OHT. Exposure: medically verified DM (n=6631); Non-exposure: verified absence of DM (n=166 144). Follow-up: 2 years. Outcome: age-standardized incidence rate (IR) of medically verified POAG. Effect measure: incidence rate ratio (i.e., relative risk).	DM POAG: n=20, IR= 1.1 /1000 p-y. Non-DM POAG: n=24, IR=0.7 /1000 p-y IRR=1.57 (0.99-2.48).
Gordon 2001 (129)	Prospective multicenter RCTs (70% White, USA, M&F) to evaluate the effect of treating OHT on development of POAG (OHTS trial). Inclusion: age >40 years, IOP ≥24 mmHg, no glaucoma, N=1636, followed-up for a median of 6 years. Of 191 patients with DM at baseline, 6 (3.1%) developed POAG. Of the 1427 patients without DM, 119 (8.3%) developed POAG. Effect measure: hazard ratio (i.e., relative risk).	With adjustment for age, baseline IOP, cup-disc ratio and corneal thickness, HR=0.37 (0.15-0.90). No DM duration effect.
Le 2003 (130)	A community-based prospective cohort study (White, Australia, M&F). Inclusion: age >40 years, medically excluded glaucoma. Followed-up for 5 years. N=2415. 15 developed at least probable and 39 developed possible OAG. A set of potential risk factors evaluated.	Association with OAG: older age, higher cup-disc ratio and IOP. DM -no effect, data not reported.
de Voogd 2006 (131)	The Rotterdam study: community-based prospective cohort (White, Rotterdam, M&F). Inclusion: age ≥55 years, medically verified absence of OAG. Exposure: medically verified DM (n= 264); Non-exposure: verified absence of DM (n= 3573). Follow-up 5-9.5 years. Outcome: incident medically verified OAG (5/264 vs 82/3573). Effect measure: relative risk.	Adjusted RR (age, BMI,, hypertension, follow-up, sex baseline IOP & treatment) = 0.64 (0.25-1.64). No DM duration effect.
Pasquale 2006 (132)	The Nurses' Health Study: nation-wide prospective cohort study (98% White, USA, only women). Inclusion: age 30-55 years, medically verified absence of OAG. N=76 318, follow-up up to 20 years. Exposure: medically verified DM (32 362 p-y, n=30 incident POAG); Non-exposure: verified absence of DM (965 930 p-y, n=399 incident POAG). Outcome: age-adjusted incidence rate of medically verified POAG. Effect measure: incidence rate ration (i.e., relative risk).	Adjusted IRR (age, ethnicity, hypertension, BMI, physical activity, alcohol, smoking, family history of glaucoma) =1.82 (1.23-2.70). No DM duration effect.
Leske 2008 (133)	The Barbados eye study: community-based prospective cohort study (Black, Barbados, M&F). Inclusion: age >40 years, medically verified absence of definite OAG. Exposure: medically verified DM (n=536); Non-exposure: verified absence of DM (n=2675). Follow-up 9 years for all. Outcome: incident medically verified OAG (5.8% DM vs. 4.2% non-DM). Effect measure: relative risk.	Adjusted RR (age, sex, baseline IOP and treatment, blood pressure and treatment, education, cataract) = 1.2 (0.7-1.8). No DM duration effect.
Wise 2011 (134)	The Black women's health study: nation-wide prospective cohort (Black, USA, only women). Inclusion: age 21-69, medically verified absence of glaucoma. Exposure: medically verified DM (n=1055). Non-exposure: verified absence of DM (n=31 294). Follow-up up to 12 years. DM: 57 medically verified incident POAG/23 488 p-y; non-DM: 308 incident POAG/416 171 p-y. Effect measure: incidence rate ratio (i.e., relative risk).	Adjusted IRR (age, follow-up, education, alcohol, smoking, hypertension, physical activity, BMI) = 1.58 (1.17-2.13). No DM duration effect.

POAG = Primary Open Angle Glaucoma; OAG = Open Angle Glaucoma; OHT = Ocular Hypertension; IOP = Intraocular Pressure;

DM = Diabetes Mellitus; BMI= Body Mass Index; M= male; F= Female; OHTS =The Ocular Hypertension Treatment Study;

RCTs = Randomized Controlled Clinical Trial; IR = Incidence Rate; IRR = Incidence Rate Ratio; HR = Hazard Ratio; RR = Relative Risk.

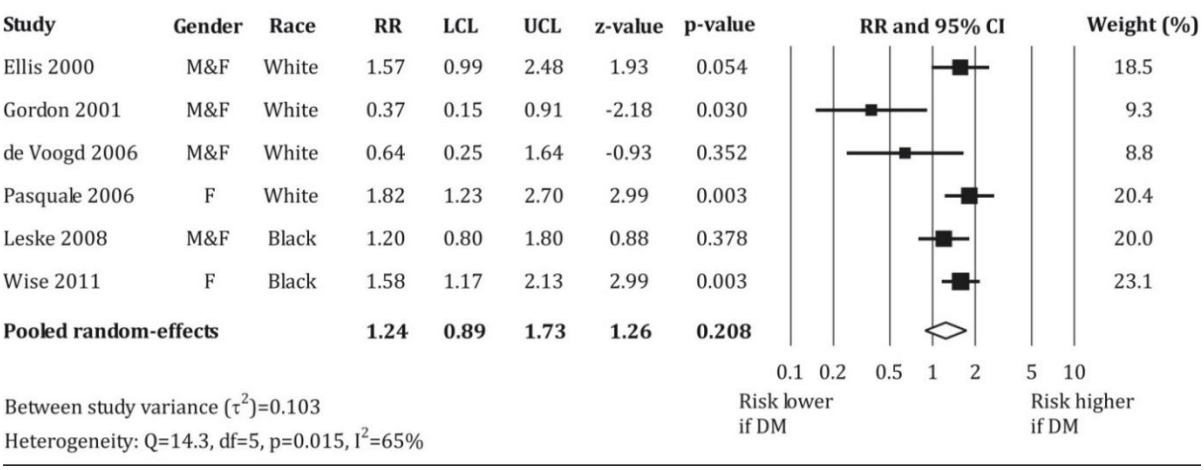

Figure 4. Random-effects meta-analysis of prospective cohort studies assessing diabetes mellitus (DM) as a risk factor for incident POAG.

A standard (DerSimonian-Laird) random-effects meta-analysis was performed using adjusted relative risk outcome measures: although slightly different by nature (relative risk, hazard ratio, incidence rate ratio), all the reported effect measures were measures of relative risk.

Ln-transformed values were used for data pooling, and were then "returned" to the "raw scale" (anti-log) (RRs actually represent "raw" measures of the relative risk).

We used Comprehensive Meta-analysis software.

Figure 4. presents random-effects meta-analysis of the 6 studies that provided numerical data. Data suggest no effect of DM on the risk of incident POAG (Figure 4). However:

- heterogeneity was appreciable (Q-statistic p=0.015, I^2=65%);
- the two studies including only women [(Pasquale 2006 (132) and Wise 2011(134)] each showed a higher risk in DM patients, whereas the remaining four with a "mixed" population indicated (i) no effect or (ii) a reduced risk (129).

Therefore, we repeated the analysis separating the two studies embracing exclusively women from those with a mixed population. Results are depicted in Figure 5. We used two approaches:

a) a standard random-effects subgroup analysis and

b) a meta-regression analysis with "gender composition" as a covariate.

Both approaches demonstrated that, with adjustment for "gender composition", the overall estimate remains in line with the conclusion of no effect of DM on the incidence of POAG. This is particularly so in studies with a mixed male-female population (Figure 5).
As for the effect of DM in women, the two methods yielded numerically identical point-estimates, but the regression approach yielded (expectedly) somewhat higher variance and wider confidence intervals resulting in "no statistical significance", whereas subgroup analysis indicated a slightly increased risk of POAG in diabetic women (Figure 5).

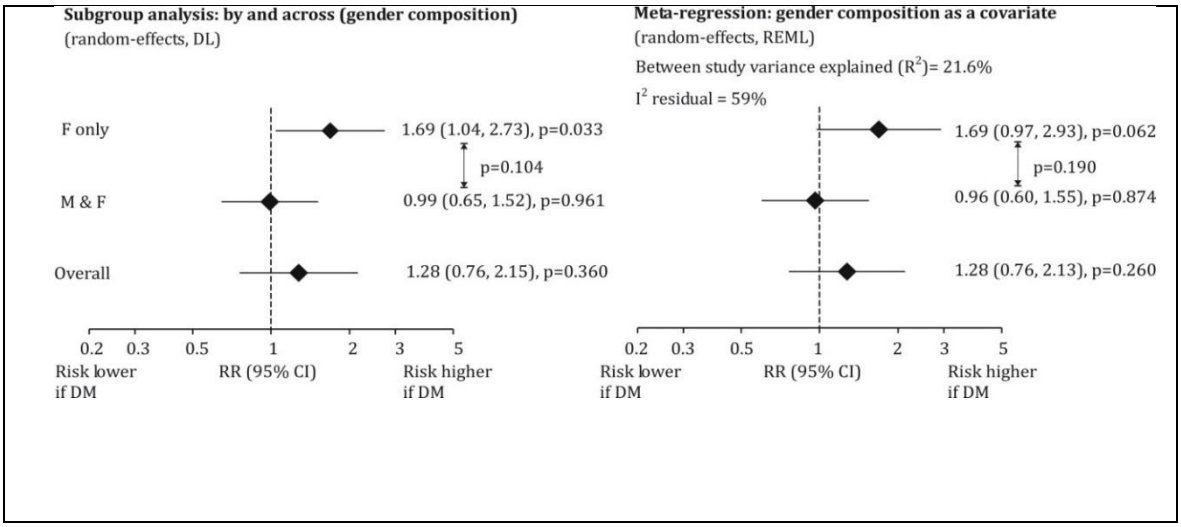

Figure 5. Diabetes mellitus (DM) as a risk factor for incident POAG: subgroup analysis (left) and meta-regression (right) in respect to gender composition of the 6 prospective cohort studies.

The subgroup analysis is a standard random-effects (DerSimonian-Laird, DL) meta-analysis by and across the two subgroups, whereas meta-regression is a random-effects meta-regression using restricted maximum likelihood (REML) estimation.
We used Comprehensive Meta-analysis and SAS (proc mixed) software (126).

Overall, it is safe to conclude that there is a ***high quality*** body of evidence (GRADE⊕⊕⊕⊕) that supports a conclusion that in women, DM weakly increases the risk of POAG.
Although data were not available separately for women and for men, it is also intuitive to conclude that DM does not affect the risk of POAG in men: in the four studies with "mixed" samples [and the one without numerical data, but reporting "no effect of DM" on the risk of POAG Le et al. 2003 (130)], relative risk was around unity.

4.1.2.3. Myopia

One systematic review (Marcus 2011) (122) addressed myopia as a risk factor for OAG. Actually, the 11 meta-analyzed studies were all cross-sectional studies – hence, they recorded prevalence, not incidence. However, one additional case-control study and one prospective cohort study were included and the pooled estimate from the cross-sectional studies was in "the same direction" as that form the prospective cohort observations.

The latter, prospective cohort study (135) actually assessed myopia as a risk factor for VF progression in POAG patients in the Rotterdam study. As already mentioned, this was a high-quality prospective epidemiological study. Data about myopia refer to 3684 participants (both genders, ≥ 55 years of age) who were followed-up (ophthalmological check-ups) for at least 6 and a maximum of 16 years (135) (total exposure ~38000 p-y). With adjustment for age, sex, IOP, IOP treatment, family history of glaucoma and GON, high myopia was an independent risk factor for incident VF loss – HR = 2.31 (1.19-4.49).

Therefore, the body of evidence about myopia as a risk factor for POAG is of low quality (only cross-sectional studies) and indicative but inconclusive. There is, however, moderate quality of evidence (only one prospective cohort study) that myopia is a risk factor for GVFD.

4.1.2.4. Circulating levels of total homocysteine, folic acid, vitamin B12 and B6 and an SNP in the MTHFR gene as risk factors for POAG

As depicted in Table 14 the systematic review (Xu 2012) (123) assessing total plasma homocysteine (tHcy) levels, serum folic acid, vitamin B12 or B6 levels as risk factors for POAG provided only very low quality of evidence: the embraced case-control studies did not account for confounders (i.e., factors affecting the levels of these analyses as well as factors known to be associated with POAG). Additionally, inconsistency was high considering tHcy and vitamin B6. Under these circumstances, the pooled estimate (12 case-control studies) indicating higher tHcy in patients with POAG vs. controls does not support any sound conclusion about the relationship between tHcy and POAG. Similarly, pooled estimates indicating no difference between POAG patients and controls regarding serum folic acid, vitamin B12 and vitamin B6 levels – provide no basis for a sound conclusion on the relationship between circulating levels of these vitamins and the risk of POAG.

The limitations are less severe in the case of the evaluated SNP (C677T) in the *MTHFR* gene and the 10 embraced primary studies consistently indicated no association between this SNP and POAG.

4.1.3. Systematic reviews of genetic studies for POAG

The genetic background of glaucoma and in particular POAG is extremely complex and has been intensively investigated for over 20 years.
Three types of primary studies (apart from animal models) have been conducted: familial linkage studies in families with common occurrence of glaucoma that lead to identification of glaucoma-causative genes; population candidate-gene association studies and population based genome-wide association studies (GWAS).

Of the 20 identified systematic reviews dealing with the genetic factors in POAG, 15 were meta-analyses of small "candidate-gene association" case-control studies (136-150). Their characteristics are summarized in Table 18. They were all published by Chinese authors.
A recent review demonstrated an overwhelming prevalence of genetic-association meta-analyses published from China (151) and shared common characteristics typical from "Chinese genetic meta-analyses":

- did not include GWAS study results;
- were based exclusively on "candidate gene" case-control studies with prevalent (not incident) cases that frequently had less controls than cases;
- were based on allele frequencies and not adjusted measures of associations (e.g., adjusted odds ratios).

Overall, all these meta-analyses, although in technical sense frequently well conducted, provide only very low level of quality of evidence (i.e., not reliable for conclusions on particular genetic variants as risk factors) (151).
Therefore, they were not further evaluated in the present work.

Table 18. Main characteristics of 15 systematic reviews/meta-analyses of small "candidate-gene association" case-control studies.

Ref.	Objective	Criteria for primary studies	Studies (k), patients(n) Cases/controls	Primary study assessments
Liu 2008 (136)	*MYOC*.mt1 SNP as a risk factor for POAG.	Case-control studies.	k=4; n= 835/530.	Quality: case ascertainment, genotyping method. Analysis: Fixed-effect pooling.
Chen 2010 (137)	*LOXL1* SNPs as risk factors for XFG or POAG.	Case-control, cohort; SNPs rs1048661, rs2165241 and rs3825942.	POAG; Case-control k=9; n=2223 /16664.	Quality: not assessed; HWE for each study Analysis: allelic distribution, overall associations, random-effects, sensitivity.
Cheng 2010 (138)	*OPTN* SNPs as risk factors for POAG (HTG).	Case-control, cohort; SNPs M98K, T34T, R545Q.	Case-control k=25; n=4436/3838.	Quality: blinding, genotyping method and HWE. Analysis: fixed and random-effects pooling; sensitivity analysis for non-HWE.
Cheng 2012 (139)	SNPs in *MYOC* gene as risk factors for POAG.	Case-control SNPs R46X, R76K, Y347Y, T353I, Q368X.	k=32; n= 7128 /5259.	Quality: not assessed. Analysis: fixed and random-effects pooling. Subgroup analysis by ethnicity.
Dong 2012 (140)	SNPs in *CYP1B1* as risk factors for POAG.	Any type. SNPs rs180040, rs1056836, rs10012, rs1056827, rs1056837, rs2567206.	Case-control k=6; n=2292 / 1717.	Quality: not assessed. Analysis: Random-effects pooling.
Guo 2012a (141)	SNPs in *OPA1* gene as risk factors for POAG NTG/HTG.	Case-control, nested case-control, or cohort. SNPs rs166850, rs10451941.	Case-control k=12; NTG n=713 /964; HTG n=1200/971.	Quality: not assessed. Analysis: Fixed and random-effects pooling. Subgroup by POAG type and ethnicity; sensitivity.
Guo 2012b (142)	SNPs in *TP53* gene as risk factors for POAG.	Case-control, nested case-control, or cohort. SNPs codon 72, intron 3.	Case-control k=9; n=1930/ 1463.	Quality: not assessed. Analysis: Fixed and random-effects pooling; subgroup by ethnicity.
Yu 2012 (143)	SNP in *TNF-α* –308G/A as a risk factor for POAG.	Case-control.	k=7; n=1199 /1189.	Quality: not assessed. Analysis: Pooled estimates by subgroups: ethnicity and source of controls.
Huang 2013 (144)	SNPs in *GSTM1*, *GSTT1* genes as risk factors for POAG.	Case–control.	k=11; n=1339 /1412.	Quality: NoS scale. Analysis: Fixed or random-effects pooling; subgroup by ethnicity, genotyping technique, source of controls.
Huo 2013(145)	SNP C677T in *MTHFR* gene as a risk factor for POAG.	Any type.	Case-control k=10; n=1224 /1105.	Quality: NoS scale. Analysis: Fixed or random-effects pooling; subgroup analysis by ethnicity; sensitivity by study quality.
Lu 2013(146)	SNPs in *GSTM1*, *GSTT1* genes as risk factors for POAG.	Case–control.	*GSTM1* k=14; n=1711/1537. *GSTT1* k=10; n=1306/ 1114.	Quality: not assessed. Analysis: Fixed or random-effects pooling; subgroup by ethnicity.
Song 2013 (147)	*APOE* polymorphisms as risk factors for POAG.	Case-control studies. *APOE* ε2/ε3/ε4 polymorphisms.	k=9; n=1928/ 1793.	Quality: not assessed. Analysis: Fixed or random-effects pooling; subgroup by ethnicity; sensitivity.
Wang 2013 (148)	*APOE* polymorphisms as risk factors for POAG.	Case-control; hospital or population-based APOE ε2/ε3/ε4 polymorphisms.	k=12; n=1916 / 1756.	Quality: not assessed. Analysis: Fixed or random-effects pooling; subgroup by ethnicity; sensitivity "leave-one-out".
Xin 2013 (149)	*TNF-α* gene SNPs & *TNF-α* AH level risk factor for OAG.	Case-control; SNPs rs1800629, rs361525, rs645836 or rs1799724.	k=3 to k=14 (by SNP).	Quality: not assessed. Analysis: Fixed or random-effects pooling; subgroup by ethnicity; sensitivity "leave-one-out".
Yu 2013 (150)	SNPs in *GSTM1*, *GSTT1*, *GSTP1* genes as risk factors for POAG.	Case-control; English language.	*GSTM1* k=12, n=1908/1457; *GSTT1* k=10 n= 1414 /1177; *GSTP1* k=4, n=543 / 511.	Quality: not assessed. Analysis: Fixed or random-effects pooling; subgroup by ethnicity; sensitivity "leave-one-out".

POAG = Primary Open Angle Glaucoma; PXFG = Pseudoexfoliation Glaucoma; HTG= High Tension Glaucoma; NTG = Normal Tension Glaucoma; AH = Aqueous Humour; SNP = Single Nucleotide Polymorphism; HWE = Hardy-Weinberg Equilibrium**;** NoS = Newcastle-Ottawa Scale; *CYP1B1* = Cytochrome P450, Family 1, Subfamily B, Polypeptide; *MYOC* = Myocilin; *LOXL1* = Lysyl Oxidase-Like 1; *OPTN* = Optineurin; *APOE* = Apolipoprotein E; *TNF-α* = Tumour Necrosis Factor α**;** *OPA1* = Optic Atrophy 1; *TP53* = Tumor Protein 53; *GSTM1, GSTT1, GSTP1* = Glutathione S Transferase Polymorphisms; *MTHFR*= Methylenetetrahydrofolate Reductase.

The next subset of "genetic" reviews addressing risk of POAG comprises three publications (152-154) that were not systematic reviews – rather, these were meta-analyses of data from GWAS studies conducted by a consortium of researchers who shared the overall data pool to provide pooled estimates of risks of POAG associated with several genes detected (and replicated) in the primary GWAS studies. All primary studies were conducted in White populations. General characteristics of these combined analyses are depicted in Table 19.

Table 19. Main characteristics of pooled analyses of several GWAS primary studies.

Ref.	Objective	Criteria for primary studies	Studies (k), patients(n) Cases/controls	Primary study assessments
Ramdas 2011a (152)	SNPs in 8 genes as risk factors for POAG.	SNPs in *ATOH7*, *CDC7*, *SALL1*, *CDKN2B*, *SIX1*, *SCYL1*, *CHEK2*, *DCLK1*.	Nested case-control (incident POAG): k=1. Case-control (prevalent POAG): k=5;n=3161/42837.	Quality: not assessed. Analysis: pooled fixed-effect estimates of adjusted odds ratios (age and sex) from individual studies.
Ramdas 2011b (153)	SNPs in 6 genes as risk factors for OAG.	SNPs in *MYOC*, *OPTN*, *WDR36*, *ATOH7*, *CDKN2B*, and *SIX1*.	Nested case-control (incident POAG): k=1. Case-control (prevalent POAG) k=1. Family-based: k=1;n=776/7426.	Quality: not assessed. Analysis: pooled data to assess "probability" of OAG with increasing number of mutant alleles.
van Koolwijk 2012 (154)	SNPs in 2 novel genes as risk factor for POAG.	SNPs in *GAS7* and *TMCO1*.	Population based k=4 ;n=11972. Cohort: k=4;n=7482.	Quality: not assessed. Analysis: pooled analysis of 4 discovery and 4 replication GWAS studies.

POAG = Primary Open Angle Glaucoma; OAG = Open Angle Glaucoma; SNP = Single Nucleotide Polymorphism; *GAS7* = Growth Arrest-Specific 7; *TMCO1* = Transmembrane and Coiled-Coil Domains 1; *CHEK2* = Checkpoint Kinase 2; GWAS = Genome-Wide Association Study; *ATOH7* = Atonal Homolog 7; *MYOC* = Myocilin; *OPTN* = Optineurin; *CDC7*= Cell Division Cycle 7; *SALL1*= Spalt-Like Transcription Factor 1; *WDR36* = WD Repeat Domain 36 Gene; *CDKN2B* = Cyclin-Dependent Kinase Inhibitor 2B; *SIX1*= SIX Homeobox 1; *SCYL1* = SCY1-Like 1; *DCLK1* = Doublecortin-Like Kinase 1.

Finally, the two last publications included in the present overview are two narrative reviews (155, 156) that intended to summarize and synthesise the complete knowledge on the genetic background of POAG. The first one was published in 2012 embracing literature published by the end of 2011 (a comprehensive systematic search of the literature between 1987 and end of 2011) (155). The second and a more comprehensive one, reviewed more than 120 GWAS, "candidate gene" association and familial studies in humans, as well a broad variety of animal (e.g., knock-out and functional studies) (156).

The common characteristics of these two reviews are that genetic background of POAG is not addressed only through simple associations, but also includes functional studies on the role of proteins coded by the assessed genetic markers and their role in pathophysiology of glaucoma.

The main findings can be summarized as follows:

a. There are 14 loci depicted as GLC1 (glaucoma, primary open angle), harboring 5 genes where a number of different mutations were found that are considered causative to POAG based mainly on familial linkage studies (Table 20).

b. Janssen et al. 2013 (156) identified further "most likely" causative genes for POAG (each with several SNP variants) for which, however, final confirmatory data are still lacking (Table 21).

To what extent, a part of understanding the pathophysiology of glaucoma, will these markers turn-out relevant in terms of assessing the risk of POAG remains to be seen.

Table 20. Genes identified in familial linkage studies as causative to POAG (156).

Locus	Region	Trait	Population	Genes in region
GLC1A	1q21-q24	POAG	USA	**MYOC**
GLC1B	2cen-q13	POAG	UK	*e.g. ADRA2B, PAX8, IL1A, IL1B*
GLC1C	3q21-q24	POAG	USA	*e.g. CD10, IL12A, TF, CP*
GLC1D	8q23	POAG	USA	*e.g. EBAG9, TRHR, COL14A1*
GLC1E	10p14-p15	POAG	UK	**OPTN**
GLC1F	7q35-q36	POAG	USA	**ASB10**
GLC1G	5q22.1	POAG	USA	**WDR36**
GLC1H	2p15-p16	POAG	UK	*XPO1, OTX1*
GLC1I	15q11-q13	POAG	USA	*e.g. PAR5, NPAP1, GABRB3*
GLC1J	9q22	POAG	USA	*e.g. FOXE1, ROR2, TGFBR1*
GLC1K	20p12	POAG	USA	*e.g. BMP2, RRBP1, SLC4A11*
GLC1L	3p21-22	POAG	Australia	*e.g. VII1, LZTFL1, MAP4*
GLC1M	5q22.1-q32	JOAG	China	*e.g. WDR36, NRG2*
GLC1N	15q22-24	JOAG	China	*e.g. NR2E3, SMAD6, CLN6*
GLC1P	12q14	CODA	USA	*e.g. GDF11, NEUROD4, WIF1*
GLC1Q	4q35.1-q35.2	POAG	UK	*e.g.LRP2BP, UFSP2, CYP4V2*
GLC3A	2p21	PCG+ POAG	USA	**CYP1B1**
	2q33-34	POAG	Africa	*e.g. CLK1, HSPE1, CASP8*
	10p12-13	POAG	Africa	*e.g. MLLT10, NRP1, MSRB2*
	14q11	POAG	Africa	*e.g. PRKD1, ZNF219, JH4*

POAG = Primary Open Angle Glaucoma; JOAG = Juvenile Open Angle Glaucoma; PCG = Primary Congenital Glaucoma; CODA = Cavitary Optic Disk Anomalies;

Bold genes: POAG genes: *MYOC* = Myocilin; *OPTN* = Optineurin; *ASB10* = Ankyrin Repeat and SOCS Box Containing 10; *WDR36* = WD Repeat Domain 36 Gene; *CYP1B1* = Cytochrome P450, Family 1, Subfamily B, Polypeptide;

Italic genes: genes situated on the locus, need further research to identify the candidate POAG disease gene(s).

Table 21. Genes most likely causative to POAG based on GWAS and SNP-association studies, as identified by Janssen et al. 2013 (156).

Gene	Locus	Gene	Locus	Gene	Locus
APOE	19q13.2	*NCKAP5*	2q21.2	*TMTC2*	12q21.31
ATOH7	10q21.3	*NTF4*	19q13.33	*TNF-α*	6p21.3
CAV1/CAV2	7q31.1	*OPA1*	3q28-q29	*ZP4*	1q43
CDC7/TGFBR3	1p22	*PLXDC2*	10p12.31		
CDKN2B	9p21	*SIX1/SIX6*	14p22-23		
GAS7	17p31.1	*SRBD1*	2p21		
GSTM1	1p13.3	*TMCO1*	1q24		

APOE = Apolipoprotein E; *ATOH7* = Atonal Homolog 7; *CAV1/CAV2* = Caveolin 1/Caveolin 2;

CDKN2B = Cyclin-Dependent Kinase Inhibitor 2B; *TNF-α* = Tumor Necrosis Factor α;

CDC7/ TGFBR3 = Cell Division Cycle/Transforming Growth Factor, Beta Receptor III;

GAS7 = Growth Arrest-Specific 7; *GSTM1* = Glutathione S-Transferase Mu 1; *OPA1* = Optic Atrophy 1;

NCKAP5 = NCK-Associated Protein 5; *NTF4* = Neurotrophin 4; *PLXDC2* = Plexin Domain Containing 2;

SIX1/SIX6= SIX Homeobox 1/ SIX Homeobox 6; *SRBD1* = S1 RNA Binding Domain 1;

TMC01 = Transmembrane and Coiled-Coil Domains 1; *ZP4* = Zona Pellucida Glycoprotein 4;

TMTC2 = Transmembrane and Tetratricopeptide Repeat Containing 2.

4.2. Mono-compound IOP-lowering drugs in POAG/OHT

4.2.1. Eligible studies

The flow of study selection is depicted in Figure 6. The initial search retrieved 597 records. All were screened by titles and abstracts and duplicate publications were removed. The remaining 133 records were once again screened by titles and abstracts and 21 articles were retrieved in full text for the final evaluation of eligibility. At this step, 5 articles (157-161) were excluded (Table 22) and the remaining 16 (162-177) dealing with efficacy or safety of mono-compound topical IOP-lowering drugs were included for quality assessment and data synthesis. No study that evaluated cost-effectiveness profile of these drugs was found. No relevant article was identified through a hand search.

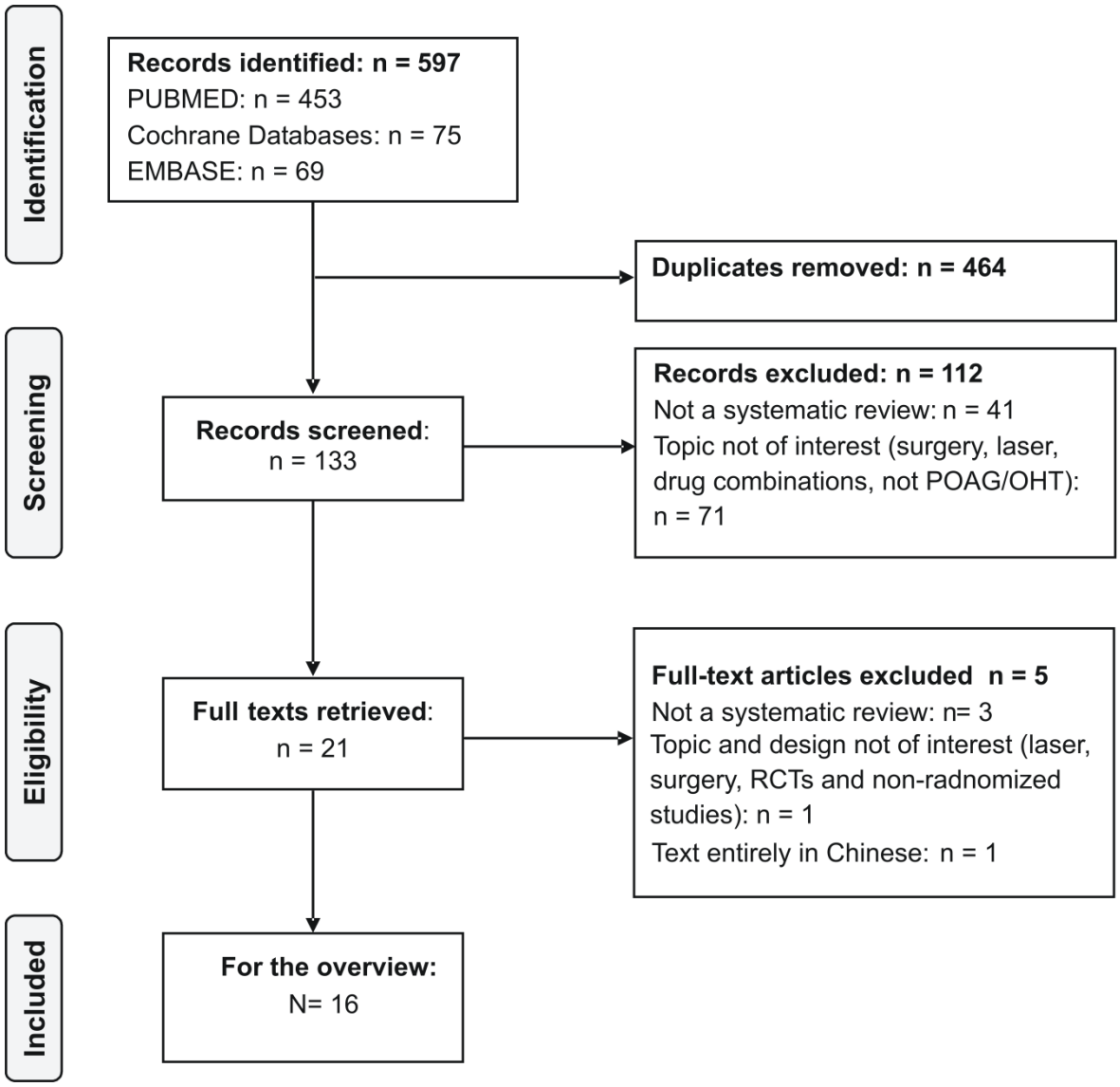

Figure 6. PRISMA flow-chart of study selection of studies.

Table 22. Records excluded after full text reading.

Article	Reason for exclusion
Hedman K, Alm A. A pooled-data analysis of three randomized, double-masked, six-month clinical studies comparing the intraocular pressure reducing effect of latanoprost and timolol. Eur J Ophthalmol 2000;10:95-104.	Not a systematic review, many patients with other types of glaucoma.
Hedman K, Alm A, Gross RL. Pooled-data analysis of three randomized, double-masked, six-month studies comparing intraocular pressure-reducing effects of latanoprost and timolol in patients with ocular hypertension. J Glaucoma 2003;12:463-5.	The same material as above.
Qian ZG, Ke M, Huang G, Zou J. Efficacy and safety of latanoprost versus travoprost for primary open-angle glaucoma and ocular hypertension: A meta-analysis. Chin J EBM 2011;11:965-70.	Manuscript entirely in Chinese.
Beidoe G, Mousa SA.Current primary open-angle glaucoma treatments and future directions. Clin Ophthalmol 2012;6:1699-707.	A narrative review.
Boland MV, Ervin AM, Friedman DS, Jampel HD, Hawkins BS, Vollenweider D, Chelladurai Y, Ward D, Suarez-Cuervo C, Robinson KA. Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013;158:271-9.	Not only RCTs, but also non-randomized and observational studies. Cited in the *Introduction*.

4.2.2. Study characteristics

Table 23 summarizes main characteristics of the 16 included reviews. They were published between 2000 and 2010.

Most (10/16) were focused on both efficacy and tolerability/safety (as a secondary objective) (163, 165, 167-172, 174, 177), five addressed only efficacy (162, 164, 166, 173, 176) and one addressed exclusively local tolerability, specifically conjunctival hyperemia (175).

Two reviews (176, 177) synthesized data using network meta-analysis, whereas the others were declared as "classical" meta-analyses.

Two authors published more than one review [Cheng et al. (169, 172, 173)], even on the same primary studies [Van der Valk et al. (164, 176)].

The assessed treatments and primary study selection criteria varied. One network meta-analyses (176) aimed to assess "the most commonly prescribed mono-compounds", whereas the other (177) evaluated also combination treatments, but the focus of the present overview is on mono-compounds. Another review (167) also addressed mono-compound and "adjunctive treatment" comparisons, but was included as it provided the most comprehensive comparison between latanoprost and brimonidine. Two further reviews tended to evaluate "all most commonly prescribed mono-compound treatments" (164, 173).

Overall, the following mono-compound medications were evaluated through different modes of mutual comparisons: placebo; β-blockers – timolol (always as an individual compound),

betaxolol (as an individual compound or referred to as "other β-blockers" together with e.g., carteolol, levobunolol and others); α-agonists – brimonidine; carbonic anhydrase inhibitors (CAI) – brinzolamide and dorzolamide (as individual compounds or as "CAI as a group"); and prostaglandin analogues (PGAs) – latanoprost, travoprost and bimatoprost.
Doses, formulations and dosing regimens of specific drugs differed and were sometimes counted as a single drug. For some drugs, data were not available.
One review (173) explicitly included only trials in NTG patients. Considering the inclusion/exclusion criteria for primary studies combined with the displayed structures of the embraced patients (in the primary studies), it is safe to conclude that all other reviews assessed the treatments in the setting of (predominantly) POAG/OHT.
Only 1/16 reviews included, among the primary studies, several non-randomized trials (i.e., 4/16) (174). All other primary trials in all other reviews were RCTs, although 2 reviews intended to include also quasi-randomized trials (167, 171).
Two reviews (166, 177) did not assess primary study quality, and the others implemented different tools, most commonly the Jadad score.

4.2.3. Study quality

The AMSTAR checklist and quality scores for the included reviews are depicted in Table 24. Some elements of scoring are self-evident (e.g., whether conflict of interest was declared or whether publication bias was assessed), but some require clarifications, particularly if "N" or "?" was assigned to an item. More details on the rational for the assigned scores are listed in Table 26.
We assigned "?" to the first AMSTAR item to four reviews because there was a discrepancy between the declared aim and actually implemented procedures (162, 164, 173, 174). For example, two reviews (164, 173) intended to evaluate a large number of individual treatments without defining the method, but did not use network meta-analysis.
The reason for assigning "?" to the fifth AMSTAR item in most of the reviews is the fact that the lists of the included but not the lists of excluded primary trials were reported.
Next, reviews that did not consider primary trial quality when drawing conclusions from the meta-analytical results were assigned an "N" for the eighth AMSTAR item (165, 166, 169, 175-177).

Table 23. Main characteristics of the included reviews (in chronological order).

Ref.	Objective	Criteria for primary studies	Studies (k), patients (n)	Primary study assessments
Einarson 2000 (162)	Indirectly compare LAT with BRIM for IOP reduction in POAG.	RCT, English language. POAG with IOP ≥20 mmHg. At least one arm includes LAT or BRIM. Peak, trough or diurnal IOP; duration 3-12 months.	k=9 (DB, parallel), none comparing LAT to BRIM. LAT: k=6; BRIM: k=3.	Quality: Jadad score. Efficacy: ΔIOP vs. baseline and % with controlled IOP for LAT and BRIM as individual treatments. Safety: not assessed. Random-effects.
Zhang 2001 (163)	Compare LAT with TIM for IOP reduction and safety in OAG/OHT.	RCT. OAG/OHT. Directly compare LAT and TIM.	k=11 (10 DB, 1 SB; 7 parallel, 4 cross-over); n = 1256; 410 POAG, 465 OHT, 137 OAG.	Quality: Jadad score. Efficacy: ΔIOP vs. baseline at 4 time-points. Safety: local, systemic, AE withdrawals. Random or fixed-effect.
van der Valk 2005 (164)	Estimate IOP reduction at peak and trough by the most commonly prescribed mono compounds in POAG-HTG/OHT.	RCT, English, German, Dutch or French language. POAG-HTG or OHT. Compare (any): Placebo; TIM 0.5% bid; BET 0.5% bid; BRIM 0.2% bid; DORZ 2.0% bid; BRINZ 1.0% tid; LAT 0.005% qd; TRAV 0.004% qd; BIMA 0.03% qd.	k=27, n=6053 for peak and 6861 for trough IOP. Placebo k=3; BET k=5; TIM k=15; BIMA k=6; LAT k=12; TRAV k=5; BRIM k=4, BRINZ k=1, DORZ k=6.	Quality: Delphi score. Efficacy: absolute and relative ΔIOP vs. baseline for peak and trough for each individual treatment;1-6 months pooled as 1 time-point. Safety: not assessed. Random-effects.
Li 2006 (165)	Compare TRAV with LAT, BIMA and TIM for IOP reduction and safety in OAG/OHT.	RCT, English or Chinese language. OAG or OHT; Compare TRAV vs. other PGA or TIM. Report IOP or AEs.	k=12 (parallel, 8 DB, 4 SB); n=3048, 2060 POAG, 840 OHT, 114 other. TRAV 0.004% vs. TIM k=4; TRAV 0.004% vs. BIMA k=5; TRAV 0.004% vs. LAT k=5.	Quality: Cochrane tool for risk of bias. Efficacy: ΔIOP vs. baseline; 8/12 trials ITT analysis. Safety: local. Random or fixed-effect.
Denis 2007 (166)	Compare TRAV with LAT and BIMA for IOP reduction in OAG/OHT.	RCT, parallel, English of French language. OAG or OHT. Any comparison of TRAV, LAT, BIMA; Report on IOP.	k=9; n=1318, 378 OHT, 919 OAG, 21 other. Comparing all 3 (three-arm trials) k=2. Comparing any two (two-arm trials) k=7.	Quality: Not assessed. Efficacy: IOP at study end (average) and % responding for each individual treatment. Safety: Not assessed. Random-effects.
Fung 2007 (167)	Compare LAT with BRIM for IOP reduction and safety in OAG/OHT.	RCT or quasi-RCT. OAG/NTG/OHT. Compare LAT to BRIM; adjunctive treatment possible. Duration ≥1 month. Reports on efficacy or safety.	k=15 (all RCT, 11 parallel, 4 cross-over; 4 DB, 7 SB, 4 unknown). n=1824, 1299 OAG, 390 OHT, 64 NTG, 60 other. Mono-treatment k=9; adjunctive treatment k=6.	Quality: Allocation concealment, blinding and IOP measurement method. Efficacy: ΔIOP vs. baseline, peak or diurnal. 5/15 trials ITT analysis. Safety: local and systemic. Random-effects.
Aptel 2008 (168)	Compare BIMA, LAT and TRAV for IOP reduction and safety in POAG/OHT.	RCT, DB. POAG or OHT >90%. Compare LAT 0.005%, TRAV 0.004% or BIMA 0.03% 1 drop/day between 6 and 10 PM. Report diurnal IOP and conjunctival hyperaemia. Duration 1-6 months.	k=8 (parallel). n=1610; LAT vs BIMA k=4; TRAV vs BIMA k=2; LAT vs TRAV k=1; LAT vs TRAV vs BIMA k=1.	Quality: Jadad score. Efficacy: Δ IOP vs. baseline (4 daily values: 8 AM, 12 noon, 4 PM, 8 PM separately), all trial duration as one time-point. Safety: conjunctival hyperemia. Fixed-effect.
Cheng 2008 (169)	Compare BIMA with LAT for IOP reduction and safety in glaucoma/OHT.	RCT. Glaucoma or OHT, NTG excluded. Directly compare LAT and BIMA. Report on IOP reduction or % patients achieving the target IOP.	k=13 (5 DB, 8 SB, 10 parallel, 3 cross-over). n=1302; 754 POAG, 327 OHT, 211 other. LAT 0.005% vs. BIMA 0.03%; 1 x evening	Quality: Jadad score. Efficacy: Δ IOP vs. baseline (morning/diurnal) or % patients achieving IOP≤17; 3 different time-points. Safety. Local. Random-effects. ITT basis.
Hodge 2008 (170)	Compare PGAs with BRIM and DORZ for IOP reduction and safety in OAG/OHT.	RCT, English language. OAG/OHT, ACG excluded. Compare PGAs and BRIM or DORZ.	k=7 (parallel); n=1131, 418 POAG, 555 OHT, 60 other, 98 unknown. LAT vs BRIM k=3 (+1 safety); LAT vs DORZ k=3.	Quality: Jadad score. Efficacy: Δ IOP vs. baseline at 3 months. 2/7 trials ITT. Safety: local, AE withdrawals. Random or fixed-effect.

Continues on the next page

Ref.	Objective	Criteria for primary studies	Studies (k), patients (n)	Primary study assessments
Loon 2008 (171)	Compare TIM with BRIM for IOP reduction and safety in glaucoma.	RCT, pseudo-RCT. Glaucoma. Directly compare TIM 0.5% to BRIM 0.2%. Report on IOP and safety, ≥ 1 month.	k=10 (all RCT, 7 DB,1 open, 2 unknown); 8 used for quantitative synthesis; n= 2387, 1442 OAG, 877 OHT, 68 other.	Quality: Allocation concealment, blinding, withdrawals, ITT/LOCF. Efficacy: Δ IOP vs. baseline (peak or mean). 8/10 trials ITT analysis. Safety: local, systemic. Random-effects..
Cheng 2009a (172)	Compare TRAV and LAT for IOP reduction and safety in OAG/OHT.	RCT. OAG/OHT with lOP >21 mmHg, NTG/ACG excluded. Compare TRAV 0.004% to LAT 0.005% once daily. Report on IOP at 9 AM and/or 5 PM.	k=17 (9 DB, 8 SB, 13 parallel, 4 cross-over), n=1491; 966 OAG, 379 OHT, 146 other.	Quality: Jadad score. Efficacy: Δ IOP vs. baseline (separately 9 AM and 5 PM) at 5 different time-points. 6/17 trials ITT analysis. Safety: local and AE withdrawals. Random-effects.
Cheng 2009b (173)	Estimate IOP reduction by the most commonly prescribed mono compounds in NTG.	RCT, any language; Advanced NPG. Compare (any): Placebo, BET 0.25/0.5% bid, TIM 0.5% bid, DORZ 0.2% tid, BRINZ 1.0% tid, BRIM 0.2% bid, LAT 0.005% qd, TRAV 0.004% qd, BIMA 0.03% qd. Report absolute and relative IOP reduction.	k=15 (5 DB, 6 SB, 4 open, 5 parallel, 10 cross-over); n= 450.	Quality: Delphi score. Efficacy: absolute and relative ΔIOP vs. baseline for peak, trough and diurnal curve for each individual treatment (0.5-2 months) as 1 time-point. Safety: Not assessed. Random-effects.
Ejawo 2009 (174)	Compare BIMA, LAT and TRAV for IOP reduction and safety in POAG/OHT.	RCT, excluded dose-finding, cross-over and short-term. POAG/OHT. Any comparison between TRAV 0.004%, LAT 0.005% and BIMA 0.03%. Report on IOP and AEs.	k=16 (4 non-RCT, unknown blinding), n=2674, 1705 POAG, 727 OHT, 242 other. TRAV vs. LAT k=9; TRAV vs. BIMA k=8; LAT vs. BIMA k=8; >2 arms k=5.	Quality: randomization, allocation concealment, ITT, blinding. Efficacy: IOP (morning) at study end (3-12 months), 6/16 trials ITT analysis. Safety: conjunctival hyperemia. Random-effects.
Hornubia 2009 (175)	Compare LAT with BIMA and TRAV for conjunctival hyperaemia in glaucoma/OHT.	RCT, English language. Glaucoma/OHT. Any comparison between LAT, BIMA or TRAV reporting on conjunctival hyperemia.	k=13 (10 parallel, 3 cross-over); n= 2222; 1364 OAG, 678 OHT and 180 other. LAT vs. BIMA k=8, LAT vs. TRAV k=6, 3 arms k=1	Quality: Jadad score. Efficacy: Not assessed. Safety: Conjunctival hyperaemia. Fixed and random-effects.
v.d.Valk 2009 (176)	Estimate IOP reduction at peak and trough by the most commonly prescribed mono compounds in POAG-HTG/OHT by MTC.	RCT, English, German, Dutch or French language. POAG-HTG or OHT. Compare (any): Placebo; TIM 0.5% bid; BET 0.5% bid; BRIM 0.2% bid; DORZ 2.0% bid; BRINZ 1.0% tid; LAT 0.005% qd; TRAV 0.004% qd; BIMA 0.03% qd.	k=27, n=6053 for peak and 6861 for trough IOP. Placebo k=3; BET k=5; TIM k=15; BIMA k=6; LAT k=12; TRAV k=5; BRIM k=4, BRINZ k=1, DORZ k=6.	Quality: Delphi score. Efficacy: absolute and relative ΔIOP vs. baseline for peak and trough using timolol as a reference;1-6 months pooled as 1 time-point. Safety: not assessed. Random-effects.
Orme 2010 (177)	Compare IOP reduction and conjunctival hyperemia of different treatments in POAG/OHT by MTC.	RCT, English language, ≥ 20 patients. POAG/OHT, excluded ACG & secondary. Include a PGA in at least one arm.	MTC Efficacy: k=18; n=2943; MetaReg Efficacy k=73, n=11519; MTC Safety: k=72. Evaluated treatments: TIM, LAT- TlM, CAI-TIM, TRAV-TIM, BIMA, TRAV, LAT, CAI, Other UC, Other β-blockers, Placebo.	Quality: Not assessed. Efficacy: MTC for 3-month outcomes - absolute IOP; predicted probability of IOP <20 mmHg or ≥20% reduction vs. baseline and NNTB vs. timolol. Safety: MTC of % patients with conjunctival hyperemia and NNTH vs. Placebo. Random-effects.

RCT = Randomized Controlled Trial; DB = Double Blind; SB = Single Blind; ITT = Intention–To–Treat; LOCF = Last Observation Carried-Forward; PP = Per-Protocol; NNTB = Number Needed To Treat To Benefit; NNTH = Number Needed To Treat To Harm; MetaReg = Meta-Regression Analysis; MTC = Random-Effects Mixed Treatment Comparisons (or Network Meta-Analysis); POAG = Primary Open Angle Glaucoma; OHT = Ocular Hypertension; NTG = Normal Tension Glaucoma; OAG = Open Angle Glaucoma; PDG = Pigment Dispersion Glaucoma; ACG = Angle Closed Glaucoma; HTG = High Tension Glaucoma; IOP = Intraocular Pressure; AEs = Adverse Events; PGAs = Prostaglandin Analogues; CAI = Carbonic Anhydrase Inhibitors; UC = Unfixed Combinations; LAT = Latanoprost; BIMA = Bimatoprost; TRAV = Travoprost; BRIM = Brimonidine; TIM = Timolol; BET = Betaxolol; DORZ = Dorzolamide; BRINZ = Brinzolamide; qd = Once a Day; bid = Twice a Day; tid = Three Times a Day.

Table 24. Quality of the included reviews based on the AMSTAR (91) checklist.

Ref.	Einarson 2000 (162)	Zhang 2001 (163)	v.d. Valk 2005 (164)	Li 2006 (165)	Denis 2007 (166)	Fung 2007 (167)	Aptel 2008 (168)	Cheng 2008 (169)	Hodge 2008 (170)	Loon 2008 (171)	Cheng 2009a (172)	Cheng 2009b (173)	Ejawo 2009 (174)	Hornubia 2009 (175)	v.d.Valk 2009 (176)	Orme 2010 (177)
Design "a priori"?	?	Y	?	Y	Y	Y	Y	Y	Y	Y	Y	?	?	Y	Y	Y
Duplicate selection/extraction?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y#	?
Comprehensive search?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y#	Y
Publication status clear?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y#	Y
List included/excluded provided?*	?	?	?	Y	?	?	?	Y	?	?	?	?	?	Y	?	Y
Study characteristics provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y#	Y
Quality assessed?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y#	N
Quality accounted for conclusions?	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	N	N	N
Appropriate method for pooling?	N	N	N	?	N	Y	?	?	Y	N	N	N	Y	?	?	Y
Publication bias assessed?	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	?	Y
Conflict of interest declared?	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
AMSTAR score	7	7	8	9	6	10	9	8	9	8	8	8	9	9	7	8

Y = yes; N = No; ? = can't tell; NA = not applicable.

*All reviews reported on included studies, but only 3 reported also on excluded studies. Hence, most reviews failed to meet this quality criterion.

#Described in the previous publication [v.d. Valk 2005 (164)].

However, the major flaws were related to methods of data pooling, i.e., statistical analysis (more details are provided in Table 26):

- Only four reviews (167, 170, 174, 177) used fully correct methods and were assigned a "Y".
- Five reviews (165, 168, 169, 175, 176) were assigned a "?" primarily due to the fact that fixed and random-effects data pooling were used alternatively without clear criteria/justification.

The relevance of inadequate pooling is best illustrated by the example of Loon et al. 2008 (171) which was, because of that, assigned an "N". This review embraced 8 RCTs comparing timolol to brimonidine. The assessed outcome was the amount of IOP drop from baseline to the end of trials (higher values represented a more pronounced IOP reduction). Fixed-effect meta-analysis was used to pool the data across subgroups of trials, i.e., for 5 trials with ~100 patients and more, for 3 trials with <50 patients, and an overall estimate ("across subgroups") was produced as illustrated in Figure 7.

The analysis indicated that in the larger trials there was a statistically significantly greater reduction in favor of brimonidine (pooled treatment difference 0.65, p<0.001), while the difference in smaller trials was smaller (Figure 7). Overall, the analysis indicated a significantly greater IOP reduction with brimonidine – difference 0.46 mmHg, p<0.001 (Figure 7). It should be noted that in both subgroups of trials and overall, there was considerable heterogeneity (high I^2 values, p<0.001 in the Q-test of heterogeneity) (Figure 7).

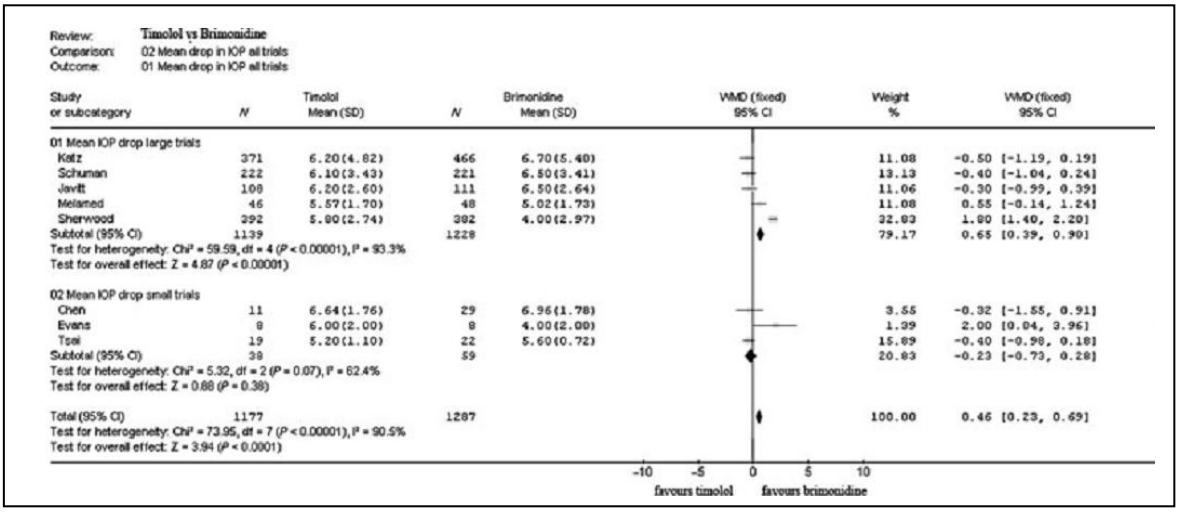

Figure 7. Forrest plot and fixed-effect meta-analysis of 8 trials comparing timolol to brimonidine for IOP reduction taken from Loon et al. 2008 (171).

The analysis was performed in subgroups of trials by size: larger (~100 or more patients) and smaller (<50 patients), and overall. The results indicate a significantly greater reduction with brimonidine in larger trials and overall.

We recalculated the data displayed in Figure 7 using random-effects pooling which is a standard procedure for pooling data from trials that differ in design characteristics, and particularly when there is any evidence of heterogeneity.
As shown in Figure 8, re-analysis of data from Figure 7 using the appropriate, random-effects pooling method clearly demonstrated no significant difference between brimonidine and timolol in IOP reduction, based on the trials included in the review by Loon et al. 2008 (171).

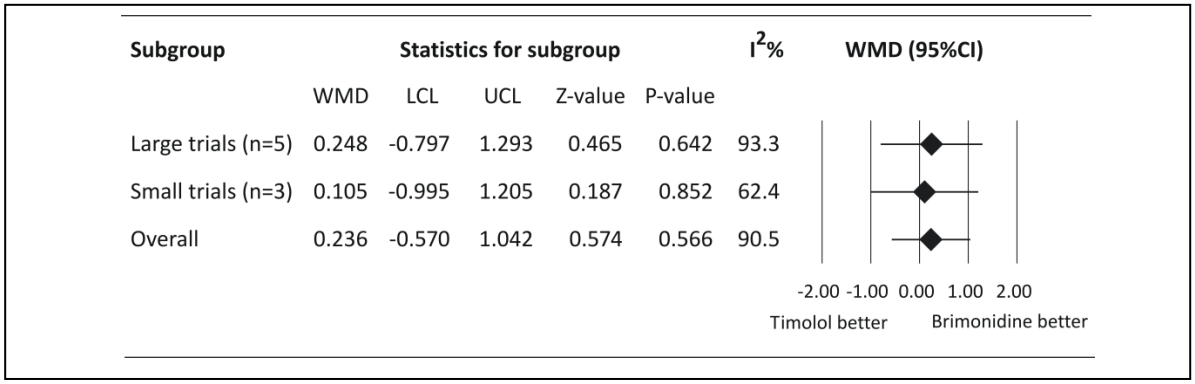

Figure 8. Summary of random-effects meta-analysis of data from Loon et al. 2008 (151) displayed in Figure 7.

Presented are pooled estimates for the subgroup of large trials, small trials and overall. It should be noted that by random-effects method no difference is observed between brimonidine and timolol – regardless of the trial size (and overall). Heterogeneity is very high.

The major reason for assigning an "N" (Table 24) to the reviews by Einarson 2000 (162), van der Valk 2005 (164), Denis 2007 (166) and Cheng 2009b (173) was the use of explicitly erroneous data pooling method that resulted in non-randomized comparisons between treatments: instead of pooling treatment differences (arising from randomized settings, i.e., RCTs), they pooled values for individual treatments across trials and then compared these pooled estimates. This approach has been called "naïve indirect comparisons" and is prone to bias, inadequate numerical estimates ("far from true treatment differences") and is no better than using data from non-randomized or observational settings. Consequently, it is strongly discouraged (178).

Both the review by Zhang et al. 2001 (163) and by Cheng et al. 2009b (173) used an erroneous method for calculation of SD of change in IOP vs. baseline, i.e., they treated it as if it came from independent samples (i.e., SD for difference between two independent groups of subjects) disregarding the correlation between measurements taken in the same patients (at baseline and at same time-point post-baseline, e.g., at the end of the trial).

Let us assume that the SD of baseline IOP is 6 mmHg and of end-of-trial IOP is also 6 mmHg. The SD of change in IOP, if calculated disregarding correlation, is 6 mmHg. However, if there is correlation (as one would expect), the estimate differs: assuming a high correlation with a correlation coefficient of 0.8, the standard deviation of IOP change is 3.8 mmHg, and assuming a low correlation, say correlation coefficient of 0.2, the standard deviation of IOP change is 7.6. Both estimates are clearly different from 6, and this then reflects on the estimated treatment differences.

Zhang et al. 2001(163) made another methodological error – for the meta-analysis, they did not use "raw" IOP change data (in mmHg), but "% change in IOP", which they calculated as "IOP reduction/IOP baseline" (where reduction is IOP mean at the end – IOP mean at baseline). This is an inadequate approach – "% change vs. baseline" can only be calculated if all individual patients data for baseline and end-of-treatment are available as:

$$Mean\ \%\ change\ in\ IOP\ vs.\ baseline = \frac{\sum_{i=1}^{n}\left(\frac{IOP_{bas\,i} - IOP_{end\,i}}{IOP_{bas\,i}}\right)}{n} \times\ 100$$

Where $\acute{\imath}$ = represents an individual patient in a trial and n= total number of patients in a trial. Hence, "% change" can be meta-analyzed only if reported by each individual study, or if all individual data are available, but not if determined from summary statistics.

A further methodological error by Zhang et al. 2001 (163) was determination of SD of the "% change vs. baseline" since it was determined as "SD of change (in mmHg)/IOP at baseline". Standard deviation of "% change vs. baseline" is actually a standard deviation of a ratio, since "% mean change" is a ratio [(baseline-end)/baseline)], and is calculated as:

$$SD\left(\frac{A}{B}\right) = \frac{A}{B} \times \sqrt{\left(\frac{SD(A)}{Mean\ A}\right)^2 + \left(\frac{SD(B)}{Mean\ B}\right)^2}$$

Assume that baseline IOP is 26 mmHg with SD 7. End-of study IOP is 17 mmHg and mean change is 9 mmHg with SD 6. If calculated as SD change /IOP baseline, then SD of % change would be 6/26=0.23, or 23%. Properly calculated, the result is 0.25 or 25%.

4.2.4. Quality of evidence

The level of quality assigned within the GRADE framework to each of the 16 included reviews (where each one is a "body of evidence") is depicted in Table 25.
The GARDE quality level assigned to a review was based on its quality, but also on the properties of the primary trials included in the review, their quality, number of patients, precision of the estimates within the review as well as on the type of treatment comparison within a review (direct, indirect or mixed).

The highest level of quality of evidence achieved was "moderate" and was attained by 5 reviews (Table 25): Li et al. 2006 (165), Fung et al. 2007 (167), Aptel et al. 2008 (168); Hornubia et al. 2009 (175) and Orme et al. 2010 (177). More detailed reasons why these 5 reviews were downgraded to "moderate" quality, as well as the reasons for quality grades assigned to other reviews are depicted in Table 26 at the end of this section.

Li et al. 2006 (165) and Aptel et al. 2008 (168) were downgraded by 1 for imprecision because certain comparisons between pairs of evaluated treatments were based on only 2-3 primary trials and/or a small number of patients resulting in very wide confidence intervals.

Fung et al. 2007 (167) and Hornubia et al. 2009 (175) were downgraded by 1 for limitations/bias since they included only a few double-blind trials and intent-to-treat analysis in primary studies was low or unknown.

In addition, the unit-of-analysis issue (unclear handling of multi-arm and cross-over trials) was highly suspected in Hornubia et al. 2009 (175).

Orme et al. 2010 (177) was downgraded by 1 for indirectness since some of the comparisons in the assessed network were predominantly or exclusively indirect.

Table 25. Quality of evidence provided by individual reviews based on the GRADE evaluation system.

Ref.	Einarson 2000 (162)	Zhang 2001 (163)	v.d. Valk 2005 (164)	Li 2006 (165)	Denis 2007 (166)	Fung 2007 (167)	Aptel 2008 (168)	Cheng 2008 (169)	Hodge 2008 (170)	Loon 2008 (171)	Cheng 2009a (172)	Cheng 2009b (173)	Ejawo 2009 (174)	Hornubia 2009 (175)	v.d.Valk 2009 (176)	Orme 2010 (177)
Limitations/bias	-1	-1	-1	Minor	-2	-1	Minor	-1	-1	-1	-1	-1	-2	-1	-1	Possible
Inconsistency	Minor	-1	Minor	Minor	-1	Minor	Minor	-1	Some	-1	Minor	Minor	Some	No	Minor	No
Indirectness	-2	Direct	-2	Direct	-2	Direct	Direct	Direct	Direct	Direct	Direct	-2	Direct	Direct	-1	-1
Imprecision	Minor	Minor	Minor	-1	Minor	Minor	-1	Some	-1	Minor	-1	Some	Minor	Minor	Minor	Minor
Publication bias	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Possible	Unlikely
Quality of body of evidence*	+ Very low	++ Low	+ Very low	+++ Moderate	+ Very low	+++ Moderate	+++ Moderate	++ Low	++ Low	++ Low	++ Low	+ Very low	++ Low	+++ Moderate	++ Low	+++ Moderate

*This is judged in respect to the primary research question posted in each review. See Materials and Methods for the GRADE system levels of quality of evidence.

Table 26. Main reasons for downgrading the AMSTAR and GRADE scores.

Einarson 2000 (162)	1. The declared aim was to indirectly compare latanoprost to brimonidine. However, erroneous data pooling and meta-analysis methods were used: instead of an indirect comparison through a network (which was possible), ΔIOP vs. baseline was pooled for the two treatments across trials that compared them to a variety of other treatments, and a non-randomized comparison was performed. 2. Seemingly erroneous calculation of variance of "within-treatment" ΔIOP vs. baseline.
Zhang 2001 (163)	1. Erroneous calculation of variance of "within-treatment" ΔIOP vs. baseline and of variance of "%Δ vs. baseline" (86)*. 2. When Q test "not significant" fixed-effect pooling. However, with a small number of trials at time points with the largest treatment differences, Q-test p-value was>0.1, but we calculated I^2 values (2)# of 56%, 20% and 34.5%, respectively. Consequently, random-effects pooling would have been more appropriate for generation of valid estimates. 3. Handling of cross-over trials not clearly stated (possible "unit-of-analysis" issue). 4. A comprehensive overview of local and systemic safety reported in individual trials was presented. However, data pooling likely inappropriate: many "zero event cells"/"no event trials" should not be pooled as random-effects relative risk or risk difference (87).
v.d. Valk 2005 (164)	1. Erroneous data pooling and meta-analysis method (86)*: ΔIOP vs. baseline for individual treatments instead of between-treatment differences; relative treatment "positioning" based on non-randomized comparisons. 2. Erroneous calculation of variance of "within-treatment" ΔIOP vs. baseline and of variance of "%Δ vs. baseline" (86)*.
Li 2006 (165)	1. Several trials with >2 arms treated as if assessing independent pair-wise comparisons ("unit-of-analysis" issue). 2. Time points that were much apart (1 week to 12 months) were pooled together (no account on trial duration) and "type" of IOP (diurnal, peak or through) not declared. This could have influenced the estimated treatment differences. 3. Some safety estimates based on only few trials with some "zero event cells".
Denis 2007 (166)	1. Erroneous data pooling and meta-analysis method (86)*: IOP at end of treatment for individual treatments instead of between-treatment differences; relative treatment "positioning" based on non-randomized comparisons. 2. Blinding and ITT analysis by trial not addressed. 3. Inclusion of secondary OAG not stated.
Fung 2007 (167)	1. Only 4 double-blind trials, only 5 with ITT analysis. 2. Still high heterogeneity in subgroup (by trial duration) analysis. 3. A comprehensive display of adverse events, but for some high heterogeneity, for others only a few trials and "zero event cells/no event trials" (random-effects risk difference not appropriate effect measure) (87).
Aptel 2008 (168)	1. Fixed-effect pooling although Q test for some outcomes p<0.05. For others, Q test p>0.1, but with only a few trials. E.g., for two largest treatment differences we calculated I^2 values (2)# of 44%, respectively (random-effects might have been more appropriate). 2. One 3-arm trial – unclear handling ("unit-of-analysis" issue?). 3. Latanoprost vs. travoprost only in 1 trial. 4. No record on ITT analysis by trial. 6. Individual trial data on conjunctival hyperaemia not displayed.
Cheng 2008 (169)	1. Erroneous calculation of variance of "within-treatment" ΔIOP vs. baseline and of "%Δ vs. baseline" (86)*. 2. Stated ITT analysis but, as detected through other reviews, at least 5 RCTs did not apply ITT analysis. While this can be corrected at the meta-analytical level for binary outcomes, a correction is impossible for continuous outcomes. 3. Efficacy treatment difference inconsistent for morning and diurnal IOP, as well as for "% achieving target". 4. Handling of cross-over trials not stated (possible "unit-of-analysis" issue). 5. Comprehensive presentation of adverse effects, but some only on few trials with "zero event cells" (random-effects risk difference not an appropriate effect measure) (87).

Continues on the next page

Hodge 2008 (170)	1. 2/4 trials comparing efficacy of latanoprost to brimonidine and 3/3 comparing it to brinzolamide - low quality (Jadad score 2). 2. Only 1 study for each comparison was based on ITT analysis. 3. All trials for latanoprost vs. dorzolamide on diurnal IOP, latanoprost vs. brimonidine on diurnal and morning mixed together (might have affected the estimates). 4. Safety outcomes assessed on only a few trials. Individual trial data not displayed, but likely some "zero event cells"/"no event trials" (risk difference not appropriate effect measure) (87).
Loon 2008 (171)	1. Erroneous data pooling: efficacy subgroup analysis by trial size using fixed-effect despite very high I^2 concluded treatment difference in large trials. Re-calculated by random-effects – no difference I. 2. Erroneous weighing in subgroup analysis by trial duration (relative weight distributed as if there were 16 trials). 3. Unclear meta-regression procedure (could not be replicated). 4. Safety outcomes assessed on trials with high prevalence of "zero event cells/trials" (random-effects relative risk not appropriate effect measure) (87).
Cheng 2009a (172)	1. Erroneous calculation of variance of "within-treatment" ΔIOP vs. baseline (86)*. 2. Stated ITT, but 11/17 included RCTs did not apply ITT analysis. While this can be "corrected" at the meta-analytical level for binary outcomes, a correction is impossible for continuous outcomes. 3. Handling of cross-over trials not stated (possible "unit-of-analysis" issue). 4. No sensitivity analysis in respect to ITT and blinding. 4. Inconsistent results for diurnal and afternoon IOP reduction. 5. A comprehensive display of adverse events, but some assessed on only a few trials. Unknown prevalence of "zero event cells"/"zero event trials" (random-effects relative risk not appropriate effect measure) (87).
Cheng 2009b (173)	1. Erroneous data pooling and meta-analysis method (86)*: ΔIOP vs. baseline for individual treatments instead of between-treatment differences; relative treatment "positioning" based on non-randomized comparisons. 2. Erroneous calculation of variance of "within-treatment" ΔIOP vs. baseline and of variance of "%Δ vs. baseline" (86)*.
Ejawo 2009 (174)	1. Aimed to include only RCTs, but 4/16 trials were non-randomized. 2. The 5 3-arm trials handled as if independently assessing pair-wise comparisons - "unit-of-analysis" issue. 3. No reference to individual study blinding, randomization and ITT analysis. 4. Individual study data on conjunctival hyperaemia not displayed.
Hornubia 2009 (175)	1. One 3-arm trial treated as if assessing independent pairwise comparisons – "unit-of-analysis" issue. 2. Unclear handling of cross-over trials (further "unit-of-analysis problem"?). 3. ITT approach and blinding by study not addressed.
v.d.Valk 2009 (176)	1. A network ("multiple-treatment") meta-analysis based on previously identified (van der Valk et al. 2005) RCTs – likely erroneous (as in the previous publication) calculation of variance of "%Δ vs. baseline" .2. No up-dated trial search. 3. Ranking based on individual treatment difference vs. timolol, but a limited number of direct comparisons for many treatments in the network. 4. Traditional meta-analysis not performed. 5. ITT analysis and blinding by trial not addressed.
Orme 2010 (177)	1. A network ("multiple-treatment") meta-analysis using latanoprost as a reference, but with a limited number of direct comparisons for many treatments in the network. 2. ITT analysis and blinding by trial not addressed. 3. Classical meta-analysis not performed.

*Reported in a previous assessment (86); $^{\#}I^2 = 100\% \times (Q - df)/Q$; IOP = Intraocular Pressure; ITT = Intention-To-Treat.

IIn STATA (metan), CMA and R (metafor), random-effects meta-analysis by trial size subgroups based on displayed data. Using displayed data on trial size (>100 or <100; or continuous), duration (<6 or >6 months; or continuous) and allocation concealment (yes/no), could not replicate the reported meta- regression results (SAS proc mixed; metareg in STATA; metafor in R).

4.2.5. Relationship between different compounds

Only the reviews achieving moderate level of quality of evidence (165, 167, 168, 175, 177) were considered for evaluation of relationship between treatments.

4.2.5.1. Efficacy

Based on IOP reduction after 3 months of treatment, Orme et al. (177) ranked 6 mono-compound medications in the following order (most effective to least effective): bimatoprost, latanoprost, travoprost, CAI group, *β*-blockers group without timolol, timolol.
However, many of the differences between treatments were very small and although statistically significant they do not appear practically relevant. Table 4 summarizes point-estimates of pair-wise differences in IOP reduction reported by Orme et al. (177).

Assuming that the limits of -1.0 to +1.0 mmHg for IOP reduction are reasonable limits of therapeutic equivalence (174), the three PGAs appear to be equivalent. In a series of pair-wise comparisons, Aptel et al. (168) calculated somewhat larger differences between bimatoprost and latanoprost, and between bimatoprost and travoprost but still, all were well within the -1.0 to +1.0 range. Li et al (165) compared travoprost to bimatoprost and reported zero difference (point-estimate 0.08 mmHg), while the difference between travoprost and latanoprost was -0.57 mmHg. Despite these variations, it appears reasonable to conclude that the IOP-reducing potential of the three PGAs is not relevantly different.

According to Orme et al. (177), PGAs are more effective than other evaluated drugs, but in this respect they should be considered individually. Bimatoprost seems to be relevantly superior to CAI, *β*-blockers other than timolol, and timolol, whereas latanoprost and travoprost showed a relevant difference only in relation to timolol (Table 27).
The findings of Li et al. (165) confirmed the size of the difference between travoprost and timolol, whereas Fung et al. (167) reported a relevant difference between latanoprost and brimonidine (point-estimate 1.10 mmHg).

Finally, according to Orme et al. (177), CAI as a group, timolol and other *β*-blockers do not seem to relevantly differ regarding their IOP-reducing potential (Table 27). However, these relationships were estimated practically exclusively through indirect comparisons and we found no other evidence of at least moderate quality that would relate these treatments to each other.

Table 27. Point-estimates of differences (mmHg) between pairs of treatments in IOP reduction at 3 months vs. baseline as determined in a network meta-analysis by Orme et al (177). A positive value indicates a greater reduction by the "row drug" vs. a "column drug" and a negative value indicates the opposite. Bolded are values that exceed a difference of ± 1.0 mmHg and underlined are the differences close to this limit.*

	Bimatoprost	Latanoprost	Travoprost	CAI as a group	BB w/o timolol	Timolol
Bimatoprost	---	0.45	0.47	0.97	**1.09**	**1.41**
Latanoprost	-0.45	---	0.02	0.52	0.64	0.96
Travoprost	-0.49	-0.02	---	0.50	0.62	0.94
CAI as a group	-0.97	-0.52	-0.50	---	0.12	0.44
BB w/o timolol	**-1.09**	-0.64	-0.62	-0.12	---	0.32
Timolol	**-1.41**	-0.96	-0.94	-0.44	-0.32	---

BB = *β*-Blockers; CAI = Carbonic Anhydrase Inhibitors; w/o = Without

* We assumed that the limits of -1.0 to +1.0 mmHg for a difference in IOP reduction could be reasonably accepted as limits of equivalence (174).

4.2.5.2. Tolerability/safety

The only adverse event addressed by all 5 reviews was conjunctival hyperemia.
The most comprehensive assessment was that by Orme et al. (177), i.e., through a network meta-analysis including 73 RCTs. Ranking of mono-compound drugs from the lowest to the highest incidence of conjunctival hyperemia was: timolol, dorzolamide, brimonidine, latanoprost, travoprost and bimatoprost. Betaxolol was also ranked, but based only on one trial arm with only 34 patients (177). Table 28 summarizes point-estimate odds ratios (ORs).

Odds of hyperemia with latanoprost appear to be around 3-fold and around 5-fold lower than with travoprost and bimatoprost, respectively (Table 28). Similar estimates were reported by Hornubia et al. (175), whereas estimates provided by Aptel et al. (168) and Li et al. (165) where somewhat smaller (1.5-2.0-fold lower odds).
While Orme et al. (177) indicated no relevant difference between travoprost and bimatoprost (Table 28), Aptel et al. (168) and Li et al. (165) reported a significantly lower incidence with travoprost – ORs around 0.86 (168) and around 0.65 (175), respectively.
Overall, it seems reasonable to conclude that latanoprost conveys the lowest risk of conjunctival hyperemia among PGAs, whereas evidence on travoprost vs. bimatoprost is inconclusive.

The review by Orme et al. (177) is the only evidence of at least moderate quality about safety relationships between non-PGA compounds and indicates no relevant difference between timolol, brinzolamide and brimonidine in respect to conjunctival hyperemia (Table 28).
It also demonstrates that, in this respect, bimatoprost is considerably worse than any of these drugs, whereas latanoprost and travoprost appear worse than timolol (Table 28).
Data from Li et al. (165) and Fung et al. (167) confirm higher incidence with travoprost vs. timolol (OR 11.5) and no difference between latanoprost and brimonidine (relative risk around unity), respectively.

Fung et al. (167) compared latanoprost to brimonidine in respect to a number of AEs besides hyperemia (e.g., eyelid disorders, visual disturbances, keratopathy, dry eye, hypertrichosis, fatigue, headache) indicating no difference between the two.
Li et al. (165) indicated considerably higher odds of eye-lash changes and iris pigmentation with travoprost as compared to timolol or latanoprost.
However, considering the specifics of the systematic reviews of Adverse Events (AEs) (87), in respect to these assessments quality of evidence provided by the two reviews is less than moderate:

- none of the included primary trials was specifically designed to assess safety/tolerability;
- neither review evaluated the quality of primary trials specifically in respect to AEs recording, evaluation and reporting;
- data on most of the outcomes were available from only a few trials and prevalence of "zero event cells" was rather high.

4.2.5.3. Combining efficacy and safety

None of the five reviews (165, 167, 168, 175, 177) attempted to rank treatments based on a composite criterion combining efficacy and tolerability/safety.

Data suggest that among PGAs latanoprost has the most favorable trade-off between efficacy and tolerability. However, none of the presented reviews included trials with preservative-free PGA formulations that have recently emerged (179-183), and this conclusion might change in the near future.

The existing evidence does not point-out to any relevant difference regarding efficacy and safety of non-PGA compounds dorzolamide, brimonidine, timolol and "other" β-blockers**.**

Compared to PGAs, and in addition to (at least somewhat) lower efficacy, they are limited by the fact of twice or thrice daily administration (vs once daily). It appears reasonable to consider them as alternative options when PGAs are contraindicated or not tolerated.

Table 28. Differences between pairs of treatments in incidence of conjunctival hyperemia as determined in a network meta-analysis by Orme et al (177). Differences are expressed as odds ratios: values >1.0 indicate a greater incidence for the "row drug" vs. a "column drug", and values <1.0 indicate the opposite.

	Timolol	Dorzolamide	Brimonidine	Latanoprost	Travoprost	Bimatoprost
Timolol	---	~1*	~1*	0.56	0.18	0.11
Dorzolamide	~1*	---	~1*	~1*	~1*	0.22
Brimonidine	~1*	~1*	---	~1*	~1*	0.21
Latanoprost	1.78	~1*	~1*	---	0.32	0.21
Travoprost	5.55	~1*	~1*	3.12	---	~1*
Bimatoprost	9.09	4.54	4.76	4.76	~1*	---

*Odds ratios around 1 (~1) indicate a lack of a statistically significant difference (95% confidence intervals around the odds ratio extend from below to above unity).

5. DISCUSSION

Glaucoma in general is a complex and multifaceted condition. Since it is the leading cause of irreversible blindness worldwide, its epidemiology, etiology and treatment have been extensively investigated.

The present work addressed only one component of this group of optical neuropathies, but the one that bears the major part of the healthcare burden – primary open angle glaucoma (POAG) and ocular hypertension (OHT). Within this still broad field, the focus was on three specific questions:

- What is the existing evidence on factors other than the increased IOP that are potentially modifiable or could be used for timely identification of people at an increased risk of POAG?
- What is the existing evidence on relative efficacy and safety of mono-compound topical IOP-lowering medications in treatment of POAG/OHT?
- What is the existing evidence on relative cost-effectiveness of the mono-compound topical IOP-lowering medications in treatment of POAG/OHT?

These questions are relevant for practical reasons:

a) although treatment of increased IOP has been clearly shown to preclude progression of OHT to POAG, it is of interest to introduce, if possible, other measures that would either be supportive to the treatment of IOP or would reduce occurrence of IOP (and thus preclude the need for treatment). Likewise, it is of interest to timely identify subjects with an increased risk of POAG;

b) mono-compound topical treatments are the preferred initial IOP-reducing treatment and identification of those with the best trade-off between efficacy and safety would help optimize the treatment. Whereas identification of drugs with the best cost-effectiveness profile would be particularly useful for developing countries with restricted public health resources.

In line with the methodology implemented in the attempts to resolve the posed questions, the results are discussed in the format that is standard for overview of reviews.

5.1. Risk factors for POAG

5.1.1. Overall completeness and applicability of evidence

Age, gender and ethnicity have long been recognized as factors associated with POAG, but the quest for factors other than IOP influencing POAG (or IOP) occurrence has been particularly focused on potentially modifiable factors.
The present systematic review of reviews identified a number of narrative reviews dealing with a number of lifestyle, environmental and co-morbidity factors that were considered in relation to POAG occurrence. However, the number and quality of the individual primary studies were limited not allowing sound conclusions.
On the other hand, genetic risk factors were evaluated in a large number of systematic reviews and meta-analyses. However, most of them included small candidate-gene association studies providing a very low level of quality of evidence and were not further evaluated in the present work.
We included 3 meta-analyses of data from genome-wide association studies (GWAS) and 2 narrative reviews that intended to summarize and synthesize the complete knowledge on the genetic background of POAG to emphasize that the genetic background of POAG is not addressed only through simple associations, but remains extremely complex.

5.1.2. Quality of evidence

Our research question was very complex as it pertained to different risk factors for POAG development: those potentially modifiable for preventive purposes and those that could serve as "markers" of high risk of POAG, although not necessarily modifiable.
Considering lifestyle factors (which are potentially modifiable) and co-morbidity factors (which, if present, could "signal" a potentially increased risk of glaucoma) different levels of quality of evidence were established:

- evidence of relationship between POAG and myopia (myopia can be treated, but treatment of myopia has no effect on the posterior segment and on the "link" between myopia and POAG) and circulating levels of homocysteine, folic acid, vitamin B12 and vitamin B6 (potentially modifiable by diet) – low quality of evidence; inconclusive;

- evidence of relationship between cigarette smoking (modifiable lifestyle) and POAG and between diabetes mellitus (DM) and POAG (potentially modifiable by treatment) – low quality of evidence from the existing systematic reviews/meta-analyses of primary studies. However, we identified several large cohort studies that provided high quality evidence about the relationship between DM, cigarette smoking and POAG.

Systematic reviews/meta-analyses addressing non-modifiable but "identifying" risk factors for POAG were exclusively genetic studies. The vast majority of these systematic reviews were of low quality and inconclusive. However, 3 pooled analyses of large GWAS studies provided high quality of evidence of a causative role of certain genes in POAG.

5.1.3. Potential biases in the overview process

We avoided any conclusions where the overall body of evidence was not at least of moderate quality. In this way, we avoided potential biases that could have been introduced by low-quality primary studies or systematic reviews.

Regarding potentially modifiable risk factors, high quality of evidence was available regarding smoking and DM as risk factors for POAG. However, this high quality evidence was not derived from the existing systematic reviews but from primary studies that we identified and meta-analysis that we performed. Protection from bias in this case was achieved by a thorough literature search and implementation of multivariate meta-analysis.

Regarding genetic factors in POAG; three pooled analyses of large GWAS studies provided high quality of evidence since all individual studies as well as the data pooling methodology were appropriate.

At the overview level, we could have introduced bias by omission of one systematic review that was written in Chinese.

5.1.4. Agreements and disagreements with other studies or reviews

To the best of our knowledge, this is the only overview of systematic reviews dealing with risk factors for POAG.

5.1.5. Conclusions

5.1.5.1. Implications for practice

Over the years, different studies proposed several modifiable and non-modifiable risk factors besides IOP to play a role in the POAG development. The present overview indicates that despite a large number of studies, elevated IOP still remains the major risk factor.

The observed association between DM and occurrence of POAG in women most likely has no practical relevance – the association was weak, indicating only a minor (if any) contribution of DM to POAG. *Vice-versa*, POAG is of only a minor relevance in the broad spectrum of consequences of DM.

The evidence about genetic factors in the development of POAG, at the moment, appears also to be of minor practical relevance – according to the existing data, individual genes provide only minor contributions to the risk of POAG and do not seem to be interesting as "markers" to be used in early detection of "subjects at a particular risk". However, these associations are particularly relevant in understanding the pathophysiology of POAG and potential development of future therapies.

5.1.5.2. Implications for research

A large number of potentially modifiable risk factors for POAG have been addressed over the years: lifestyle (e.g., smoking, alcohol consumption, physical activity, diet/nutrition) and co-morbidity (e.g., DM, hypertension, myopia), but most of them (apart from DM and smoking) apparently only superficially.

The existing data do not provide any relevant "signals" that relevant discoveries in this area should be expected. However, it should be kept in mind that low quality of evidence is no sound basis for either confirmative or negative conclusions. On the other hand, considerable developments have been made in the field of understanding the genetic basis of glaucoma – primarily in identification of genes and genetically determined "defects" in functioning of molecules involved in the development of glaucoma.

On one hand, these discoveries might, provide the basis for development of future therapies. On the other hand, they might set the grounds for evaluation of a potential interplay between genetically determined factors and modifiable factors.

5.2. Mono-compound IOP-lowering drugs in POAG/OHT

5.2.1. Overall completeness and applicability of evidence

The present work addressed only a segment of pharmacological treatment of glaucoma, i.e., only POAG/OHT and only mono-compound drugs, and aimed to address evidence of their relative efficacy, tolerability and cost-effectiveness profile specifically through evaluation of systematic review/meta-analysis and not individual trials.

The choice of the method resulted in the fact that all currently most commonly used mono-compound drugs were embraced by the present evaluation, but some older individual drugs or drug classes (e.g., α-agonists, β-blockers or CAI; cholinomimetics) and newer products like preservative-free formulations, were not - simply due to the fact that so far they have not been subject to systematic reviews. Cost-effectiveness profile of these drugs was not evaluated as no study related to this topic was found. However, these facts do not pose any major limitation to the present work.

Over the years, the evaluated drugs have positioned themselves as preferable to most of the older ones and have become standards. In respect to new developments, they could be considered as "of progressively declining interest". However, assessment of their relative efficacy and safety is of practical relevance for at least two reasons:

a) full evaluation of newer or emerging treatments will take some time;

b) new products, regardless of whether conveying conceptually new treatment options or "just" potential improvements to known strategies, are inevitably more expensive particularly considering the fact that "standards" are already available in generic versions.

While new options might eventually prove to be highly cost-effective, optimization of the use of pharmacological armamentarium at hand seems a reasonable effort.

5.2.2. Quality of evidence

Our research question was relatively complex as it pertained to a number of individual mono-compound drugs and also to both efficacy and safety.

None of the assessed reviews provided high quality evidence and five were considered to provide evidence of moderate quality. However, this judgment does not apply uniformly to all of the addressed topics.

A moderate quality body of evidence is available for:

a) assessment of relationships between PGAs latanoprost, bimatoprost and travoprost in respect to efficacy and incidence of conjunctival hyperemia;

b) assessment of relationships between the three PGAs and non-PGA compounds timolol, other β-blockers, brimonidine and CAI (dorzolamide, or combined data for dorzolamide and brinzolamide) in respect to efficacy and conjunctival hyperemia.

Evidence about relationships between non-PGA compounds regarding efficacy and evidence regarding any other safety/tolerability aspect apart from conjunctival hyperemia is of less than moderate quality.

5.2.3. Potential biases in the overview process

All conclusions on mutual treatment comparisons in the present overview are based on evidence of moderate quality. Where this level of quality was not available, no conclusions were drawn. In this way, the conclusions are fairly protected from biases that could have been introduced by the primary trials or systematic review methodological flaws.

At the overview level, we could have introduced bias by omission of one systematic review that was written in Chinese. Another source of bias could be the fact that we did not include individual studies, i.e., not even those published since the last systematic review on the topic.

5.2.4. Agreements and disagreements with other studies or reviews

To the best of our knowledge, this is the only overview of systematic reviews dealing with efficacy and safety of mono-compound IOP-lowering drugs in POAG/OHT.

5.2.5. Conclusions

5.2.5.1. Implications for practice

Over the years, PGAs have emerged as preferred mono-compound treatments in POAG/OHT. The present overview indicates that among PGAs, latanoprost has the most favorable trade-off between efficacy and tolerability.

Use of travoprost or bimatoprost as a first-line treatment of POAG/OHT is not very likely to result in a relevantly better efficacy, but is highly likely to result in conjunctival hyperaemia, a common cause of patient-driven discontinuation of treatment.

Non-PGA treatments should be considered as alternatives when PGAs are contraindicated or not tolerated. While traditionally *β*-blockers, particularly timolol, have been considered as the major non-PGA treatment option, there is no clear-cut evidence that supports preference of timolol over CAI or brimonidine either regarding efficacy or regarding safety.

5.2.5.2. Implications for research

The medications addressed in the present overview represent the current standard choice of mono-compound IOP-lowering drugs and are likely to remain relevant for at least some time in the future. Still, certain questions about their relative efficacy and tolerability cannot be answered with certainty since the body of available evidence does not meet the criteria of at least moderate quality. Furthermore, we could not find any systematic review/meta-analysis that evaluated cost-effectiveness profile of these drugs.

With the on-going pharmacological developments in the field, these drugs are not very likely to be engaged in major primary trials in the future. However, the number of the existing primary trials – those addressed in the overviewed systematic reviews and those published over the last few years (or still on-going) is considerable, and many of those are actually high-quality individual trials. Under such circumstances, new developments in the field of research synthesis seem a convenient and powerful tool for converting the existing primary data into evidence of relevant quality.

Many of the reviews assessed in the present work suffered for serious methodological limitations, but they could all be avoided. It appears likely that adequate quality of evidence could be generated with improved assessment of quality of the primary trials, inclusion of only high-quality primary data, appropriate assessment of data combinability, sensitivity analyses and appropriate implementation of "standard" and novel (network) data-pooling techniques.

6. OVERALL CONCLUSIONS

Despite a number of individual studies and systematic reviews in the field of POAG and continuous research interest in this topic, many questions still remain unanswered. Relationship between individual risk factors and development of POAG is difficult to prove as POAG most likely results from complex interactions between genetic and demographic, lifestyle, environmental and co-morbidity factors. Based on the available evidence evaluated in this overview we conclude that:

1. Several lifestyle factors (which are potentially modifiable) and co-morbidity factors (which, if present, could "signal" a potentially increased risk of glaucoma) apart from IOP were identified (smoking, DM, coffee or alcohol drinking, hormone replacement therapy, physical activity, diet, etc.).

2. Available evidence on most of the addressed potentially modifiable POAG risk factors in general derives from low quality reviews and primary trials, therefore data do not provide the basis for sound conclusions.

3. A few high quality individual cohort studies confirm that there is no association between smoking and the risk of POAG, whereas DM weakly increases the risk of POAG in women.

4. Available evidence on associations between occurrence of POAG and presence of certain genetic markers derives from very low quality reviews and primary trials, therefore were not further evaluated in the present work. Only 3 pooled analyses from large GWAS studies provide high quality evidence of involvement of several genetic "defects" in pathophysiology of POAG.

5. Observational studies with low risk of bias are needed to assess the relationship between POAG and risk factors. Long-term follow-up cohort studies, adjusted for confounders should be designed to assess non-genetic risk factors, whereas GWAS are needed for genetic ones.

6. Available evidence of at least moderate quality on efficacy and safety of mono-compound topical IOP-lowering medications in treatment of POAG/OHT was identified.

7. The existing evidence indicates that among prostaglandin analogues (PGAs), latanoprost has the most favourable trade-off between efficacy and tolerability.

8. Use of travoprost or bimatoprost as a first-line treatment is not very likely to result in a relevantly better efficacy, but is highly likely to result in conjunctival hyperaemia, a common cause of patient-driven discontinuation of treatment.

9. Non-PGA treatments should be considered as alternatives when PGAs are contraindicated or not tolerated. There is no clear-cut evidence that supports preference of timolol over carbonic anhydrase inhibitors or brimonidine either regarding efficacy or regarding safety.

7. SUMMARY

AIM: A systematic synthesis of the existing research evidence in the field of POAG is an appropriate methodological approach to achieve the aim of improved overall management of the disease. In the present study we focused on evidence on risk factors other than intraocular pressure (IOP) that are potentially modifiable and/or could be used for timely identification of people at high risk of POAG; and on relative efficacy, tolerability and cost-effectiveness profile of mono-compound topical IOP-lowering medications in treatment of POAG/OHT.
METHODS: Systematic review of systematic reviews/meta-analysis of primary prognostic studies and randomized controlled trials (RCTs). A thorough and sensitive search of Medline, Scopus and Cochrane Databases was performed. Methodological quality of reviews and quality of evidence were assessed using the AMSTAR checklist and the GRADE system, respectively. Comprehensive Meta-Analysis softaware version 2.2.064 2011 (Biostat Inc., Englewood, NJ, USA) and SAS for Windows 9.2 (SAS Institute Inc., Cary, NC, USA) (macros for multiple modifier meta-regression) were used for data analyses. Conclusions were based on the evaluation of the best available evidence.
RESULTS: 3606 records were identified through two different search strategies; 25 studies met the inclusion criteria for evaluation of POAG risk factors and 16 for the evaluation of efficacy and safety of mono-compound topical IOP-lowering drugs. Only six reviews achieved an overall "moderate" quality of evidence. Reviews dealing with risk factors were of low quality in general, whereas individual studies indicated that there were no association between smoking and POAG and a weakly increased risk of POAG in diabetic women. "Moderate quality" reviews dealing with therapy indicate that prostaglandin analogues (PGAs) should be considered equivalent regarding efficacy, but latanoprost is relevantly better tolerated than bimatoprost or latanoprost. Non-PGA compounds do not relevantly differ between each other in either efficacy or safety. Timolol and brimonidine are relevantly less effective than all PGAs. The same is true for CAI vs. bimatoprost. Regarding tolerability, timolol is superior to all PGAs and brimonidine and CAI are superior to bimatoprost.
Conclusion: Several potential risk factors for POAG apart from IOP were identified, however, no conclusion regarding their contribution could be drawn as the available information derives from low quality evidence. Available evidence of mono-compound IOP-lowering medications in treatment of POAG/OHT was identified. Moderate quality evidence indicates latanoprost as a mono-compound topical treatment with a most favourable trade-off between benefits and harms.

8. SAŽETAK

CILJ: U svrhu poboljšanja cjelokupnog upravljanja bolešću, poduzeta je sustavna sinteza postojećih znanja u području primarnog glaukoma otvorenog kuta (POAG). U ovom smo se istraživanju usredotočili na dokaze o postojanju čimbenika rizika za POAG, mimo povišenog intraokularnog tlaka (IOP), koji su potencijalno promjenjivi i/ili bi se mogli koristiti za pravovremenu identifikaciju ljudi s visokim rizikom za POAG; i na relativnu djelotvornost, podnošljivost i isplativost monokomponentnih topikalnih lijekova za snižavanje IOP u liječenju POAG, odnosno, okularne hipertenzije (OHT).

METODE: Pregled sustavnih pregleda/meta-analiza primarnih prognostičkih studija i randomiziranih kontroliranih pokusa (RCT). Poduzeto je temeljito i osjetljivo pretraživanje Medline, Scopus i Cochrane baze podataka. Metodološka kvaliteta ocijenjena pomoću AMSTAR ljestvice a ukupna kvaliteta dokaza uporabom GRADE sustava. Za analizu podatka korišteni su ComprehensiveMetaAnalysis softaware verzija 2.2.064 2011. (Biostat Inc., New Jersey, USA) i SAS za Windows 9.2 (SAS Inc., Cary, NJ, USA) (makro za multiplu meta-regresiju). Zaključci se temelje na najboljim dostupnim dokazima.

REZULTATI: Identificirano je 3606 zapisa uporabom dvije različite strategije pretraživanja; 25 studija zadovoljilo je kriterije za uključivanje u procjenu čimbenika rizika za POAG, a 16 studije za uključivanje u procjenu djelotvornosti i sigurnosti monokomponentnih topikalnih lijekova za snižavanje IOP u bolesnika s POAG/OHT. Samo šest sustavnih pregleda postiglo je "srednju" razinu kvalitete dokaza. Studije čimbenika rizika bile su, sveukupno, niske kvalitete, a pojedinačne studije pokazale su da nema povezanosti između pušenja i POAG, te da je u žena s dijabetesom blago povećan rizik za nastanak POAG. Dokazi " srednje kvalitete" pokazuju da prostaglandinske analoge (PGA) treba smatrati ekvivalentnima u pogledu djelovornosti, te da je latanoprost znatno bolje podnošljiv od travoprosta i bimatoprosta.. Ostali, „ne-PGA“, lijekovi, ne razlikuju se bitno jedni od drugih u pogledu djelotvornosti i sigurnosti. Timolol i brimonidin relevantno su manje djelotvorni od svih PGA. Isto vrijedi i za inhibitore karboanhidraze (CAI) u usporedbi s bimatoprostom. U pogledu podnošljivosti, timolol je superioran u odnosu na sve PGA i brimonidin, a CAI su superiorni bimatoprostu.

ZAKLJUČAK: Identificirano je nekoliko potencijalnih čimbenika rizika za POAG osim IOP, međutim, s obzirom na nisku razinu dokaza, nisu mogući racionalni zaključci o doprinosu pojedinih čimbenika riziku za nastanak POAG. Dokazi srednje kvalitete pokazuju da kao monokomponentni topikalni tretman, latanoprost ima najbolji odnos djelotvornosti i sigurnosti.

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10. CURRICULUM VITAE

Name: Qëndresë Daka

Date of birth: 27/May/1984

Place of birth: Prishtinë, Kosovo

Nationality: Kosovo

Affiliation: Department of Ophthalmology; University Clinical Centre Of Kosova

Department of Patophysiology; Medical Faculty, University Of Prishtina, Kosovo

Education: 2010/11- PhD studies "Biomedicine and Health Sciences"; School of Medicine, University of Zagreb, Croatia

2010 - 2014 Resident of Ophthalmology; University Clinical Centre Of Kosova

2002/03 - 2007/08 Medical School; University Of Prishtina, Kosovo

Work experience:

2009 - 2011 Department of Pharmacology; Medical Faculty, University Of Prishtina, Kosovo

2008 - 2009 Department of Physiology of Sports; Faculty of Physical Education and Sports, University of Prishtina, Kosovo

2008 - 2010 Kosovo Commission for Medicines Evaluation; Ministry of Health, Kosovo Medicines Agency, Kosovo

Other:

2013-2014 Department of Ophthalmology; University Clinical Centre of Ljubljana, Slovenia

October 2013 Salzburg Medical Seminars, Salzburg, Austria

September 2011 Berlin School of Public Health at Charite, Berlin, Germany

2007 Dartmouth Hitchcock Medical Centre, Dartmouth New Hampshire, USA

Volunteer of Kosova Red Cross and" The Foundation for Healthy Mothers and Babies"

Language: Albanian, English, German, Slovenian, Serbo-Croatian.

Publication from this study: Daka Q, Trkulja V. Efficacy and tolerability of mono-compound topical treatments for reduction of intraocular pressure in patients with primary open angle glaucoma or ocular hypertension: an overview of reviews. Croat Med J. 2014;55:468-80.