



PubliComm

Via Paleocapa 17/7
17100 Savona - Italy
www.publicomm.it

GECA Srl
Printed in EU
October 2020

Copyright © 2020 European Glaucoma Society

No parts of this text, illustrations, tables or flowcharts can be reproduced, copied, translated or stored by any means including magnetic, electronic or multimedia formats without written permission of the European Glaucoma Society.

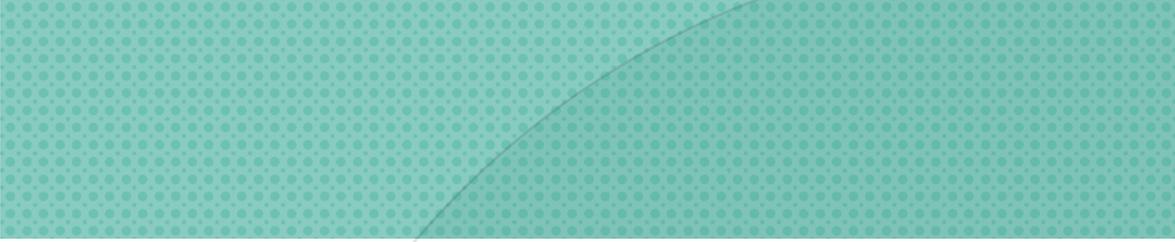
5th Edition

TERMINOLOGY
and **GUIDELINES**
for **GLAUCOMA**



European Glaucoma Society

Innovation, Education, Communication, Implementation



Contents

	Page
Foreword	10
Glossary	14
Part I	17
I.1 Background to Guideline development	19
I.2 Mission statement	19
I.3 Key questions and evidence-based recommendations	20
I.4 Things to avoid - choosing wisely	28
I.5 What matters to patients	30
I.5.1 Anxiety associated with glaucoma	
I.5.2 The information gap	
I.6 Glaucoma epidemiology	33
I.6.1 Burden of glaucoma	
I.6.2 Natural history of glaucoma and blindness	
I.6.3 Risk factors for glaucoma	
I.6.4 Under- and overdiagnosis of glaucoma	
I.7 Landmark randomised controlled trials for glaucoma	36
I.7.1 Treatment vs no treatment trials in open angle	
I.7.1.1 Collaborative normal tension glaucoma study (CNTGS)	
I.7.1.2 The ocular hypertension treatment study (OHTS)	
I.6.1.3 European glaucoma prevention study (EGPS)	
I.7.1.4 Early manifest glaucoma trial (EMGT)	
I.7.1.5 United Kingdom glaucoma treatment study (UKGTS)	
I.7.2 Treatment vs. no treatment trials on angle closure	
I.7.2.1 The ZAP trial	
I.7.3 Studies comparing treatments in open angle	
I.7.3.1 Advanced glaucoma intervention Study (AGIS)	
I.7.3.2 Collaborative initial glaucoma treatment study (CIGTS)	
I.7.3.3 The LiGHT trial	
I.7.4 Studies comparing treatments in angle closure	
I.7.4.1 Effectiveness of early lens extraction for the treatment of primary angle closure glaucoma (EAGLE)	
I.8 Cost-effectiveness of glaucoma care	49
I.8.1 Case detection and screening for glaucoma	
I.8.2 Clinical and cost effectiveness of diagnostic tests used for screening, detection and monitoring for glaucoma	
I.8.3 Effectiveness of treatment of glaucoma and ocular hypertension in preventing visual disability	
I.8.4 Follow-up practices and models of care	
I.9 Terminology and classification	51

Contents

	Page
Part II	
Chapter 1	53
II.1.1 Intraocular pressure and tonometry	55
II.1.1.1 Methods of measurement	
II.1.1.1.1 Goldmann applanation tonometry	
II.1.1.1.2 Alternative tonometers	
II.1.1.1.3 Self-tonometry	
II.1.1.2 Intraocular pressure and central corneal thickness	
II.1.2 Gonioscopy	60
II.1.2.1 Anatomy	
II.1.2.1.1 Reference landmarks	
II.1.2.1.2 Other anatomical features	
II.1.2.2 Techniques	
II.1.2.2.1 Gonioscopy technique without indentation	
II.1.2.2.2 'Dynamic' gonioscopy by indentation or compression	
II.1.2.3 Grading of the anterior chamber angle	
II.1.2.3.1 Slit lamp-grading of peripheral AC depth - The Van Herick method	
II.1.2.4 Anterior segment imaging techniques	
II.1.3 Optic nerve head and retinal nerve fibre layer	70
II.1.3.1 Clinical examination	
II.1.3.1.1 Neuroretinal rim	
II.1.3.1.2 Retinal nerve fibre layer	
II.1.3.1.3 Optic disc haemorrhages	
II.1.3.1.4 Vessels at the optic disc	
II.1.3.1.5 Parapapillary atrophy	
II.1.3.1.6 Optic disc size	
II.1.3.1.7 Rim width and cup to disc ratio	
II.1.3.2 Recording of the optic nerve head and RNFL features	
II.1.3.2.1 Quantitative imaging	
II.1.3.2.2 OCT for glaucoma diagnosis	
II.1.3.2.3 Detection of progression with OCT	
II.1.4 Perimetry	80
II.1.4.1 Perimetry techniques	
II.1.4.1.1 Automated threshold perimetry	
II.1.4.1.2 Non-conventional perimetry	
II.1.4.1.3 Patient instructions	
II.1.4.2 Interpreting test results	
II.1.4.2.1 Test data elements commonly seen in perimetry reports	
II.1.4.2.2 Reliability indices	
II.1.4.2.3 Visual field indices	

Contents

	Page
II.1.4.2.4 Interpretation methods and aids	
II.1.4.2.5 Confirmation of classification	
II.1.4.2.6 Detecting and quantifying glaucomatous visual field deterioration	
II.1.4.2.7 Number and frequency of tests	
II.1.4.3 Staging of visual field defects	
II.1.5 Artificial intelligence	86
II.1.6 Genetics	87
II.1.6.1 Mendelian mutations	
II.1.6.2 Complex variants	
II.1.6.3 Third party genotyping	
Chapter 2	91
II.2.1 Primary childhood glaucomas / Juvenile glaucomas	93
II.2.1.1 Primary congenital glaucoma: from birth to the first years of life	
II.2.1.2 Late-onset childhood open angle glaucoma with onset from more than two years of age to puberty	
II.2.1.3 Secondary childhood glaucoma	
II.2.1.3.1 Glaucoma associated with non-acquired ocular anomalies	
II.2.1.3.2 Glaucoma associated with non-acquired systemic disease or syndrome	
II.2.1.3.3 Glaucoma associated with acquired condition	
II.2.1.3.4 Glaucoma following childhood cataract surgery	
II.2.2 Open angle glaucoma	97
II.2.2.1 Primary open angle glaucoma	
II.2.2.1.1 Primary late-onset juvenile glaucoma	
II.2.2.1.2 Primary open angle glaucoma suspect	
II.2.2.1.3 Ocular hypertension	
II.2.3 Secondary open angle glaucomas	102
II.2.3.1 Secondary open angle glaucomas caused by ocular disease	
II.2.3.1.1 Pseudoexfoliative or exfoliative glaucoma	
II.2.3.1.2 Pigmentary glaucoma	
II.2.3.1.3 Lens-induced open angle glaucoma	
II.2.3.1.4 Glaucoma associated with intraocular haemorrhage	
II.2.3.1.5 Uveitic glaucoma	
II.2.3.1.6 Neovascular glaucoma	
II.2.3.1.7 Glaucoma due to intraocular tumours	
II.2.3.2 Secondary open angle glaucoma due to ocular trauma	
II.2.3.3 Iatrogenic secondary open angle glaucomas	
II.2.3.3.1 Glaucoma due to corticosteroid treatment	
II.2.3.3.2 Secondary open angle glaucoma due to ocular surgery and laser	
II.2.3.3.3 Glaucoma associated with vitreoretinal surgery	

Contents

	Page
II.2.3.4 Secondary open angle glaucoma caused by extraocular disease	
II.2.3.4.1 Glaucoma caused by increased episcleral venous pressure	
II.2.4 Angle closure	110
II.2.4.1 Primary angle closure	
II.2.4.1.1 Primary angle closure suspect or 'occludable' angle	
II.2.4.1.2 Primary angle closure and primary angle closure glaucoma	
II.2.4.1.3 Acute angle closure attack due to pupillary block or mixed mechanisms	
II.2.4.1.4 Status post-acute angle closure attack	
II.2.5 Secondary angle closure	118
II.2.5.1 Secondary angle closure with pupillary block	
II.2.5.2 Secondary angle closure with anterior 'pulling' mechanism synechial closure without pupillary block	
II.2.5.2.1 Neovascular glaucoma	
II.2.5.2.2 Iridocorneal endothelial syndrome	
II.2.5.2.3 Epithelial and fibrous ingrowth after anterior segment surgery or penetrating trauma	
II.2.5.3 Secondary angle closure with posterior 'pushing' mechanism without pupillary block	
II.2.5.3.1 Aqueous misdirection or malignant glaucoma	
II.2.5.3.2 Iris and ciliary body cysts, intraocular tumors	
II.2.5.3.3 Silicon oil or other tamponading fluids or gas implanted in the vitreous cavity	
II.2.5.3.4 Uveal effusion causing angle closure	
II.2.5.3.5 Retinopathy of prematurity (stage V)	
II.2.5.3.6 Congenital anomalies that can be associated with secondary angle closure glaucoma	
Chapter 3	125
II.3.1 General principles of glaucoma treatment	127
II.3.2 Treatment options	131
II.3.3 Target IOP	131
II.3.3.1 Setting the target IOP	
II.3.3.2 Achieving and re-evaluating the target IOP	
II.3.4 General principles of medical management	136
II.3.4.1 Start with monotherapy	
II.3.4.2 Switch to another monotherapy	
II.3.4.3 Add second drug / combination therapy	
II.3.5 IOP-lowering drugs	142
II.3.5.1 Prostaglandin analogues	

Contents

	Page
II.3.5.2 Local toxicity of topical treatment: the role of preservatives	
II.3.5.3 Generic IOP-lowering topical medications	
II.3.6 Dietary supplementation and alternative therapies and glaucoma	150
II.3.7 Management of glaucoma during pregnancy and breast-feeding	150
II.3.8 Neuroprotection and glaucoma treatment	154
II.3.9 Practical considerations related to topical medical treatment	154
II.3.10 Adherence, compliance and persistence in glaucoma	155
II.3.10.1 Terminology	
II.3.10.2 Factors associated with non-adherence	
II.3.10.3 Identifying non-adherence	
II.3.10.4 Improving adherence	
II.3.11 Laser surgery	156
II.3.11.1 Laser peripheral iridotomy	
II.3.11.2 Laser trabeculoplasty	
II.3.11.3 Thermal laser peripheral iridoplasty	
II.3.12 Cyclodestructive procedures	161
II.3.13 Incisional surgery	162
II.3.13.1 General principles	
II.3.13.2 Techniques	
II.3.13.2.1 Penetrating glaucoma surgery	
II.3.13.2.1.1 Trabeculectomy	
II.3.13.2.1.2 Trabeculotomy and goniotomy	
II.3.13.2.2 Non-penetrating glaucoma surgery	
II.3.13.2.3 Long-tube glaucoma drainage devices	
II.3.13.2.4 Additional surgical techniques	
II.3.13.3 Methods of preventing filtering bleb scarring	
II.3.13.3.1 Antifibrotic agents	
II.3.13.3.1.1 General precautions for the use of anti-fibrotics	
II.3.13.3.1.2 Administration	
II.3.13.3.2 Alternative methods of preventing filtering bleb scarring	
II.3.14 Cataract and glaucoma surgery	169

Foreword

The only time is now. Every “now” is unique. Responsible persons ask themselves, “How can I act well now?” The answers will differ for every person, because just as every situation is unique, so is every person different from every other person. But surely there must be some algorithm that will assist us in coming to the right answer. Unfortunately, no, for there is no right answer. There is only an answer that is as appropriate as we can conclude at that moment in that situation. No written guidelines can apply appropriately to every unique situation.

Unfortunately we physicians have been suckled on a fallacy: “What’s good for the goose is good for the gander.” Phrased in medical terms, “normal findings are good, and abnormal findings are bad.” This is too simple, and often wrong.

Good clinicians know that care must be personalized for it to be optimal. So-called normal findings give rough guidance, sometimes applicable to groups, but frequently wrong for individuals. Consider intraocular pressure (IOP). A normal IOP of 15 mmHg good for some and bad for others, and an abnormal IOP of 30 mmHg is good for some and bad for others. We are so bombarded by the myth of the sanctity of the standard distribution curve that it is hard to think independently and specifically. Also, unfortunately, doctors are prone to decide for patients, often on the basis of normative data that is not relevant or important for the particular patient. That we do this is not surprising, as we want to help, and so we default to what seems to be the easy, safe (non-thinking) way, in which we do not have to hold ourselves accountable for the outcome.

Somebody HAS to decide, or else we would be living in an anarchical world. Also true. And because none of us knows as much as we need to know to act appropriately, we seek advice from so-called “experts.” For us to care for people well it is essential that we consider what others recommend. So we look to experts, as we should. However, experts are sometimes right and sometimes wrong. Remember that von Graefe in 1860 recommended surgical iridectomy for all glaucoma, Elliot recommended mustard plaster between the shoulders for glaucoma, Becker based treatment on tonographic findings, Weve reported 100% success with penetrating cyclotherapy in glaucoma, Lichter advised against laser trabeculoplasty, many thought Cypass was great, and the investigators in

Foreword

the Advanced Glaucoma Intervention Study indicated that an IOP usually around 12 mmHg was better than one usually around 20 mmHg. All wrong. What the authors of these guidelines have done excellently, is to provide a general framework on which ophthalmologists can hang pieces of evidence, so as to be able to evaluate the validity and the importance of that evidence. In doing this meticulously they have provided a valuable service to all ophthalmologists, none of whom individually have either the time or the skill to be fully informed. In their own practices the authors consider whether valid information is relevant for the particular person being considered. That process of considering relevance is essential, always. And relevance is based on the particular unique patient, unique doctor and unique situation. The only guideline the authors can provide in this regard is to remind us all to consider relevance with all patients in all situations, and from the patient's perspective. Even more important than the service to ophthalmologists is the benefit to patients that will result from thoughtful use of these guidelines. We need, also, to remember that diagnoses are generic, and that within every diagnosis there are differences. For example what does a diagnosis of primary open angle mean? Some of those affected will rapidly go blind despite the most thoughtful treatment and others will keep their sight even without treatment. What does a diagnosis of Chandler's Syndrome mean? In some, surgery works well, and, in others, poorly. So one never directs diagnosis and treatment at a condition, but rather at the person, the objective being the wellness of that person. The previous European Glaucoma Society Guidelines are used internationally. It is good that the EGS is again providing updated, useful information. The Guidelines are a practical, inspirational contribution.

*George L. Spaeth, BA, MD.
Esposito Research Professor, Wills Eye Hospital/Sidney Kimmel Medical
College/Thomas Jefferson University*



The Guidelines Writers, Authors and Contributors

Augusto Azuara-Blanco
(*Editor*)

Luca Bagnasco
Alessandro Bagnis
Joao Barbosa Breda
Chiara Bonzano
Andrei Brezhnev
Alain Bron
Carlo A. Cutolo
Barbara Cvenkel
Stefano Gandolfi
Ted Garway Heath
Ilmira Gazizova
Gus Gazzard
Franz Grehn
Anders Heijl
Cornelia Hirn
Gábor Holló
Anton Hommer
Michele lester
Ingrida Januleviciene
Gauti Jóhannesson
Miriam Kolko
Tianjing Li
José Martínez de la Casa
Frances Meier-Gibbons
Maria Musolino
Marta Pazos
Norbert Pfeiffer
Sergey Petrov
Luis Abegao Pinto
Riccardo Scotto
Ingeborg Stalmans
Gordana Sunaric
Mégevand
Ernst Tamm
John Thygesen
Fotis Topouzis
Marc Töteberg-Harms
Carlo E. Traverso
(*Editor*)
Anja Tuulonen
Zoya Veselovskaya
Ananth Viswanathan
Ilgaz Yalvac
Thierry Zeyen

Guidelines Committee

Augusto Azuara-Blanco
(*Chair*)
Carlo E. Traverso
(*Co-chair*)
Manuele Michelessi
(*NGP Co-chair*)

Luis Abegao Pinto
Michele lester
Joao Breda
Carlo A. Cutolo
Panayiota Founti
Gerhard Garhoefer
Andreas Katsanos
Miriam Kolko
Francesco Oddone
Marta Pazos
Verena Prokosch-Willing
Acknowledgments
Cedric Schweitzer
Andrew Tatham
Marc Toteberg-Harms

Aknowledgments

Anja Tuulonen
Ted Garway Heath
Richard Wormald
Tianjing Li
Manuele Michelessi
Jenny Burr
Azuara-Blanco
for their methodological oversight.
Tianjing Li and
Riaz Qureshi
(US Cochrane Eye
and Vision Group) and
Manuele Michelessi
(EGS) for leading the
evidence review.

Manuele Michelessi
Gianni Virgili
Joao Barbosa Breda
Carlo A. Cutolo
Marta Pazos
Andreas Katsanos
Gerhard Garhofer
Miriam Kolko
Verena Prokosch
Panayota Founti
Francesco Oddone
Ali Ahmed Al Rajhi
Tianjing Li
Riaz Qureshi
and Azuara-Blanco
for their contribution to
the evidence review.

Karen Osborn and
Joanna Bradley from
Glaucoma UK charity
for their contribution
to the section: 'What
matters to patients'
(<https://glaucoma.uk>)

Additional contributions were made by the following people on specific topics

Eleftherios
Anastasopoulos
Panayiota Founti
Gus Gazzard
Franz Grehn
Anders Heijl
Gábor Holló
Fotis Topouzis
Anja Tuulonen
Ananth Viswanatham

The team of Clinica Oculistica of the University of Genoa for medical editing and illustrations

Luca Bagnasco
Alessandro Bagnis
Chiara Bonzano
Carlo A. Cutolo
Michele lester
Maria Musolino
Roberta Parodi
Riccardo Scotto

We would like to thank the following colleagues for their help in reviewing/ editing section 1.7. Landmark randomised controlled trials for glaucoma

Joe Caprioli
Ted Garway Heath
Gus Gazzard
Divakar Gupta
Anders Heijl
Michael Kass
Stefano Miglior
David Musch
Norbert Pfeiffer
Thierry Zeyen

External reviews

We would like to thank
the following societies
and experts: World
Glaucoma Association:
Parul Ichhpujani

Monisha Nongpiur
Tanuj Dada
Sola Olawoye
Jayme Vianna
Min Hee Suh
Farouk Garba
Simon Skalicky
Alex Huang
Farouk Garba
Pradeep Ramulu
Verena Prokosch
Carolina Gracitelli;
American Glaucoma
Society; Josh Stein;
and Latin-American
Glaucoma Society:
Daniel Grigera

We would like to thank
the external reviewers
whose comments
are listed on [https://
www.eugs.org/eng/
guidelines.asp](https://www.eugs.org/eng/guidelines.asp)

The EGS executive committee

Ted Garway Heath
(*President*)
Fotis Topouzis
(*Vice President*)
Ingeborg Stalmans
(*Treasurer*)
Anja Tuulonen
(*Past President*)
Luis Abegao Pinto
Andrei Brezhnev
Alain Bron
Gauti Jóhannesson
Norbert Pfeiffer

The board of the European Glaucoma Society Foundation

Carlo E. Traverso
(*Chair*)
Fotis Topouzis
(*Vice Chair*)
Franz Grehn
Anders Heijl
John Thygesen
Thierry Zeyen

Glossary

5-FU	5-fluorouracil
AAC	Acute angle closure
ACG	Angle closure glaucoma
AGIS	Advanced glaucoma intervention study
AH	Aqueous humour
AI	Artificial intelligence
ALT	Argon laser trabeculoplasty
BAC	Benzalkonium chloride
CCT	Central corneal thickness
CDR	Cup to disc ratio
CIGTS	Initial glaucoma treatment study
CNTGS	Collaborative normal tension glaucoma study
DCT	Dynamic contour tonometry
EAGLE	Effectiveness of early lens extraction for the treatment of primary angle closure glaucoma
EGPS	European glaucoma prevention study
EGS	European glaucoma society
EMA	The european medicines agency
EMGT	Early manifest glaucoma trial
FC	Flow chart
FDT	Frequency doubling technology
FC	Fixed combination
FL	Fixation losses
FN	False negatives
FP	False positive
GAT	Goldmann applanation tonometry
GHT	The glaucoma hemifield test
GRADE	Grading of recommendations, assessment, development and evaluations
HRT	Heidelberg retina tomography
ICE	Irido-corneal endothelial syndrome
IOL	Intraocular lens
IOP	Intraocular pressure
ITC	Iridotrabecular contact
IV	Intravenous
LIGHT	Laser in glaucoma and ocular hypertension trial
LPI	Laser peripheral iridotomy
LV	Loss variance
MD	Mean defect or mean deviation
MMC	Mitomycin C
NCT	Non-contact tonometry
Nd:YAG	Neodymium-doped yttrium aluminum garnet
NTG	Normal tension glaucoma
OAG	Open angle glaucoma
OCT	Optical coherence tomography
OHT	Ocular hypertension
OHTS	The ocular hypertension treatment study
ONH	Optic nerve head
ORA	Ocular response analyser

Glossary

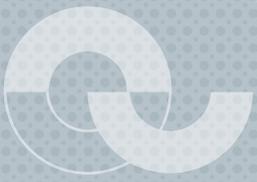
OSD	Ocular surface disease
PAC	Primary angle closure
PACG	Primary angle closure glaucoma
PACS	Primary angle closure suspect
PAS	Peripheral anterior synechiae
PCG	Primary congenital glaucoma
PDS	Pigment dispersion syndrome
PGA	Prostaglandin analogue
POAG	Primary open angle glaucoma
PG	Pigmentary glaucoma
PSD	Pattern standard deviation
PXF	Pseudoexfoliation syndrome
PXFG	Pseudoexfoliation glaucoma
RCT	Randomised controlled trial
RNFL	Retinal nerve fiber layer
RoP	Rate of progression
SAP	Standard automated perimetry
SITA	Swedish interactive threshold algorithm
SLT	Selective laser trabeculoplasty
SWAP	Short-wavelength automated perimetry
TLPI	Thermal laser peripheral iridoplasty
TM	Trabecular meshwork
UBM	Ultrasound biomicroscopy
UGH	Uveitis-glaucoma-hyphema syndrome
UKGTS	United Kingdom glaucoma treatment study
VEGF	Vascular endothelial growth factor
VF	Visual field
VFI	Visual field index
ZAP	Zhongshan angle closure prevention trial





Part I





I.1 Background to Guideline development

The aim of these Guidelines is to support ophthalmologists in managing people with, or at risk of, glaucoma, and to provide useful information to trainees. For this 5th edition, we initiated the process to update the Guidelines by identifying key questions on diagnosis, monitoring and treatment that were then prioritised by a group of experts. To answer these key questions, we identified and assessed currently available evidence. Evidence was gathered in 2019 in collaboration with the USA-Cochrane Eyes and Vision Group by conducting an overview of systematic reviews on glaucoma interventions and diagnostic technologies (see I.3). Differing from previous editions, a grading system for rating the quality of evidence and strength of recommendation, following grading of recommendations, assessment, development and evaluations (GRADE), has been used only for answering our key questions. The rest of recommendations and suggestions throughout the text are consensus based among experts.

In this 5th edition we chose to provide only references of high-quality systematic reviews, landmark glaucoma trials and population-based studies. This is because we recognise that the process of selecting references to include in guidelines can be biased, and most publications do not provide direct information for clinical decision making and there is a risk of misinterpretation of information by non-experienced readers.

Patients' care and wellbeing are at the core of our values and we collaborated with the Glaucoma UK charity which has helped us to confirm the most important questions that ophthalmologists should ask patients with glaucoma, and to identify what are their most common concerns.

The Guidelines should be considered as a guidance rather than strict decision-making protocols.

Decision making ultimately should be individualised to patients' needs and circumstances, ideally guided by best available evidence.

The European Glaucoma Society (EGS) and all contributors disclaim responsibility and all liability for any adverse medical or legal effects resulting directly or indirectly from the use of any of the definitions, diagnostic techniques or treatments described in the Guidelines. The EGS does not endorse any product, procedure, company or organisation.

I.2 Mission statement

The goal of care for people with, or at risk of, glaucoma is to promote their well-being and quality of life (QoL) within a sustainable health care system. Well-being and QoL are influenced by a person's visual function, the psychological impact of having a chronic progressive sight-threatening condition and the costs and side-effects of treatments. Costs include inconveniences to the individual and their care givers as well as the financial cost of examinations, diagnostic procedures and therapies, both to the individual and society. The effect of visual function on well-being and QoL is variable; in general, early to moderate glaucoma has only a modest influence, whereas advanced visual function loss in both eyes may considerably reduce QoL.

I.3 Key questions and evidence-based recommendations

Methods:

Topics and questions were prioritised by a group of experts during two dedicated meetings (October 2018 Camogli, Italy and February 2019 Mainz, Germany). Evidence pertinent to these questions was gathered in collaboration with the USA-Cochrane Eyes and Vision Group by conducting an overview of systematic reviews on glaucoma interventions and diagnostic technologies (see <https://www.eugs.org/eng/guidelines.asp>).

Recommendations are proposed using GRADE methodology, according to the level of evidence: high, moderate, low, very low; as well as strength of recommendation: strong or weak. A strong recommendation should be interpreted as “we recommend” and/or “very relevant in clinical practice”, and a weak recommendation as “we suggest” and/or “less relevant in clinical practice”.

Evidence and strength of recommendations were discussed among experts and scientists in a 3-day meeting in Genoa, Italy in November 2019.

Q1. What are the recommended tests at first assessment?

The following tests are recommended at first assessment:

Visual acuity and refractive error (strength of recommendation: strong)

Slit lamp examination (strength of recommendation: strong)

Gonioscopy (strength of recommendation: strong)

Tonometry (strength of recommendation: strong)

Central corneal thickness (CCT) (strength of recommendation: weak) - Use of CCT-adjusted intraocular pressure (IOP) values is not recommended.

Visual field (VF) testing (strength of recommendation: strong)

Clinical assessment of the optic nerve head (ONH), retinal nerve fiber layer (RNFL) and macula. Binocular examination under pupil dilatation is preferable (except in angle closure). Optic disc and RNFL photography can be used (strength of recommendation: strong)

Optical coherence tomography (OCT) of disc/RNFL/macula can be useful but the diagnosis of glaucoma cannot be made on the basis of OCT alone. (strength of recommendation: weak)

Level of evidence: The direct evidence addressing this specific question is ‘very low’ for all recommendations.

Q2. Alternative tonometers other than Goldmann applanation tonometry (GAT): are they recommended in clinical practice?

Recommendation: Consensus could not be reached about which alternative tonometers other than GAT can be used in clinical practice.

Level of evidence: very low

Strength of recommendation: weak

Comment: Many forms of tonometry have been licensed for clinical use through comparison with GAT which is considered the current reference standard.

In general, all measurements with tonometers which applanate the cornea are influenced by corneal biomechanics (both geometry, e.g. thickness and curvature, and material properties, e.g. stiffness and viscoelasticity). The effect is greater with tonometers which applanate the cornea more quickly (such as air-puff and rebound tonometers).

In recent times, new tonometers have been introduced which intend to make IOP measurements less influenced by corneal parameters. The impact of tonometer inaccuracy and/or imprecision on clinical outcomes has not been established.

There is sizeable inter- and intra-observer variability observed for all tonometers, including GAT.

The accuracy and precision of a tonometer should influence the choice for use in clinic. For a given patient, the same tonometer should be used for follow-up.

Q3. Is it recommended to set a target IOP?

Recommendation: A target IOP should be set as a treatment goal at diagnosis. Target IOP should be updated at each monitoring visit on the basis of changes in glaucoma or other ocular or systemic diseases.

Level of evidence: low

Strength of recommendation: strong

Comment: Therapy in glaucoma management aims to lower IOP to slow the rate of VF deterioration sufficient to maintain the patient's QoL.

Target IOP is the upper limit of IOP judged to be compatible with this treatment goal. We recommend the use of target IOP. It should be re-evaluated regularly and modified accordingly when progression of the disease is identified or when ocular or systemic comorbidities develop. If the target IOP has not been reached, but the glaucoma is stable, then the target may be revised upwards. There is no single target IOP level that is appropriate for every patient, so the target IOP needs to be estimated separately for each eye of every patient, and adapted to changing patient status.

Q4. Central corneal thickness (CCT): is it recommended to use CCT to risk profile patients? (see also Q1 and Q2)

Recommendation: CCT may be useful for baseline risk profiling.
Level of evidence: low
Strength of recommendation: weak

Comment: CCT is one parameter which influences the accuracy of most tonometers. In eyes with thin corneas IOP tends to be underestimated. Thinner CCT is associated with a higher risk of conversion of ocular hypertension (OHT) to glaucoma and a higher risk of glaucoma progression in multiple variable models. However there is no strong evidence that CCT is an independent risk factor. IOP correction algorithms based on CCT are not validated and should be avoided.

Q5. Anterior chamber angle evaluation with imaging tests: are they recommended to diagnose people with angle closure?

Recommendation: Anterior chamber angle imaging cannot replace gonioscopy. Gonioscopy should be performed in every patient being evaluated for glaucoma.
Level of evidence: low
Strength of recommendation: strong

Comment: Anterior chamber angle imaging devices can be useful to identify the iris configuration of a narrow angle, to assess the influence of the lens, for triage or in eyes where the angle cannot be visualised by gonioscopy. However anterior chamber angle imaging should not replace gonioscopy since features as peripheral anterior synechia, pigment and other secondary causes of trabecular dysfunction may be missed.

Q6. Optical coherence tomography (OCT): what is the role of OCT for diagnosis of glaucoma? Answered in Q1 (see also flow chart (FC) III).

Q7. What are the recommended tests for monitoring?

Visual acuity (strength of recommendation: strong)

VF testing (strength of recommendation: strong) - Same instrument and strategy are recommended for follow-up tests

Use software-based progression analyses

VF remains the most important test to monitor progression

Clinical examination of the optic disc and RNFL (strength of recommendation: strong).

Tonometry (strength of recommendation: strong)

OCT disc/RNFL/macula imaging (strength of recommendation: weak)

OCT disc/RNFL/macula scan using the same instrument with the software-based analysis can be useful

OCT progression analysis cannot replace VF progression analysis

At present OCT progression analysis is not age-corrected (there is an aging-related decline)

Apparent OCT progression and VF progression are not always correlated

Repeated gonioscopy in some circumstances (strength of recommendation: weak)

Level of evidence: The direct evidence addressing this specific question is 'very low' for all recommendations.

Q8. What is the role of OCT for monitoring glaucoma? Answered in Q7

Q9. Alternative models of care: virtual clinics / asynchronous decision making: are they acceptable?

Recommendation: virtual clinics / asynchronous decision making can be an efficient way of delivering glaucoma care.

Level of evidence: very low

Strength of recommendation: weak

Comment: Models of care with virtual clinics / asynchronous decision making are potentially valuable when improvements in access to care is needed. Proper governance and safety measures must be in place. Patients acceptability and preferences should be confirmed.

Q10. Medical treatment: what is the most effective and what is the first-choice medication for open angle glaucoma?

Recommendation: Prostaglandin analogues (PGAs) are the most effective medication and they are usually recommended as first choice treatment for open angle glaucoma.

Level of evidence: High for IOP reduction but very low for other outcomes.

Strength of recommendation: strong

Comment: Factors like possible adverse effects, co-morbidities, systemic therapy, adherence, patient preferences, life expectancy, cost and availability should be considered in selecting a drug for a given patient.

Q11. What interventions can improve adherence to medical treatment?

Recommendation: simplified regime, education, effective communication (e.g., ask open questions), alarms/messages.

Level of evidence: very low

Strength of recommendation: weak

Q12. Is selective laser trabeculoplasty (SLT) recommended as initial treatment?

Recommendation: SLT can be offered as a first choice treatment for open angle glaucoma.

Level of evidence: moderate (only one high quality trial, LiGHT see I.7.3.3)

Strength of recommendation: strong

Comment: One high quality trial showed that SLT is at least as effective as eye drops and SLT should be considered as an option for initial treatment in patients with mild or moderate open angle glaucoma or OHT (LiGHT trial, see I.7.3.3). There is no evidence regarding effectiveness of SLT in patients with severe glaucoma and pigmentary glaucoma (PG). SLT and argon laser trabeculoplasty (ALT) probably have similar efficacy. Factors like co-morbidities, systemic therapy, adherence, ability to administer drops, patient preference, cost and availability should be considered when offering laser trabeculoplasty as a first choice treatment.

Q13. What is the recommended surgical treatment for open angle glaucoma?

Recommendation: Trabeculectomy augmented with antifibrotic agents is recommended as an initial surgical treatment for open angle glaucoma.

Level of evidence: low

Strength of recommendation: strong

Comment: Trabeculectomy with antifibrotic agents is the standard glaucoma surgical procedure. Depending on patient circumstances such as target pressure, safety profile and patient preferences, other options can be considered, e.g., drainage devices (glaucoma shunts) in people with high risk of trabeculectomy failure, or less invasive filtering surgery, or bleb-less surgery such as canaloplasty, or minimally invasive glaucoma surgery in people with early disease may be considered. Factors like cost, availability and surgeon's preference should also be considered when selecting a type of surgery.

Combined glaucoma surgery with phacoemulsification may be considered in some patients with coexisting glaucoma and cataract.

Q14. What is the recommended intervention for primary angle closure disease?

With the exclusion of eyes with cataract, following an acute attack of angle closure (AAC) or nanophthalmos.

Interventions depend on the spectrum of disease and presence of cataract.

Laser and surgical treatment is typically combined with medical treatment.

Primary angle closure suspect (PACS):

Comment: Not all patients with PACS need laser peripheral iridotomy (LPI). Evidence from China suggests that there is a low risk of disease progression without LPI (ZAP trial, see 1.7.2.1). No studies in white European eyes.

Recommendation: LPI in high risk individuals, e.g., high hyperopia, patients requiring repeated pupil dilatation for retinal disease or with difficult access to healthcare facilities.

Level of evidence: low

Strength of recommendation: “weak”

Primary angle closure (PAC) and primary angle closure glaucoma (PACG), for people under 50 years of age:

Recommendation: LPI

Level of evidence: low

Strength of recommendation: “strong”

PAC and PACG, for people over 50 years of age:

Comment: Lens extraction is associated with better clinical and QoL outcomes (EAGLE trial, see 1.7.4.1), but risk considerations need to be individualised.

Recommendation: lens extraction or LPI

Level of evidence: moderate (one good quality trial, EAGLE)

Strength of recommendation: strong

Q15. Medical treatment: what is the most effective and the first choice medication for PACG (after interventions for widening the anterior chamber angle have been done)?

Recommendation: Prostaglandin analogues are the most effective medication.

Level of evidence: low

Strength of recommendation: strong

Comment: Trials in East Asia may not be generalisable to European populations. Factors like possible adverse effects, co-morbidities, systemic therapy, adherence, patient preferences, life expectancy, cost and availability should be considered in selecting a drug for a given patient.

In some exceptional cases long-term treatment with miotics may be recommended (e.g, plateau iris syndrome after LPI and with recurrent attacks of angle closure and when lens extraction cannot be done).

Q16. Glaucoma surgery for PACG (after interventions for widening the anterior chamber angle have been done)?

Interventions depend on the lens status and glaucoma severity.

Pseudophakic with PACG:

Recommendation: filtration surgery (trabeculectomy)

Level of evidence: very low

Strength of recommendation: strong

Phakic with PACG:

Recommendation: phacoemulsification alone or combined phacoemulsification + glaucoma surgery

Level of evidence: very low

Strength of recommendation: strong

Comment: In patients with severe glaucoma phaco-trabeculectomy may be advisable.

1.4 Things to avoid - choosing wisely



- 1) CCT-adjusted IOP algorithms.
IOP correction algorithms based on CCT are not validated and should be avoided.
- 2) Short-wavelength automated perimetry (SWAP) for glaucoma.
There is no evidence of better performance of swap and it has no role in current clinical practice.
- 3) Glaucoma diagnosis and progression based only on OCT.
OCT on its own does not provide a clinical diagnosis of glaucoma, just a statistical deviation from a reference database.
One should not rely on OCT only to diagnose progression.
- 4) Cup to disc ratio (CDR) for diagnosis of glaucoma or to detect progression.
Due to the large differences in size and shape of optic discs CDR cannot be used to diagnose glaucoma. In addition, the assessment of CDR, even by experts, has high variability and is not useful to detect progression.
- 5) Anterior chamber angle imaging to replace gonioscopy.
The accuracy of anterior segment imaging to diagnose angle closure is suboptimal.
- 6) Routine genetic testing and direct to consumer genetic genotyping.
Do not offer genotyping routinely to glaucoma patients.
Genetic information obtained with online home testing kits may be unreliable and should not be used to guide diagnosis or treatment.
- 7) Glaucoma management decisions based only on artificial intelligence.
Technologies may support but do not replace clinical judgement.
- 8) Provocation test for angle closure.
A negative provocative test does not exclude risk of acute angle closure.
A positive test may not represent real life circumstances.
- 9) Interventions for blind painless eyes with very high IOP.
Once the vision is lost, there is no need to perform further interventions except for painful eyes when pain is due to high IOP.
- 10) Laser trabeculoplasty for primary late-onset juvenile glaucoma.
There is no evidence that laser trabeculoplasty is effective in juvenile glaucoma.
- 11) Carbonic anhydrase inhibitors and hyperosmotic agents in patients with sickle-cell disease.
In patients with sickle-cell disease these drugs may cause an acute haemolytic crisis and should be avoided.
- 12) Lowering IOP to just below 21 mmHg in advanced glaucoma.
In patients with advanced glaucoma low IOP e.g., low teens is needed.

FC I – Suggested questions for your glaucoma patient



At baseline

History/risk factors
 Specifically enquire about
 All medications
 Family history (general/ophthalmological/blindness)
 Corticosteroid therapy (topical/systemic)
 Ocular trauma or inflammation
 Refractive surgery
 Cardiovascular or respiratory diseases/other chronic or severe diseases
 Vascular disorders
 Drug allergies

Do you have any questions or anything that you would like to discuss?



Direct questions at follow-up

How are you?
 How do you think your eyes are doing?
 Do you think your condition is better, stable or worse? Do you have difficulty with your daily tasks?
 Do you understand your diagnosis?
 Are you having any problems with your drops?
 Are you worried about your sight?
 Have you been using your eye drops as prescribed?
 Do you administer the drops by yourself or by a relative?
 If by yourself, please show me how you do it
 Do you have any questions or anything that you would like to discuss?

I.5 What matters to patients?

I.5.1 Anxiety associated with glaucoma

Diagnosis - especially when unexpected - is an obvious moment of anxiety for patients, and one which can be mitigated by the provision of timely support or more information. Empathy is particularly important when providing a diagnosis - put yourself in the patient's shoes, try to understand what they are thinking and feeling and give them plenty of opportunity to ask questions and express their fears.

Anxiety does not dissipate once the shock of diagnosis has passed: concerns about future deterioration in sight, about ability to hold a driving license, about difficulties with healthcare provision, and about age-related difficulty in managing treatment are all common. The perception of disease is likely influenced by family history and how family members have been affected by glaucoma.

I.5.2 The information gap

A lack of information can in itself be a source of anxiety and uncertainty. Not understanding clinical systems, being unable to formulate pertinent questions and feeling undervalued in clinical consultations are all common experiences for patients, and exacerbate the information gap. In contrast, the presence of information can enable engagement in self-care and can support changes in lifestyle which result in a more effective management of glaucoma.

Key information gaps include:

Nature of glaucoma sight loss

Even long-term patients may struggle to understand the nature of glaucoma sight loss. Helping people to understand the specifics of their own field loss can also help them develop techniques to avoid trips and falls. People may assume that surgery or laser will improve vision, so volunteering the correct information is often helpful.

Glaucoma and driving

This is one of the major sources of stress and anxiety for patients, yet there is confusion amongst professionals about local driving regulations and when a patient may need to notify the authorities, and patients continue to receive incorrect or inconsistent advice. This anxiety is understandable given the potential impact of losing a driving licence.

Eye drops

Patients' ability to manage their condition varies depending on their personal circumstances. Drops change, personal circumstances change, attitudes to treatment evolve. Continue checking in with your patients, encourage discussion and frame questions to avoid judgement or censure. E.g., "Do you have any concerns or difficulties with your eye drops?"

For the patient, it often seems that every clinician thinks drops is someone else's job. Every clinic should have a health care professional who takes proactive responsibility for drop education. Patients need ongoing information about adherence – not just when their drop regime changes or when there are supply issues or side effects. Patients need to be encouraged to speak up when they have problems with drops, and need to know where they can go for help.

Surgery and laser

The route to making a treatment decision is complex, and many patients need considerable support, advice and time. Take the time to explain to patients the possible outcomes and risks of their condition and treatment, in a manner suitable to each individual. Trabeculectomy or another glaucoma surgery is a routine procedure for a surgeon, but for the patient, the prospect of someone taking a knife to their eye is terrifying, and they're likely to forget how you delivered the news to them. Providing accurate timely written information for people to take away can mean patients are reassured and empowered to go ahead with treatment, and where an informed patient declines surgery, they are in a better position to understand the risk they are taking and the potential impact.

Asking questions is difficult

Patients often find it hard to ask for information from healthcare professionals. Some find the clinical setting is not conducive to engagement, others describe doctors who do not want to engage with them, and many ration their time with their healthcare provider because they feel guilty about using doctors' time. For others, the difficulty lies in not knowing how to frame questions about their glaucoma. It might be that a lack of knowledge makes it hard for them to shape or construct meaningful questions, they may lack confidence, or it might be difficulties with memory or hearing that inhibits people. Clinicians should help by inviting questions at every single appointment, encouraging patients to bring written questions with them, or to bring a friend or relative along for support.

Glaucoma support groups

These are excellent vehicles for information dissemination and valuable peer support opportunities.

In summary, remember that patients' information needs are complex – and equally complex for those newly diagnosed as those diagnosed decades ago. Even patients who initially appear well-informed often lack key information or skills to manage their condition. Offer them information about their condition and treatment and encourage them to ask questions. And provide a means for them to get back in touch with the clinic if required.

Functional loss over time guides Individualised treatment

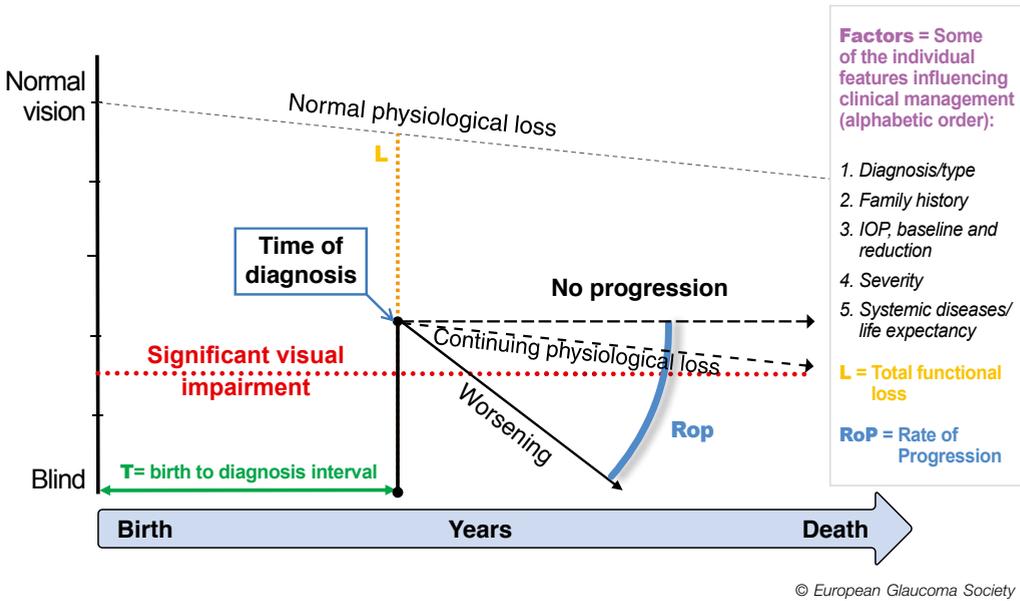


Figure 1.4.1 Evaluation of functional loss/time for individualised treatment

IOP = IOP level causing damage

L = difference of visual function between the age-matched normal and the function at the time of diagnosis

RoP = angle representing physiological loss and disease progression

T = time interval between birth and the time of diagnosis

I.6 Glaucoma epidemiology

Epidemiological studies have contributed immensely to the better understanding of glaucoma and its impact to society. A synopsis of key epidemiologic findings is presented below.

Population-based studies on glaucoma have been conducted in several parts of the world, including in some European countries.¹⁻⁸

Very few among those, have re-examined their population to provide highly valued longitudinal data.^{3,9-13} Based on population-based studies, we have gained knowledge on: a) the burden of glaucoma, b) the natural history and blindness caused by glaucoma c) risk factors for glaucoma, and d) other important public health issues, such as the under- and over-diagnosis of glaucoma.

I.6.1 Burden of glaucoma

Glaucoma is among the leading causes of blindness worldwide.¹⁴ The estimated global prevalence of open angle glaucoma (OAG) is 3.5% in 40-80-year olds and of angle closure glaucoma (ACG) 0.50%.^{15,16} The number of people with glaucoma was estimated to be 76 million in 2020 and expected to increase to 112 million by 2040. The prevalence of glaucoma is influenced by race: OAG is more prevalent in black populations, while ACG is more prevalent in East Asian populations.

I.6.2 Natural history of glaucoma and blindness

While OAG is far more common than ACG, blindness is more likely to happen in ACG than in OAG (estimated 25% and 10% over the patient lifetime, respectively).^{14,15} Due to the established benefit of IOP-lowering treatment in glaucoma, there have been very few opportunities to study the course of untreated glaucoma over time. Valuable data on the natural course of OAG have also been provided by the Early Manifest Glaucoma Trial (EMGT, see I.7.1.4), the United Kingdom Glaucoma Treatment Study (UKGTS, see I.7.1.5) and the Collaborative Normal-Tension Glaucoma Study (see I.7.1.1). In the untreated arm of the EMGT, the overall natural rate of progression in the VF was 1.08 dB/year. Participants with different disease phenotypes exhibited different rates of progression (1.31 dB/year in high tension glaucoma, 0.36 dB/year in normal tension glaucoma and 3.13 dB/year in pseudoexfoliative glaucoma (PXFG)).¹³

I.6.3 Risk factors for glaucoma

Older age, elevated IOP, non-White ethnicity (particularly Black), family history of glaucoma, pseudoexfoliation, disc haemorrhage and myopia (see also II.2.2) have been reported as major risk factors for the development of OAG.^{15,17,18} Highest prevalence of PACG appears in East-Asian and Chinese race.¹⁵

I.6.4 Under-and overdiagnosis of glaucoma

Several population-based studies have reported that at least 50% of glaucoma cases remain undiagnosed in Europe.^{8,18,19} Glaucoma associated with normal range of IOP is more likely to be underdiagnosed. Higher rates of undiagnosed glaucoma have been reported in Asia and Africa.

Conversely, there are very limited data on the overdiagnosis and overtreatment of OAG, which is also expected to occur in clinical practice. The Thessaloniki Eye Study recently reported that the overdiagnosis of OAG is actually substantial in an elderly, white European population.²⁰

References, with an emphasis on European studies:

1. Dielemans I, Vingerling JR, Wolfs RC, Hofman A, Grobbee DE, de Jong PT. The prevalence of primary open angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology* 1994;101:1851-55
2. Topouzis F, Wilson MR, Harris A, Anastasopoulos E, Yu F, Mavroudis L, Pappas T, Koskosas A, Coleman AL. Prevalence of open angle glaucoma in Greece: the Thessaloniki Eye Study. *Am J Ophthalmol* 2007;144:511-19.
3. Astrom S, Stenlund H, Linden C. Incidence and prevalence of pseudoexfoliations and open angle glaucoma in northern Sweden: II. Results after 21 years of follow-up. *Acta Ophthalmol* 2007;85:832-37.
4. Höhn R, Kottler U, Peto T, Blettner M, Münzel T, Blankenberg S, Lackner KJ, Beutel M, Wild PS, Pfeiffer N. The ophthalmic branch of the Gutenberg Health Study: study design, cohort profile and self-reported diseases. *PLoS One* 2015 16;10(3):e0120476.
5. Saarela V, Karvonen E, Stoor K, et al. The Northern Finland Birth Cohort Eye Study: Design and baseline characteristics. *BMC Ophthalmol* 2013;13:51. Published 2013 Oct 8.
6. Chan MPY, Broadway DC, Khawaja AP, et al. Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study. *BMJ* 2017;358:j3889. Published 2017 Sep 13.
7. Karvonen E, Stoor K, Luodonpaa K, et al. Prevalence of glaucoma in the Northern Finland Birth Cohort Eye Study. *Acta Ophthalmol* 2019;97:200-207.
8. McCann P, Hogg R, Wright DM, et al. Glaucoma in the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA): cohort profile, prevalence, awareness and associations. *Br J Ophthalmol* 2020 Feb 7;bjophthalmol-2019-315330.
9. Bengtsson BO. Incidence of manifest glaucoma. *Br J Ophthalmol* 1989;73:483-87.
10. De Voogd S, Ikram MK, Wolfs RC, Jansonijs NM, Hofman A, de Jong PT. Incidence of open angle glaucoma in a general elderly population: the Rotterdam Study. *Ophthalmology* 2005;112:1487-93.
11. Czudowska MA, Ramdas WD, Wolfs RC, Hofman A, De Jong PT, Vingerling JR, Jansonijs NM. Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam Study. *Ophthalmology* 2010;117:1705-12.
12. Springelkamp H, Wolfs RC, Ramdas WD, Hofman A, Vingerling JR, Klaver CC, Jansonijs NM. Incidence of glaucomatous visual field loss after two decades of follow-up: the Rotterdam Study. *Eur J Epidemiol* 2017;32:691-99.
13. Heijl A, Bengtsson B, Hyman L, Leske MC. Natural history of open angle glaucoma. *Ophthalmology* 2009;116:2271-76.
14. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP. Global data on visual impairment in the year 2002. *Bull World Health Organ* 2004;82:844-51.

15. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 2014;121:2081-90.
16. Day AC, Baio G, Gazzard G, et al. The prevalence of primary angle closure glaucoma in European derived populations: a systematic review. *Br J Ophthalmol* 2012;96:1162-67
17. Topouzis F, Harris A, Wilson MR, Koskosas A, Founti P, Yu F, Anastasopoulos E, Pappas T, Coleman AL. Increased likelihood of glaucoma at the same screening intraocular pressure in subjects with pseudoexfoliation: the Thessaloniki Eye Study. *Am J Ophthalmol* 2009;148:606-613.
18. Burr JM, Mowatt G, Hernandez E, et al. The clinical and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11(41):iii-190.
19. Topouzis F, Coleman AL, Harris A, Koskosas A, Founti P, Gong G, Yu F, Anastasopoulos E, Pappas T, Wilson MR. Factors associated with undiagnosed open angle glaucoma: the Thessaloniki Eye Study. *Am J Ophthalmol* 2008;145:327-35.
20. Founti P, Coleman AL, Wilson MR, Yu F, Anastasopoulos E, Harris A, Pappas T, Koskosas A, Kilintzis V, Salonikiou A, Raptou A, Topouzis F. Overdiagnosis of open angle glaucoma in the general population: the Thessaloniki Eye Study. *Acta Ophthalmol* 2018;96:e859-e864.

Clinical care should be individualised and guided by evidence. Landmark Randomised Controlled Trials provide helpful information for clinical recommendations. The cost-effectiveness of management options should also be considered by physicians, in order to provide sustainable healthcare.

I.7 Landmark randomised controlled trials for glaucoma

In the following pages we briefly summarize results from some high quality, randomised controlled trials (RCTs) for glaucoma and derive comments relevant to clinical decision-making.

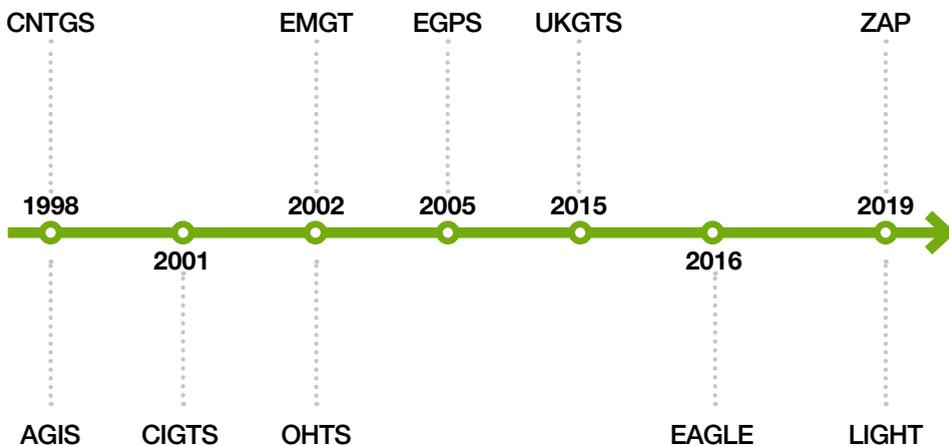


Figure I.7.1 Landmark RCTs for glaucoma and year of first published results.

I.7.1 Treatment vs no treatment trials in open angle

I.7.1.1 Collaborative normal tension glaucoma study (CNTGS)

CNTGS compared treatment versus no treatment in normal tension glaucoma in a multicentre randomised trial. 230 eligible patients entered the study. Only those who exhibited verified progression of VF loss or threat to fixation were randomised (n=140). The primary outcome measure was disease progression as evident from VF or stereo disc photographs.¹

Summary of results²⁻⁵:

- A 30% IOP reduction from baseline was the treatment goal and was maintained in nearly 50% of patients. Progression occurred in 12% (7/61) of treated eyes and 35% (28/79) of controls.

- In the intent-to-treat analysis no benefit of treatment was found.
- A beneficial effect of IOP lowering was found only after the data were censored for the effect of cataract formation on the VF.
- Cataracts were more common in patients treated with surgery.
- Progression rates varied a lot. The mean progression rate in the untreated arm was 0.41 dB/year. Prior documented progression did not increase the risk of future progression.

References:

1. Group CN-TGS. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *Am J Ophthalmol* 1998;126(4):487-97.
2. Group CN-TGS. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol* 1998;126(4):498-505.
3. Drance S, Anderson DR, Schulzer M. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. *Am J Ophthalmol* 2001;131(6):699-708.
4. Anderson DR, Drance SM, Schulzer M. Factors that predict the benefit of lowering intraocular pressure in normal tension glaucoma. *Am J Ophthalmol* 2003;136(5):820-29.
5. Anderson DR, Drance SM, Schulzer M. Natural history of normal-tension glaucoma. *Ophthalmology* 2001;108(2):247-53.

1.7.1.2 The ocular hypertension treatment study (OHTS)

The OHTS was a multicentre, randomised, clinical trial, designed to study the effect of topical medication in delaying or preventing the onset of glaucoma in patients with OHT. A total of 1,636 patients were recruited. Randomisation was between treatment with medications and no treatment. The treatment goal was to lower the IOP to < 24 mmHg and at least 20% from baseline. The primary outcome was the development of primary open angle glaucoma (POAG) defined as reproducible VF defects or reproducible optic disc deterioration. After the 5-year initial results were reported the control group received treatment.¹

Summary of results²⁻⁶:

- Mean IOP reduction was 22.5% in the treated group. The control group showed a decrease of IOP of 4.0%.
- Risk factors for development of glaucoma were: thinner CCT, higher IOP, disc haemorrhages, older age, larger vertical and horizontal CDR, greater VF pattern standard deviation (PSD).
- Disc haemorrhages detectable in photographs had been missed at 87% of clinical examinations. Rate of conversion was higher in eyes with haemorrhages.
- After 5 years 4.4% of patients in the treated group had developed signs of glaucoma damage versus 9.5% in controls ($p < 0.0001$), a 50% reduction of relative risk.
- In addition, more than 90% of untreated patients had not converted to glaucoma after 5 years.
- After 13 years 22% of patients who had initially been randomised to the control group had converted to glaucoma versus 16% in the group that was treated at the start of the study.

- POAG conversion was detected first in disc photographs in around 50% of patients and by field testing in approximately 40%.
- A risk calculator is freely available to estimate the risk of developing glaucoma at 5 years. <http://ohts.wustl.edu/risk/calculator.htm>.
- Cataract formation was more common in the medication group.

References:

1. Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol* 1999;117(5):573-83.
2. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomised trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open angle glaucoma. *Arch Ophthalmol* 2002;120(6):701-13; discussion 829-30.
3. Kass MA, Gordon MO, Gao F, et al. Delaying treatment of ocular hypertension: the ocular hypertension treatment study. *Arch Ophthalmol* 2010;128(3):276-87.
4. Keltner JL, Johnson CA, Anderson DR, et al. The association between glaucomatous visual fields and optic nerve head features in the Ocular Hypertension Treatment Study. *Ophthalmology* 2006;113(9):1603-12.
5. Budenz DL, Anderson DR, Feuer WJ, et al. Detection and prognostic significance of optic disc hemorrhages during the Ocular Hypertension Treatment Study. *Ophthalmology* 2006;113(12):2137-43.
6. Herman DC, Gordon MO, Beiser JA, et al. Topical ocular hypotensive medication and lens opacification: evidence from the ocular hypertension treatment study. *Am J Ophthalmol* 2006;142(5):800-10.

I.7.1.3 European glaucoma prevention study (EGPS)

The EGPS was a multicentre, randomised, double-masked, placebo-controlled clinical trial. The aim of this study was to evaluate the efficacy of IOP reduction by dorzolamide in preventing glaucoma damage in patients with OHT. The patients were randomised into 2 groups: active therapy (dorzolamide) and placebo. Main outcome measures were VF and/or optic disc changes¹.

Summary of results²⁻⁶:

1081 patients were enrolled. The median duration of follow-up was 55 months. The IOP difference between the treatment and the control group was small. The mean IOP reduction was 15% after 6 months and 22% after 5 years in the dorzolamide group, but there was also a 9% reduction after 6 months and 19% after 5 years in the placebo group, to a large part attributable to high attrition.

The study failed to detect a statistically significant difference between the chosen medical therapy and placebo, either in IOP lowering effect, or in the rate of progression to POAG, and attrition was large.

The same predictors for the development of POAG were identified independently in both the OHTS observation group and the EGPS placebo group—baseline older age, higher IOP, thinner CCT, larger vertical CDR, and higher Humphrey VF PSD.

In a later paper, diuretics use were pointed as a possible risk factor.⁴ Several baseline Heidelberg retina tomograph (HRT) parameters, alone or in combination with baseline clinical and demographic factors, were significantly associated with the development of open angle glaucoma among the EGPS participants.

References:

1. Miglior S, Zeyen T, Pfeiffer N, et al. The European glaucoma prevention study design and baseline description of the participants. *Ophthalmology* 2002;109(9):1612-21.
2. Miglior S, Zeyen T, Pfeiffer N, et al. Results of the European Glaucoma Prevention Study. *Ophthalmology* 2005;112(3):366-75.
3. Miglior S, Pfeiffer N, Torri V, et al. Predictive factors for open angle glaucoma among patients with ocular hypertension in the European Glaucoma Prevention Study. *Ophthalmology* 2007;114(1):3-9.
4. Miglior S, Torri V, Zeyen T, et al. Intercurrent factors associated with the development of open angle glaucoma in the European glaucoma prevention study. *Am J Ophthalmol* 2007;144(2):266-75.
5. Hoffmann EM, Miglior S, Zeyen T, et al. The Heidelberg retina tomograph ancillary study to the European glaucoma prevention study: study design and baseline factors. *Acta Ophthalmol* 2013;91:612-19.
6. Miglior S, Zeyen T, Hoffmann T, et al. Predictive value of heidelberg retina tomograph parameters for the development of glaucoma in the European glaucoma prevention study. *Am J Ophthalmol* 2015;159:265-76.

I.7.1.4 Early manifest glaucoma trial (EMGT)

EMGT was a randomised, prospective trial comparing treatment versus no treatment to evaluate the effectiveness of IOP reduction in early, previously untreated open angle glaucoma.¹ Secondary aims were to assess factors related to glaucoma progression, and to determine the natural history of the disease.

During a population-based screening among 44,243 residents in Sweden, 316 eyes of 255 patients were recruited between 1993 and 1997, and followed prospectively until December 31, 2013.

Treated patients received a standardised treatment protocol of laser trabeculoplasty and topical betaxolol. Treatment or no-treatment remained unchanged as long as definite progression had not occurred. Primary outcome measure was progression of disease, defined by sustained VF deterioration or optic disc changes.¹

Summary of results²⁻¹⁸:

- This study was the first to prove and quantify the value of IOP reduction in patients with POAG, normal tension glaucoma (NTG) and PXFG.
- A 25% decrease of IOP from baseline (mean untreated IOP 20.6 mmHg) reduced the relative risk of progression by 50%.
- Risk of progression was smaller with lower baseline IOP values and with a larger initial IOP drop induced by treatment.
- Treatment efficacy regarding IOP reduction depended very much on pre-treatment IOP.
- Important risk factors for progression were: higher IOP, pseudoexfoliative syndrome (PXF), more baseline damage, higher age, disc haemorrhages, thinner CCT in high tension glaucoma, and low blood pressure in normal tension glaucoma.
- IOP fluctuation was not a risk factor for progression.
- IOP did not increase but remained constant over time in untreated eyes with POAG, but increased over time in eyes with PXFG.

- Increase in lens opacity occurred more in the treatment arm than in the control arm.
- There was no evidence of VF improvement on initiation of glaucoma therapy.
- Disease progression rates varied substantially between individual patients.
- Untreated progression rates (natural history) were slower in NTG than in HTG, while eyes with PXFG progressed much faster.
- Definite progression was associated with a mean worsening of mean defect (MD) of less than 2dB.
- In eyes with manifest glaucoma, progression in the VF was detected first more than 4 times as often as progression in the optic disc. Among fellow eyes without VF loss at baseline, progression was detected first as frequently in the optic disc as in the VF. Perimetric progression was detected first at all stages of the disease.
- After a few years of follow-up, vision-related QoL did not differ between treatment arms, i.e. the absence or presence of treatment did not influence QoL. An analysis after 20 years of follow-up supports the widespread, albeit arbitrary, use of a better-eye remaining VF loss greater than 50% as an important threshold for a significant reduction in vision-related QoL.
- The frequency of disc haemorrhages was higher with lower IOP, in women and with myopia and was not influenced by treatment.
- An analysis of EMGT patients followed for at least 15 years showed that a glaucoma diagnosis made by applying strict criteria to 2 initial VF tests, supported by optic disc findings if VF findings were borderline, was almost always correct.

References:

1. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology* 1999;106(11):2144-53.
2. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002;120(10):1268-79.
3. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2003;121(1):48-56.
4. Heijl A, Leske MC, Hyman L, et al. Intraocular pressure reduction with a fixed treatment protocol in the Early Manifest Glaucoma Trial. *Acta Ophthalmol* 2011;89(8):749-54.
5. Heijl A, Peters D, Leske MC, Bengtsson B. Effects of argon laser trabeculoplasty in the Early Manifest Glaucoma Trial. *Am J Ophthalmol* 2011;152(5):842-48.
6. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology* 2007;114(11):1965-72.
7. Bengtsson B, Leske MC, Hyman L, Heijl A. Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial. *Ophthalmology* 2007;114(2):205-09.
8. Hyman L, Heijl A, Leske MC, et al. Natural history of intraocular pressure in the early manifest glaucoma trial: A 6-year follow-up. *Arch Ophthalmol* 2010;128(5):601-07.
9. Bengtsson B, Heijl A. Lack of visual field improvement after initiation of intraocular pressure reducing treatment in the Early Manifest Glaucoma Trial. *Invest Ophthalmol Vis Sci* 2016;57(13):5611-15.
10. Heijl A, Bengtsson B, Hyman L, Leske MC. Natural history of open angle glaucoma. *Ophthalmology* 2009;116(12):2271-76.
11. Heijl A, Bengtsson B, Chauhan BC, et al. A comparison of visual field progression criteria of 3 major glaucoma trials in early manifest glaucoma trial patients. *Ophthalmology* 2008;115(9):1557-65.

12. Heijl A, Leske MC, Bengtsson B, Hussein M. Measuring visual field progression in the Early Manifest Glaucoma Trial. *Acta Ophthalmol Scand* 2003;81(3):286-93.
13. Öhnell H, Heijl A, Brenner L, Anderson H, Bengtsson B. Structural and functional progression in the Early Manifest Glaucoma Trial. *Ophthalmology* 2016;123(6):1173-80.
14. Öhnell H, Heijl A, Anderson H, Bengtsson B. Detection of glaucoma progression by perimetry and optic disc photography at different stages of the disease: results from the Early Manifest Glaucoma Trial. *Acta Ophthalmol* 2017;95(3):281-87.
15. Hyman LG, Komaroff E, Heijl A, et al. Treatment and vision-related quality of life in the early manifest glaucoma trial. *Ophthalmology* 2005;112(9):1505-13.
16. Peter D, Heijl A, Brenner L, Bengtsson B. Visual impairment and vision-related quality of life in the Early Manifest Glaucoma Trial after 20 years of follow-up. *Acta Ophthalmol* 2015;93(8):745-52.
17. Bengtsson B, Leske MC, Yang Z, Heijl A. Disc hemorrhages and treatment in the early manifest glaucoma trial. *Ophthalmology* 2008;115(11):2044-48.
18. Öhnell H, Bengtsson B, Heijl A. Making a correct diagnosis of glaucoma: Data from EMGT. *J Glaucoma* 2019; 28(10):859-64.

1.7.1.5 United Kingdom glaucoma treatment study (UKGTS)

UKTS was a multicentre, randomised, masked, placebo-controlled trial designed to assess visual function preservation in OAG patients given latanoprost 0.005% compared with those given placebo. 516 individuals were enrolled. The primary outcome was time to VF deterioration within 24 months. Progression was measurable in such time frame since the frequency of visual field examination was increased.¹

Summary of results²⁻⁵:

- Untreated IOP was 19.6 ± 4.6 and 20.1 ± 4.8 in the latanoprost group and in the placebo group, respectively.
- Mean reduction in IOP was 3.8 ± 4.0 mmHg in the latanoprost group and 0.9 ± 3.8 mmHg in the placebo group.
- This placebo-controlled trial is the only trial to quantify VF preservation with a single IOP-lowering drug in patients with OAG, in this case a PGAs.
- The 20% reduction in IOP in the latanoprost group, from a baseline of 19.6 mmHg, was associated with significantly longer VF preservation than in the placebo group (HR: 0.44).
- The risk of progression was 7% higher per mmHg higher baseline IOP, 59% higher if both eyes of a patient had glaucoma, and was double if baseline disc haemorrhage was present.
- Patient age and severity of VF loss were not associated with risk of progression.
- Definite progression was associated with a mean worsening of MD of about 1.6 dB.
- QoL was not different between treatment arms.
- Faster rates of retinal nerve fibre layer thinning, measured by OCT, was associated with a greater risk of VF progression.
- 25.6% patients in the placebo group reached the VF deterioration endpoint at 24 months compared with 15.2% in the latanoprost group.
- Combining VF and OCT data identified progression more quickly than using only VF data.

References:

1. Lascaratos G, Garway-Heath DF, Burton R, et al. The United Kingdom Glaucoma Treatment Study: a multicenter, randomized, double-masked, placebo-controlled trial: baseline characteristics. *Ophthalmology* 2013;120:2540-45.
2. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet* 2015;385:1295-1304.
3. Garway-Heath DR, Zhu H, Cheng Q, et al. Combining Optical Coherence Tomography With Visual Field Data to Rapidly Detect Disease Progression in Glaucoma: A Diagnostic Accuracy Study *Health Technol Assess* 2018 Jan;22(4):1-106.
4. Founti P, Bunce C, Khawaja AP, et al. Risk factors for visual field deterioration in the United Kingdom Glaucoma Treatment Study [published online ahead of print, 2020 Jun 12]. *Ophthalmology* 2020;S0161-6420(20)30527-3.
5. Jones L, Garway-Heath DF, Azuara-Blanco A, Crabb DP; United Kingdom Glaucoma Treatment Study Investigators. Are Patient Self-Reported Outcome Measures Sensitive Enough to Be Used as End Points in Clinical Trials?: Evidence from the United Kingdom Glaucoma Treatment Study. *Ophthalmology* 2019;126:682-89.

1.7.2 Treatment vs. no treatment trials on angle closure**1.7.2.1 ZAP trial:**

'Laser Peripheral Iridotomy for the prevention of angle closure: a single-centre, randomised controlled trial'

889 untreated Chinese PACS detected in a population screening (defined as irido-trabecular contact of at least 180 degrees without peripheral anterior synechiae (PAS) or raised IOP) had one eye randomly assigned to LPI and one eye to no treatment. There was a composite primary outcome: PAS or IOP over 24 mmHg or development of glaucoma.¹

Summary of the results²⁻⁴:

- After 6 years, there was a difference between treatment groups but the frequency of patients reaching the primary outcome was very low.
- A primary outcome event occurred in 19 treated eyes and 36 untreated eyes ($p=0.0041$).
- Primary outcome occurred in 4.19 per 1000 eye-years in treated eyes vs 7.97 per 1000 eye-years in untreated eyes (hazard ratio 0.53; $p=0.024$).
- The authors suggest that routine prophylactic LPI should not be performed routinely. LPI is advisable only in high risk eyes (see 1.3, question 14).
- It is uncertain whether the findings of this trial are generalisable to non-Chinese populations.

References:

1. He M, Jiang Y, Huang S, Chang DS, Munoz B, Aung T, Foster PJ, Friedman DS. Laser peripheral iridotomy for the prevention of angle closure: a single-centre, randomised controlled trial. *Lancet* 2019 Apr 20;393(10181):1609-18.

2. Jiang Y, Friedman DS, He M, Huang S, Kong X, Foster PJ. Design and methodology of a randomised controlled trial of laser iridotomy for the prevention of angle closure in southern China: the Zhongshan angle Closure Prevention trial. *Ophthalmic Epidemiol* 2010 Oct;17(5):321-32.
3. Congdon N, Yan X, Friedman DS, Foster PJ, van den Berg TJ, Peng M, Gangwani R, He M. Visual symptoms and retinal straylight after laser peripheral iridotomy: the Zhongshan Angle Closure Prevention Trial. *Ophthalmology* 2012 Jul;119(7):1375-82.
4. Jiang Y, Chang DS, Zhu H, Khawaja AP, Aung T, Huang S, Chen Q, Munoz B, Grossi CM, He M, Friedman DS, Foster PJ. Longitudinal changes of angle configuration in primary angle closure suspects: the Zhongshan Angle Closure Prevention Trial. *Ophthalmology* 2014 Sep;121(9):1699-1705.

1.7.3 Studies comparing treatments in open angle

1.7.3.1 Advanced glaucoma intervention Study (AGIS)

AGIS was a multicentre, prospective randomised study in patients with open angle glaucoma patients who could not be controlled by maximally-tolerated medical therapy alone. 591 patients (789 eyes) were randomised between two sequences of treatments.

1. ATT: ALT, followed by trabeculectomy, followed by a second trabeculectomy, or
2. TAT: trabeculectomy, followed by ALT, followed by a second trabeculectomy.

Enrolled eyes had consistent elevation of IOP of ≥ 18 mmHg. Patients with MD worse than -16 dB were excluded, thus excluding eyes with severe glaucoma. About 1/3 of patients had early glaucoma.¹

Summary of results²⁻⁹:

- After 7 years, mean reduction of IOP was greater for eyes assigned to the TAT protocol, and the cumulative probability of failure of the first intervention was greater for eyes assigned to the ATT protocol.
- The percentage of eyes with decreased visual acuity or VF progression was lower for the ATT sequence than for TAT in African American patients. Initial trabeculectomy slowed the progression of glaucoma more effectively in patients with white European ancestry.
- The probability of cataract formation after 5 years was high after trabeculectomy, 78%.
- Risk factors associated with progression were older age, longer follow-up, and increasing number of glaucoma interventions.
- IOP fluctuations were a risk factor for VF progression only in patients with low mean IOP.
- Both ALT and trabeculectomy failed more often in younger patients and in eyes with higher pre-treatment IOP.
- The surgical technique for performing trabeculectomies changed during the study period. Prior to 1990, antimetabolites were not used during surgery. After 1990, 5-fluorouracil was used postoperatively. After 1991, mitomycin-C was used intraoperatively.

- In a post-hoc analysis of patients with 6-years of follow-up or more, eyes with an average IOP > 17.5 mmHg over the first three 6-months visits showed more frequent VF deterioration compared to eyes with an average IOP < 14 mmHg. There was no average VF progression, as measured by MD, in eyes with IOP < 18 mmHg at 100% of the visits, whereas eyes with less stringent IOP control demonstrated VF progression.⁹

References:

1. Brown RH, Lynch M, Leef D, et al. The Advanced Glaucoma Intervention Study (AGIS).1. Study Design and Methods and Base-Line Characteristics of Study Patients. *Controlled Clinical Trials* 1994;15(4):299-325.
2. Ederer F, Gaasterland DA, Dally LG, et al. The Advanced Glaucoma Intervention Study (AGIS): 13. Comparison of treatment outcomes within race: 10-year results. *Ophthalmology* 2004;111(4):651-64.
3. The Advanced Glaucoma Intervention Study (AGIS) investigators: 6. effect of cataract on visual field and visual acuity. *Arch Ophthalmol* 2000;118(12):1639-52.
4. The Advanced Glaucoma Intervention Study (AGIS) investigators: 9. Comparison of glaucoma outcomes in black and white patients within treatment groups. *Am J Ophthalmol* 2001;132(3):311-20.
5. The Advanced Glaucoma Intervention Study (AGIS) investigators: 8. Risk of cataract formation after trabeculectomy. *Arch Ophthalmol* 2001;119:1771-79.
6. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology* 2004;111(9):1627-35.
7. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. *Ophthalmology* 2008;115(7):1123-9 e3.
8. The Advanced Glaucoma Intervention Study (AGIS) investigators: 11. Risk factors for failure of trabeculectomy and argon laser trabeculoplasty. *Am J Ophthalmol* 2002;134(4):481-98.
9. The Advanced Glaucoma Intervention Study (AGIS) investigators: 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000;130(4):429-40.

I.7.3.2 Collaborative initial glaucoma treatment study (CIGTS)

The aim was to find out if newly-diagnosed OAG is better treated by initial treatment with medications or by immediate filtration surgery.¹ Patients with severe OAG were excluded.

607 patients with newly diagnosed OAG were randomised to initial treatment with either medication or trabeculectomy (with or without 5-fluorouracil). A target IOP algorithm was used tailored for each individual eye. Primary outcome variables were VF progression and QoL. Secondary outcome variables were visual acuity, IOP, and cataract formation. Inclusion criteria may have allowed recruitment of some patients with OHT, resulting in a case mix with a smaller risk of showing progression.¹

Summary of results²⁻¹⁰:

- IOP reduction was larger with surgery (48%; mean post treatment IOP 14-15 mmHg) than with medications (35%; mean post treatment IOP 17-18 mmHg).

- In the first few years, mean perimetric progression among all subjects was small and similar in both groups. After 8 years 21% of surgical patients and 25% of medical patients had progressed, defined as a worsening of MD by 3 dBs.
- After adjustment for baseline risk factors, larger IOP variation measures were associated with significantly worse MD values after 3 to 9 years in the medication arm but not in the surgically treated group.
- QoL was initially better in the medically treated group but there was no difference in QoL at the last follow-up. Worry about becoming blind was reported by 50% of CIGTS participants at baseline, but decreased in both treatment groups to 25% and remained constant thereafter.
- 1.1% of surgical patients had developed endophthalmitis after 5 years.
- Patients randomised to the surgery arm underwent cataract surgery more than twice as often as patients in the medical treatment group.
- Reversal of optic disc cupping was seen in 13% in the surgical group, but was not associated with improved visual function.
- Risk factors for progression differed by treatment group. Patients with more advanced VF loss at baseline had less risk of progression when they received initial surgery versus medication, but VF progression among participants with diabetes who received surgery was greater than those receiving medication. Greater VF progression was observed among medication arm participants who reported poorer adherence to medications.
- Risk factors for progression included higher baseline IOP, worse baseline VF status, and lower level of education.

References:

1. Musch DC, Lichter PR, Guire KE, Standardi CL. The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. *Ophthalmology* 1999;106(4):653-62.
2. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001;108(11):1943-53.
3. Musch DC, Gillespie BW, Niziol LM, et al. Cataract extraction in the collaborative initial glaucoma treatment study: incidence, risk factors, and the effect of cataract progression and extraction on clinical and quality-of-life outcomes. *Arch Ophthalmol* 2006;124(12):1694-1700.
4. Musch DC, Gillespie BW, Niziol LM, et al. Factors associated with intraocular pressure before and during 9 years of treatment in the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology* 2008;115(6):927-33.
5. Musch DC, Gillespie BW, Lichter PR, et al. Visual field progression in the Collaborative Initial Glaucoma Treatment Study the impact of treatment and other baseline factors. *Ophthalmology* 2009;116(2):200-07.
6. Musch DC, Gillespie BW, Niziol LM, et al. Intraocular pressure control and long-term visual field loss in the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology* 2011;118(9):1766-73.
7. Janz NK, Wren PA, Lichter PR, et al. The Collaborative Initial Glaucoma Treatment Study: interim quality of life findings after initial medical or surgical treatment of glaucoma. *Ophthalmology* 2001;108(11):1954-65.

8. Zahid S, Musch DC, Niziol LM, Lichter PR. Risk of endophthalmitis and other long-term complications of trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS). *Am J Ophthalmol* 2013;155(4):674-80, 80.e1.
9. Parrish RK, Feuer WJ, Schiffman JC, Lichter PR, Musch DC & CIGTS Optic Disc Study Group. Five-year follow-up optic disc findings of the Collaborative Initial Glaucoma Treatment Study. *Am J Ophthalmol* 2009;147(4):717-24.e1.
10. Newman-Casey PA, Niziol LM, Gillespie BW, Janz NK, Lichter PR, Musch DC. The association between medication adherence and visual field progression in the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology* 2020;127(4):477-483.

1.7.3.3 The LiGHT trial:

Selective Laser Trabeculoplasty (SLT) versus eye-drops for first-line treatment of ocular hypertension and primary open angle glaucoma (LiGHT): a multi-centre randomised controlled trial.

Newly diagnosed patients with OHT or POAG (718) were randomised to one of two treatment pathways, 'laser-1st' or 'drops-1st'. Eyes in the SLT, 'laser-1st' arm, had up to two SLT treatments before drops if required. Treatment was to pre-set target IOPs based on severity and pre-treatment IOP. Treatment escalation was according to strict objective criteria. The primary outcome was health-related QoL assessed with the EQ-5D at 3 years. Target IOPs were revised upwards if there was no progression. Approximately 50% of study participants were OHT and another 50% were early stage glaucoma.¹

Summary of the results¹⁻⁵:

- There was no differences in health-related QoL between the two groups.
- After 3 years 74% of the laser-1st group remained within target without medication, required fewer trabeculectomies (nil vs 11) and suffered less disease progression than patients in the medication-1st arm.
- SLT was safe and cost-effective compared with medications.
- SLT could be routinely offered to all newly diagnosed patients with POAG/OHT.

References:

1. Gazzard G, Konstantakopoulou E, Garway-Heath D, Garg A, Vickerstaff V, Hunter R, Ambler G, Bunce C, Wormald R, Nathwani N, Barton K, Rubin G, Morris S, Buszewicz M. Selective laser trabeculoplasty versus drops for newly diagnosed ocular hypertension and glaucoma: the LiGHT RCT. *Health Technol Assess* 2019 Jun;23(31):1-102.
2. Gazzard G, Konstantakopoulou E, Garway-Heath D, Garg A, Vickerstaff V, Hunter R, Ambler G, Bunce C, Wormald R, Nathwani N, Barton K, Rubin G, Buszewicz M; LiGHT Trial Study Group. Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial. *Lancet* 2019 Apr 13;393(10180):1505-16.
3. Konstantakopoulou E, Gazzard G, Vickerstaff V, Jiang Y, Nathwani N, Hunter R, Ambler G, Bunce C; LiGHT Trial Study Group. The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre randomised controlled trial: baseline patient characteristics. *Br J Ophthalmol.* 2018 May;102(5):599-603.

4. Ang GS, Fenwick EK, Constantinou M, et al. Selective laser trabeculoplasty versus topical medication as initial glaucoma treatment: the glaucoma initial treatment study randomised clinical trial. *Br J Ophthalmol.* 2020;104(6):813-821.
5. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Selective laser trabeculoplasty versus drops for newly diagnosed ocular hypertension and glaucoma: the LiGHT RCT. *Health Technol Assess* 2019;23:1-102.

I.7.4 Studies comparing treatments in angle closure

I.7.4.1 Effectiveness of early lens extraction for the treatment of primary angle closure glaucoma (EAGLE)

The EAGLE was a multicentre, randomised, prospective clinical trial designed to compare the efficacy, safety, and cost-effectiveness of LPI with clear-lens extraction as the initial treatment of primary PAC and PACG. Eligible patients were aged 50 years or older, did not have cataracts, and had newly diagnosed PAC with IOP 30 mmHg or greater or PACG. 419 patients were randomised and followed up for 3 years, of whom 208 were assigned to lens extraction and 211 to LPI. Primary outcome measures included QoL, assessed with the European Quality of Life-5 Dimensions (EQ-5D), IOP, and cost-effectiveness assessed at 3 years.¹

Summary of results²⁻⁴:

- This study supports the use of initial lens extraction as a first-line intervention for PACG and PAC with high IOP. At 36 months, results show a small but unquestionable advantage of primary lens extraction over LPI for all measured primary outcomes.
- The mean health status score on the EQ-5D (range 0; 1) after lens extraction was 0.052 higher than after LPI.
- The mean IOP was 1.18 mm Hg lower after lens extraction than after LPI (clinicians were allowed to escalate treatment to achieve target IOP).
- Significantly fewer participants in the lens extraction group needed treatment including medications and glaucoma surgery to control IOP than patients who received LPI.
- The incremental cost-effectiveness ratio was better for initial lens extraction versus LPI (calculated on a subset of patients treated in the UK; not conclusive for other settings).
- Patients undergoing lens extraction became emmetropic (mean final refraction, 0.08 diopters) whereas those assigned to LPI remained hyperopic (0.92 diopters).
- VF severity at 3 years remained similar in the two treatment groups.
- Lens extraction can cause endothelial cell loss; this assessment was not part of the EAGLE trial.
- Enrolled patients had either PAC with IOP > 30 mmHg (a minority of patients with this condition) or PACG without advanced damage. The study results are not generalisable to all PAC or PACG cases.
- In this trial the participating surgeons were experienced. Lens extraction to treat angle closure can be technically challenging.

References:

1. Azuara-Blanco A, Burr J, Ramsay C, et al. Effectiveness of early lens extraction for the treatment of primary angle closure glaucoma (EAGLE): a randomised controlled trial. *The Lancet* 2016;388:1389-97.
2. Traverso CE. Clear-lens extraction as a treatment for primary angle closure. *The Lancet* 2016;388:1352-54.
3. Javanbakht M, Azuara-Blanco A, Burr JM, Ramsay C, Cooper D, Cochran C, Norrie J, Scotland G. Early lens extraction with intraocular lens implantation for the treatment of primary angle closure glaucoma: an economic evaluation based on data from the EAGLE trial. *BMJ Open*. 2017.13;7:e013254.
4. Day AC, Cooper D, Burr J, et al. Clear lens extraction for the management of primary angle closure glaucoma: surgical technique and refractive outcomes in the EAGLE cohort. *Br J Ophthalmol* 2018;102(12):1658-62.

I.8 Cost-effectiveness of glaucoma care

Cost-effectiveness is an important consideration when choosing interventions for glaucoma care.

I.8.1 Case detection and screening for glaucoma

There are no systematic reviews or studies that provide evidence for direct or indirect links between glaucoma screening and VF loss, visual impairment, optic nerve damage, IOP, or patient-reported outcomes. Also economic simulation models of cost effectiveness of screening reported inconclusive results with large uncertainties. There is no evidence that interventions (e.g., training) improve opportunistic case finding.

I.8.2 Clinical and cost effectiveness of diagnostic tests used for screening, detection and monitoring for glaucoma

Although there are numerous comparative diagnostic studies, there is no evidence which test, or combination of tests improve patient outcomes, at a sustainable cost. There is a high degree of variability in the design and suboptimal quality of studies of diagnostic accuracy of technologies for glaucoma. Moreover, cost varies with different national or regional health-systems.

I.8.3 Effectiveness of treatment of glaucoma and ocular hypertension in preventing visual disability

There is high-level evidence that treatment decreases IOP and reduces the risk of conversion to and deterioration of glaucoma compared to no treatment.

Based on the economic simulation models in the US, UK, Holland, and China, treating glaucoma is likely to be cost-effective compared to 'no treatment'. There is uncertainty about the cost-effectiveness of treating OHT.^{1,7-9}

Comment:

The published simulation models are based on characteristics of participants enrolled in RCTs which may not include all important predictors in the general population and every-day practice. In addition, RCTs may give an optimistic impression of outcomes compared to 'real life' with poorer compliance and adherence to care both in patients and clinicians in implementing the guidelines and care protocols. As the data of glaucoma inducing visual disability are limited, the blindness rates in the modelling studies use different estimates. Similarly, the data on utility values and influence of glaucoma severity in health status are limited. Retrospective observational data is incomplete and selective. Reliable and 'realistic' data (preferably from large randomised trials or prospective cohorts of 'usual patients') is not available so far.

I.8.4 Follow-up practices and models of care

There is no solid evidence of the optimum monitoring schemes, (e.g. frequency and timing of visits, technologies to be used for detecting progression) for patients with manifest glaucoma or OHT. Some modeling and retrospective studies suggest that more treatment may allow less frequent monitoring visits in OHT and stable glaucoma. It has been proposed that more frequent visits in the first two years from the first diagnosis may be cost-effective.

I.9 Terminology, classification and definitions

Classification and disease definitions are necessarily arbitrary. A consensus can be reached only if they are acceptable to most ophthalmologists on both theoretical and practical grounds. There are conditions where a precise classification is particularly challenging, such as congenital disorders associated with other anomalies.

The following features are to be considered in order to manage the patient

1. Anatomy / Structure (see II.1)
Open angle, angle closed, optic nerve head, etc.
e.g. clinical signs, pseudoexfoliation, pigment dispersion
2. Function (see II.1.4)
e.g. visual field
3. Intraocular pressure level (see II.1)
 - 3.1. At which diagnosis is made (see II.2)
 - 3.2. Target intraocular pressure (see II.3.3)
 - 3.3. General conditions: life expectancy, comorbidities
4. Identifiable cause

Primary open angle glaucoma is a chronic, progressive, potentially blinding, irreversible eye disease causing optic nerve rim and RNFL loss with related visual field defects. The angle is open with a normal appearance, and major risk factors include the level of IOP and older age. Visual disability is usually prevented by early diagnosis and treatment. See II.2.2





Part II · Chapter 1

Patient examination





Part II · Chapter 1

Patient examination

II.1.1 Intraocular pressure (IOP) and tonometry

The intraocular pressure (IOP) in the population is approximately normally distributed with a right skew. The mean IOP in adult populations is estimated at 15-16 mmHg, with a standard deviation of nearly 3.0 mmHg. Traditionally, normal IOP has been defined as two standard deviations above the mean, i.e. 21 mmHg, and any IOP above this level is considered to be elevated. However, any arbitrary threshold of IOP is a false measure to distinguish between health and disease.

The level of IOP is a major risk factor for the development of glaucoma and its progression (see II.3.3).

IOP diurnal variations can be substantial and are larger in glaucoma patients than in healthy individuals. Evaluating the IOP at different times of the day can be useful in selected patients.

II.1.1.1 Methods of measurement (tonometry)

Tonometry is based on the relationship between the IOP and the force necessary to deform the natural shape of the cornea by a given amount. Corneal biomechanical properties, such as thickness and elasticity, can affect the IOP measurements (Table 1.1). Tonometers can be described as contact or non-contact. Some instruments are portable and hand-held.

Table 1.1 Influence of corneal status, thickness and tear film on the IOP value measured with the Goldmann applanation tonometry.

Cornea Status	IOP reading erroneously high	IOP reading erroneously low
Thin central cornea		x
Thick central cornea	x	
Epithelial oedema		x
Excessive tear film		x
Insufficient tear film	x	
Corneal refractive surgery*		x

* Corneal refractive surgeries alter tonometry reading since they modify thickness, curvature and structure of the cornea.

II.1.1.1 Goldmann applanation tonometry (GAT)

The most frequently used instrument, and the current reference standard, is the GAT, mounted at the slit lamp. The method involves illumination of the biprism tonometer head with a blue light (obtained using a cobalt filter). The prism is used to flatten the anesthetised cornea which has fluorescein in the tear film. The scaled knob on the side of the instrument is then turned until the inner border of the two semi-circles of fluorescent tear meniscus, visualised through each prism, just touch (Fig. II.1.1).

There are potential problems of using GAT in that contact with the tear film and the cornea may raise concerns regarding transmissible disease. Chemical disinfection or the use of disposable tonometer heads is recommended. The tonometer calibration should be verified regularly according to the manufacturer instructions.

Errors with GAT can be due to incorrect technique (Fig. II.1.2) and to the biological variability of the cornea and eye. Valsalva's manoeuvre, breath-holding, squeezing the lids or the examiner touching the lids or a tight tie can all falsely increase the IOP reading. The Perkins tonometer is a portable version of GAT. All precautions to sterilize the GAT prism should be taken.

Technique of Goldmann Applanation Tonometry.

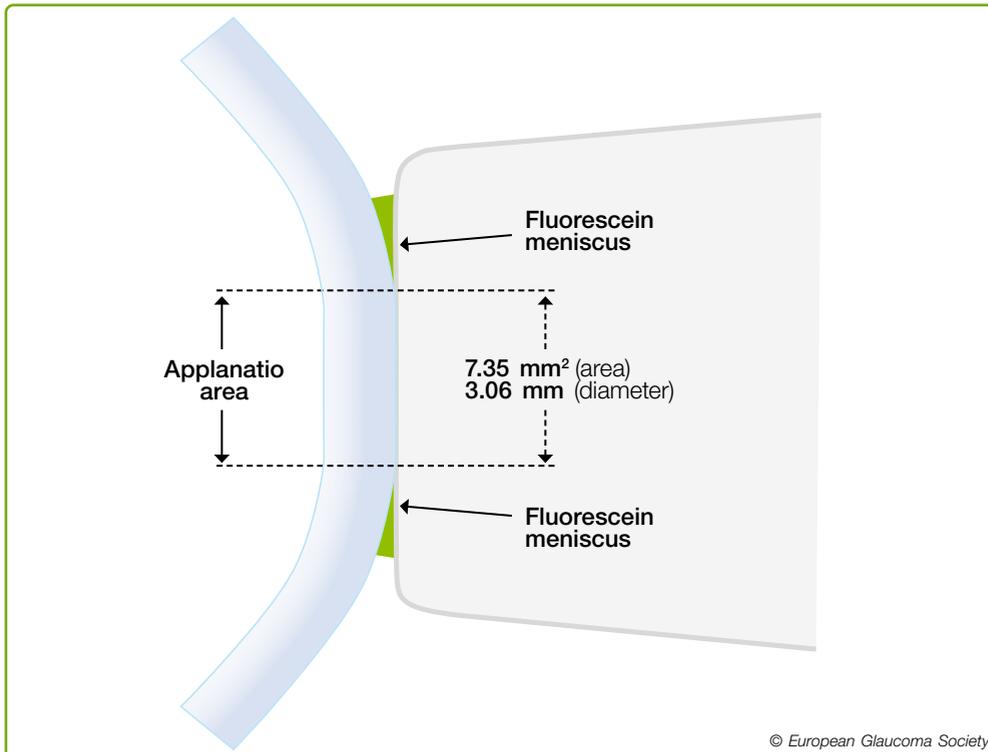


Figure II.1.1 When there is contact between the tonometer prism (right) and the cornea, the stained tear meniscus can be observed through the prism.

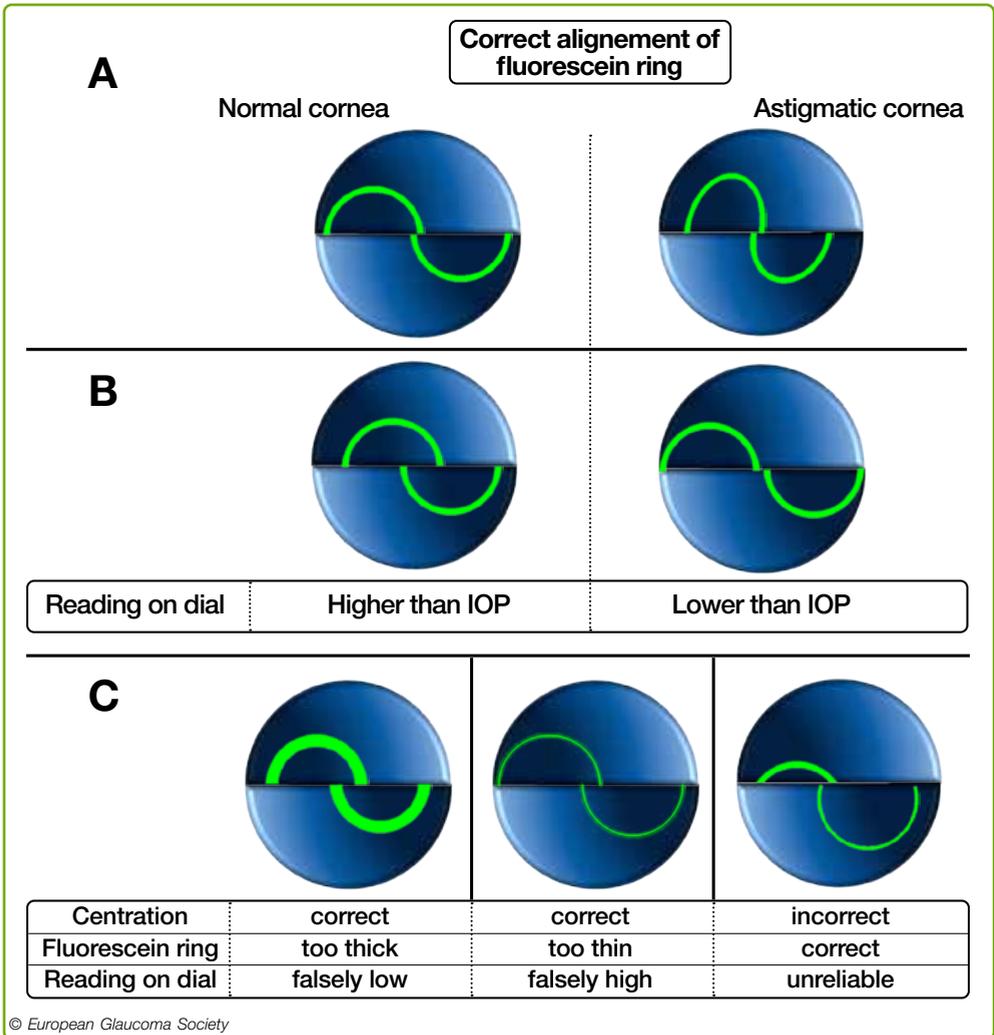


Figure 11.1.2 The correct technique is shown in (A): the prism is correctly aligned to the centre of the cornea and the applied pressure is then adjusted until the inner part of the semicircles touch each other. When the reading is taken before the semicircles are aligned as in (A), the applanation pressure will not correspond correctly to the IOP shown on the dial (B). Incorrect alignment can combine with the wrong amount of fluorescein, adding error on error (C).

Note: In case of high or irregular astigmatism, corrections should be made. One option is to do two measurements, the first with the biprism in horizontal position and the second in vertical position and the readings should be averaged. Another way of correcting large regular astigmatism (> 3 D) is to align the red mark of the prism with the axis of the minus cylinder.

II.1.1.1.2 Alternative tonometers (in alphabetical order) (see also I.3, question 2)

A complete list of all available technologies is beyond the scope of the guidelines.

Dynamic contour tonometry (DCT, or Pascal)

This slit-lamp mounted instrument contains a sensor tip with concave surface contour and a miniaturised pressure sensor. The result and a quality score measure are provided digitally. This technique may be less influenced by CCT than GAT. The DCT additionally measures the ocular pulse amplitude which is the difference between the mean systolic and the mean diastolic IOP.

Non-contact tonometry (NCT)

The NCT or air-puff tonometry uses a rapid air pulse to flatten the cornea, thus working on the same basic principle as the Goldmann tonometer. The advantages include speed, no need for topical anaesthesia and no direct contact with the eye. There are several models available in the market. Some patients find the air-puff uncomfortable. The average of several readings per eye is recommended.

Ocular Response Analyser (ORA) and 7CR

The ORA utilises air-puff technology to record two applanation measurements, one while the cornea is moving inward, and the other as the cornea returns towards its normal shape. The average of these two IOP values provides a Goldmann-correlated IOP measurement. The difference between these two IOP readings is called corneal hysteresis, a result of viscous damping in the corneal tissue. The two applanation measurements provide a basis for two additional new parameters: corneal-compensated IOP (IOP_{cc}) and corneal resistance factor. The corneal-compensated IOP is a measurement that is less affected by the corneal properties. The average of several good quality readings per eye is recommended.

Corvis ST tonometer

The Corvis ST is an air-puff tonometer combined with a high-speed Scheimpflug camera which records the corneal deformation during the air-puff. Outputs include an uncorrected IOP, a corneal biomechanically-corrected IOP and CCT.

Rebound tonometry

The rebound tonometer (iCare), is portable and easy to use. Although it is a contact tonometer topical anaesthetic drops are not required and the tonometer has a disposable tip to minimise the risk of cross-infection. The device processes the rebound movement of a rod probe resulting from its interaction with the eye; rebound increases (shorter duration of impact) as the IOP increases.

Six measurements are taken and their average is displayed. The rebound tonometer can be particularly useful in children. The iCare Home device is a variation that has been designed for self tonometry.

Tono-Pen

The Tono-Pen is a hand-held portable tonometer that determines IOP by making

contact with the cornea (central contact is recommended) through a probe tip, causing applanation/indentation of a small area. Topical anaesthetic eye drops are used. After four valid readings are obtained, the averaged measurement is given together with the standard error.

Both the iCare and Tono-Pen are useful for patients with corneal disease and surface irregularity as the area of contact is small.

II.1.1.1.3 Self-tonometry

Self-tonometry (e.g., with iCare Home) can be useful in some circumstances. However, it cannot replace clinic-based IOP measures.

II.1.1.2 Intraocular pressure and central corneal thickness (see also I.3, question 4)

CCT influences GAT readings (Table 1.1). IOP correction algorithms based on CCT are not validated and should be avoided. There are different methods to measure CCT. The normal distribution (mean \pm SD) of ultrasonic CCT is $540 \pm 30 \mu\text{m}$. CCT variations after corneal refractive surgery make difficult to interpret tonometric readings. A record of pre-operative CCT and IOP is helpful to manage patients undergoing refractive surgery.

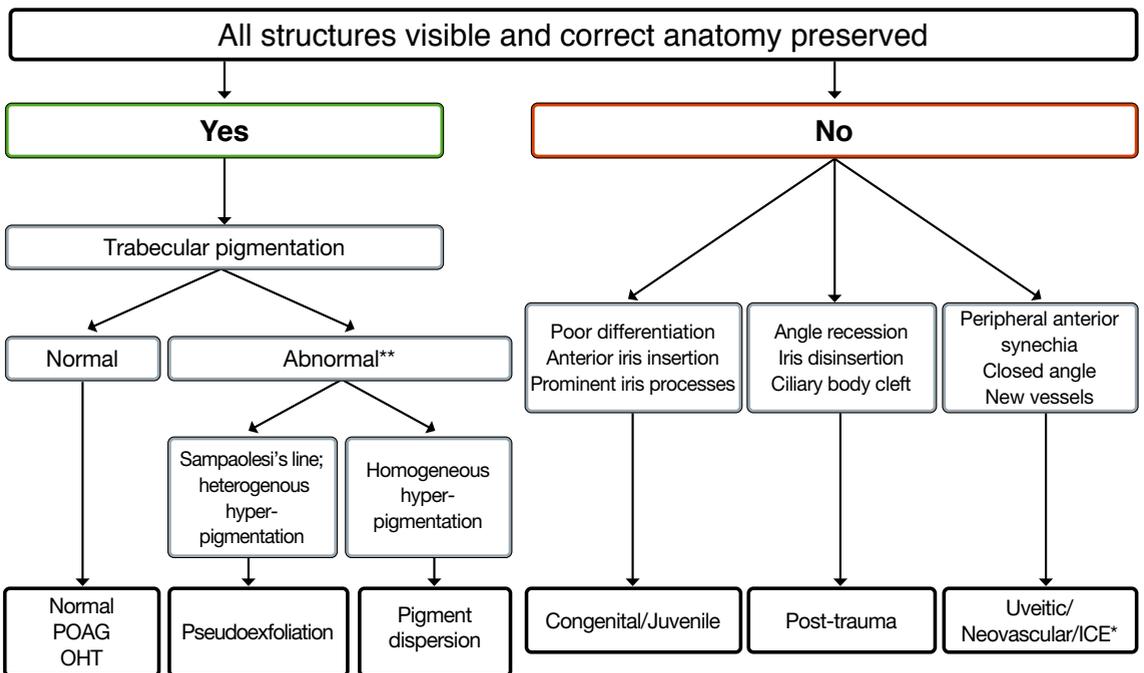
II.1.2 - Gonioscopy

Gonioscopy is essential for evaluating patients suspected of having, or who have glaucoma (See FC II and I.3 Question 5).

The purpose of gonioscopy is to inspect the anterior chamber angle. It is based on the recognition of angle landmarks and must always include an assessment of the following:

- Level of iris insertion, both apparent without indentation and true after indentation
- Shape of the peripheral iris profile either flat, convex or concave
- Width of the iridocorneal angle between peripheral iris and cornea
- Degree, type and distribution of trabecular meshwork pigmentation
- Areas of iridotrabecular apposition or synechia

FC II – Diagnostic gonioscopy in open angle glaucoma



* Irido Corneal Endothelial syndrome

** Hyperpigmentation also possible after trauma, inflammation, laser treatment of iris

II.1.2.1 Anatomy

II.1.2.1.1 Reference landmarks

Schwalbe's line: this collagen condensation of the Descemet's membrane between the trabecular meshwork (TM) and the corneal endothelium appears as a thin translucent line. Schwalbe's line may be prominent and anteriorly displaced (posterior embryotoxon), or there may be heavy pigmentation over it. A pigmented Schwalbe's line may be misinterpreted as the TM, particularly when the iris is convex and the angle is narrow. The corneal wedge method is helpful to distinguish between the structures by reliably identifying Schwalbe's line.

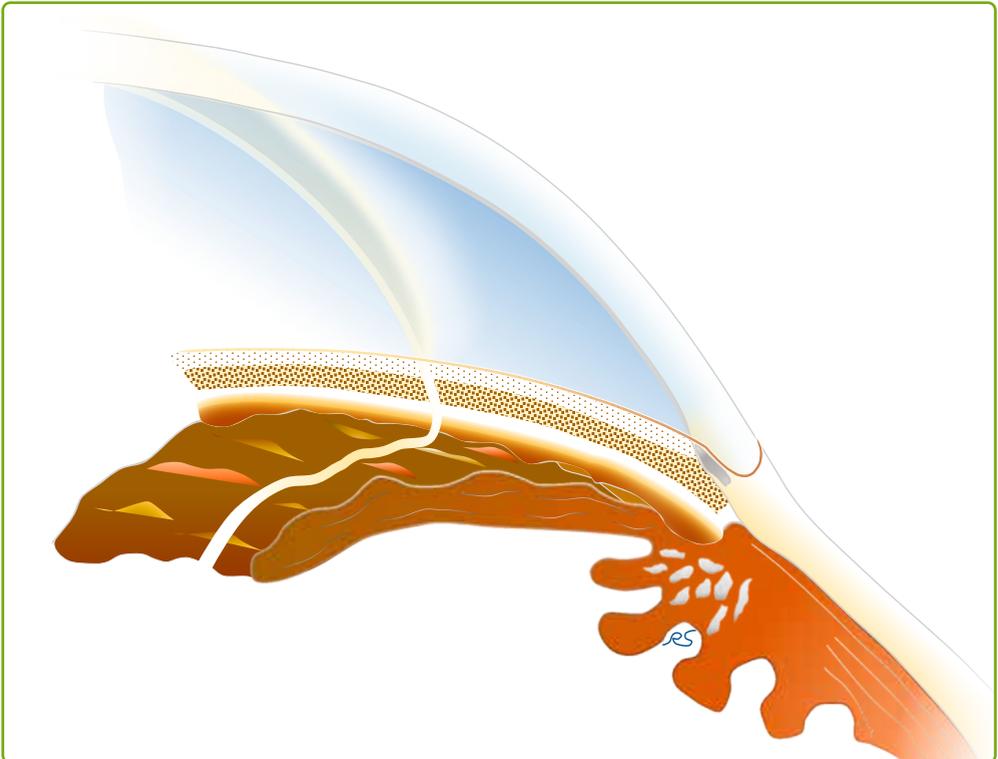


Figure II.1.3 The 'corneal wedge', is a gonioscopy technique that helps the examiner identify the Schwalbe's line in patients where the anterior border of the TM is difficult to see, either because of a lack of pigment or because of excessive pigment. By aiming a thin bright slit at the peripheral cornea, the point where the anterior and posterior reflections of the optical section of the cornea meet identifies the Schwalbe's line.

Trabecular Meshwork (TM): this extends posteriorly from Schwalbe's line to the scleral spur. Close to Schwalbe's line is the non-functional TM, blending into the posterior, functional and often pigmented TM. Most difficulties concerning examination of the TM relate to the determination of whether observed features are normal or pathological (particularly pigmentation), blood vessels and iris processes. Indentation ('dynamic') gonioscopy is helpful to detect TM in angle closure.

Schlemm's canal: it is located anterior to the scleral spur and it is not visible, though it may be seen if it contains blood. Blood reflux from episcleral veins may occur in cases of carotid-cavernous fistulae, Sturge Weber syndrome, venous compression, ocular hypotony, sickle cell disease or due to suction from the goniolens during gonioscopy.

Scleral spur: is of white appearance and located between the pigmented TM and the ciliary body.

Ciliary band and iris root: the iris insertion is usually located at the anterior face of the ciliary body, though the site is variable. The ciliary band may be wide, as in myopia, aphakia or following trauma, or narrow or not seen as in hyperopia, angle closure, and anterior insertion of the iris.

Pigmentation: pigment is found predominantly in the posterior TM. It is seen in adults, rarely before puberty and the extent can be highly variable. The most common conditions associated with dense pigmentation are: PXF, pigment dispersion syndrome (PDS), previous trauma, previous laser treatment of the iris, uveitis and after angle closure episodes.

II.1.2.1.2 Other anatomical features

Blood vessels: these are often found in normal iridocorneal angles in subjects with blue/light irides. They characteristically have a radial or circumferential orientation, have few anastomoses and do not run across the scleral spur. Pathological vessels e.g., neovascularisation, are usually thinner, have a disordered orientation and run across the scleral spur. Abnormal vessels are also seen in Fuchs' heterochromic iridocyclitis and chronic anterior uveitis.

Iris processes: are present in one third of normal eyes, more evident in younger subjects. When numerous and prominent they may represent a form of Axenfeld-Rieger syndrome/ anomaly. They are distinguished from goniosynechiae which are thicker and wider and may go beyond the scleral spur.

II.1.2.2 Techniques

Gonioscopy should be performed in a dimly-lit room, using a thin slit beam, taking care to avoid shining the light through the pupil. Pupil constriction on light exposure opens the angle resulting in an underestimation of the risk of angle closure.

Angle width grading must be performed with the eye in primary position to avoid misclassification. If the patient looks in the direction of the mirror the angle appears wider and vice versa. A common pitfall is inadvertent pressure over the cornea, which will push back the iris, and gives an erroneously wide appearance to the angle. All precautions to sterilize the goniolens should be taken.

There are two main techniques for viewing the anterior chamber angle:

Direct gonioscopy

The use of some contact goniolenses like the Koepple or Barkan lens permits the light from the anterior chamber to pass through the cornea so that the angle may be viewed (Fig. II.1.4 A).

Indirect gonioscopy

The light from the anterior chamber is made to exit via a mirror built into a contact glass (Fig. II.1.4 B).

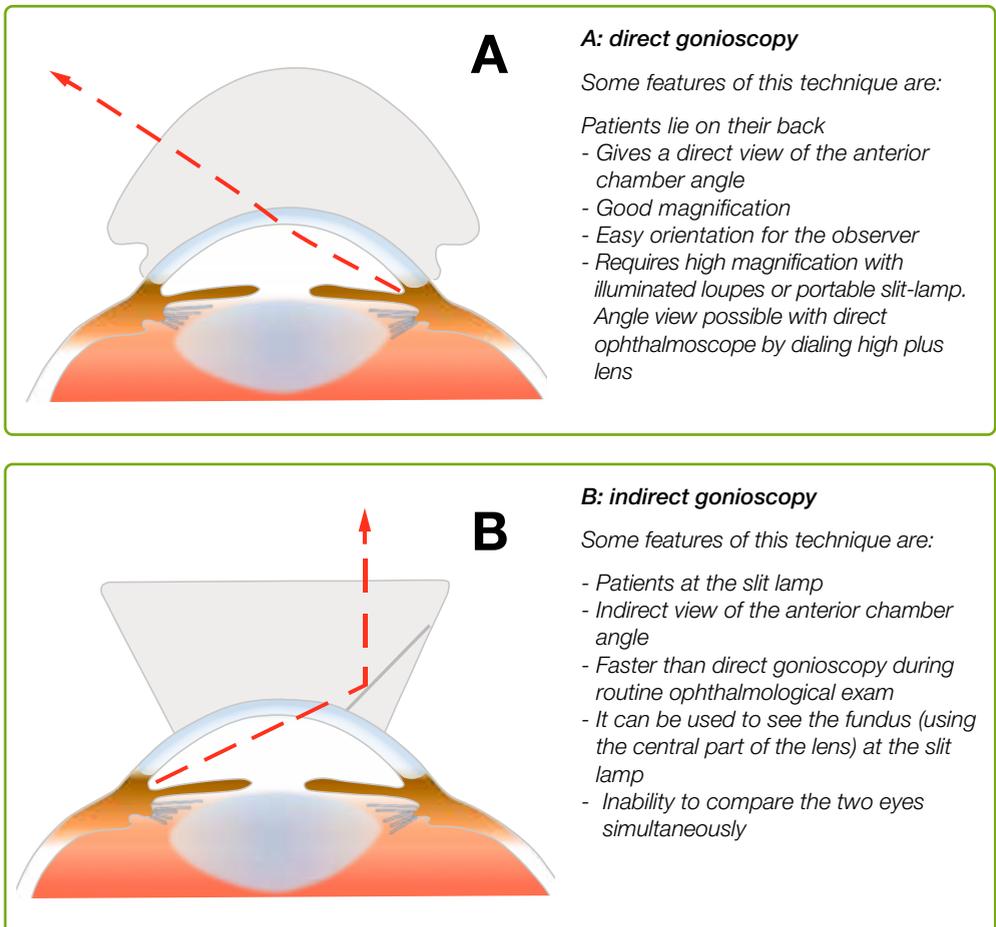


Figure II.1.4

Common gonioscopy lenses:

Direct	Koeppe (contact fluid required) Layden (sized for infants; contact fluid required) Worst Swan-Jacob
Indirect	Posner, Zeiss, Sussman or Khaw 4 mirrors (contact fluid not required) Goldmann lens, 1 to 4 mirrors (contact fluid required) CGA 1.4® Lasag (contact fluid required) Magnaview (contact fluid required)

II.1.2.2.1 Gonioscopy technique without indentation

Patient should be instructed to look straight ahead. With indirect Goldmann-type lenses it is helpful to start by viewing the inferior angle, which often appears wider and more pigmented than the superior angle. Then to continue rotating the mirror. The anterior surface of the lens should be kept perpendicular to the observation axis so that the appearance of the angle structure is not changed as the examination proceeds. The four quadrants are examined by a combination of slit-lamp movements and prism rotation.



© European Glaucoma Society

Figure II.1.5 The "double hump" is a sign observed in plateau iris.

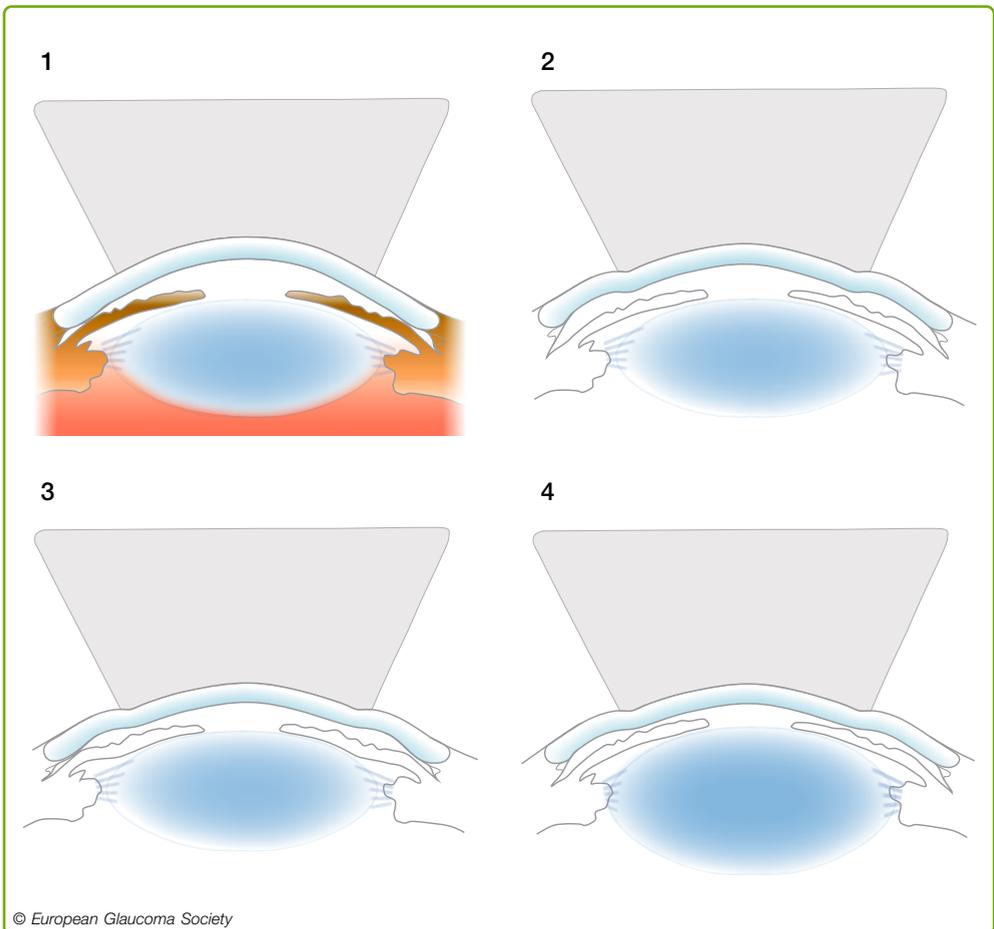


Figure II.1.6 Dynamic indentation gonioscopy. When no angle structure is directly visible before indentation, angle closure may be present, and it can be synechial or appositional (1). If during indentation the iris moves peripherally backwards and the angle recess widens (2), the picture in (1) is to be interpreted as appositional closure and a suspicion of relative pupillary block is raised (2). When during indentation the angle widens but iris strands remain attached to the angle outer wall (3), the picture in (1) is to be interpreted as synechial closure. A large and/or anteriorly displaced lens causes the iris to move only slightly and evenly backwards during indentation (4) making the lens a likely component of angle closure.

To differentiate appositional from synechial closure “indentation” or “compression” dynamic gonioscopy is essential.

II.1.2.2.2 'Dynamic' gonioscopy by indentation or compression

It is recommended to use a small diameter lens for indentation (e.g.: 4-mirror). When gentle pressure is applied by the lens on the centre of the cornea, the aqueous humour (AH) and iris are pushed back. In appositional angle closure, the angle can be re-opened. If there is adhesion between the iris and the meshwork, as with goniosynechia, that portion of angle remains closed (Fig. II.1.6 (3)).

When pupillary block is the prevalent mechanism the iris becomes peripherally concave during indentation. In plateau configuration this iris concavity will not be extended by indentation to the extreme periphery, which is a sign of anteriorly placed ciliary processes called double hump sign (Fig II.1.5). When the crystalline lens has a particularly prominent role in angle closure, indentation causes the iris to move only slightly backwards, retaining a convex profile (Fig. II.1.6 (4)).

II.1.2.3 Grading of the anterior chamber angle

The use of a grading system for gonioscopy is recommended. It encourages the observer to use a systematic approach in evaluating angle anatomy, allows comparison of findings at different times in the same patients, and classification of the angle.

The Spaeth gonioscopy grading system is the most detailed (Fig. II.1.7).

Other practical grading systems are those of Shaffer and Kanski; both are based on angle width and visibility of the angle structures.

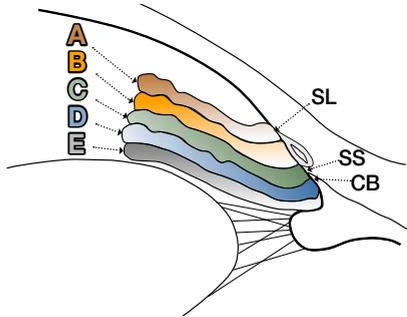
II.1.2.3.1 Slit lamp-grading of peripheral AC depth - The Van Herick method

The Van Herick grading (Fig. II.1.8) is an indirect estimation of angle width, but it is not a substitute for gonioscopy. This technique is based on the use of corneal thickness as a unit measure of the depth of the anterior chamber at the furthest periphery, preferably on the temporal side.

Grade 0 represents iridocorneal contact, i.e., angle closure.

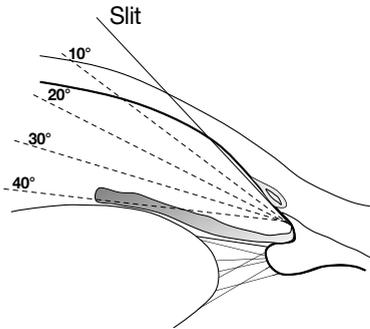
A space between iris and corneal endothelium of less than 1/4 corneal thickness, is equivalent to a Shaffer grade I and is interpreted as a high risk of anatomical angle closure. When the space is between 1/4 and 1/2 corneal thickness the grade is II, with very low risk of angle closure. A grade III is not occludable, with an irido/endothelial distance more than 1/2 corneal thickness. Alternatively, the peripheral anterior chamber depth may be expressed as a percentage of the peripheral corneal width.

Document the insertion level of the iris root before and during compression dynamic gonioscopy



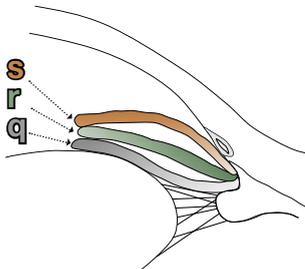
Insertion of iris root

- A** Anterior to Schwalbe's line (SL)
- B** Behind Schwalbe's line
- C** On the scleral Spur (SS)
- D** Behind the scleral spur
- E** On the ciliary band (CB)



Angular width of angle recess

- | | | |
|------|----------|--|
| Slit | Closed | |
| 10° | } Narrow | |
| 20° | | |
| 30° | } Wide | |
| 40° | | |



Configuration of the peripheral iris

- S** Steep, anteriorly convex
- R** Regular
- Q** Anteriorly concave
- P** Plateau configuration

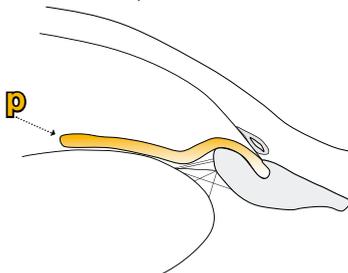


Figure II.1.7 The Spaeth Grading System of gonioscopy finding.

II.1.2.4 Anterior segment imaging techniques (see I.3, question 5)

Anterior segment imaging such as ultrasound biomicroscopy (UBM), anterior segment OCTs and Scheimpflug cameras can be useful in some circumstances but cannot replace gonioscopy. Added to gonioscopy, imaging techniques may help elucidate the mechanism of angle closure. UBM can be particularly helpful as it can image tissues behind the iris (anteriorly placed iris processes in plateau iris, tumours, cysts). Anterior segment imaging provide quantitative angle measurements and help documenting the dynamics of the chamber angle at different light conditions. Anterior segment imaging may classify more eyes as having angle closure than gonioscopy, thus it may lead to overdiagnosis. Automated 360° goniophotography is also available.

Systematic reviews:

- Jindal A, Ctori I, Virgili G, Lucenteforte E, Lawrenson JG. Non-contact tests for identifying people at risk of primary angle closure glaucoma. Cochrane Database Syst Rev. 2020;5:CD012947.

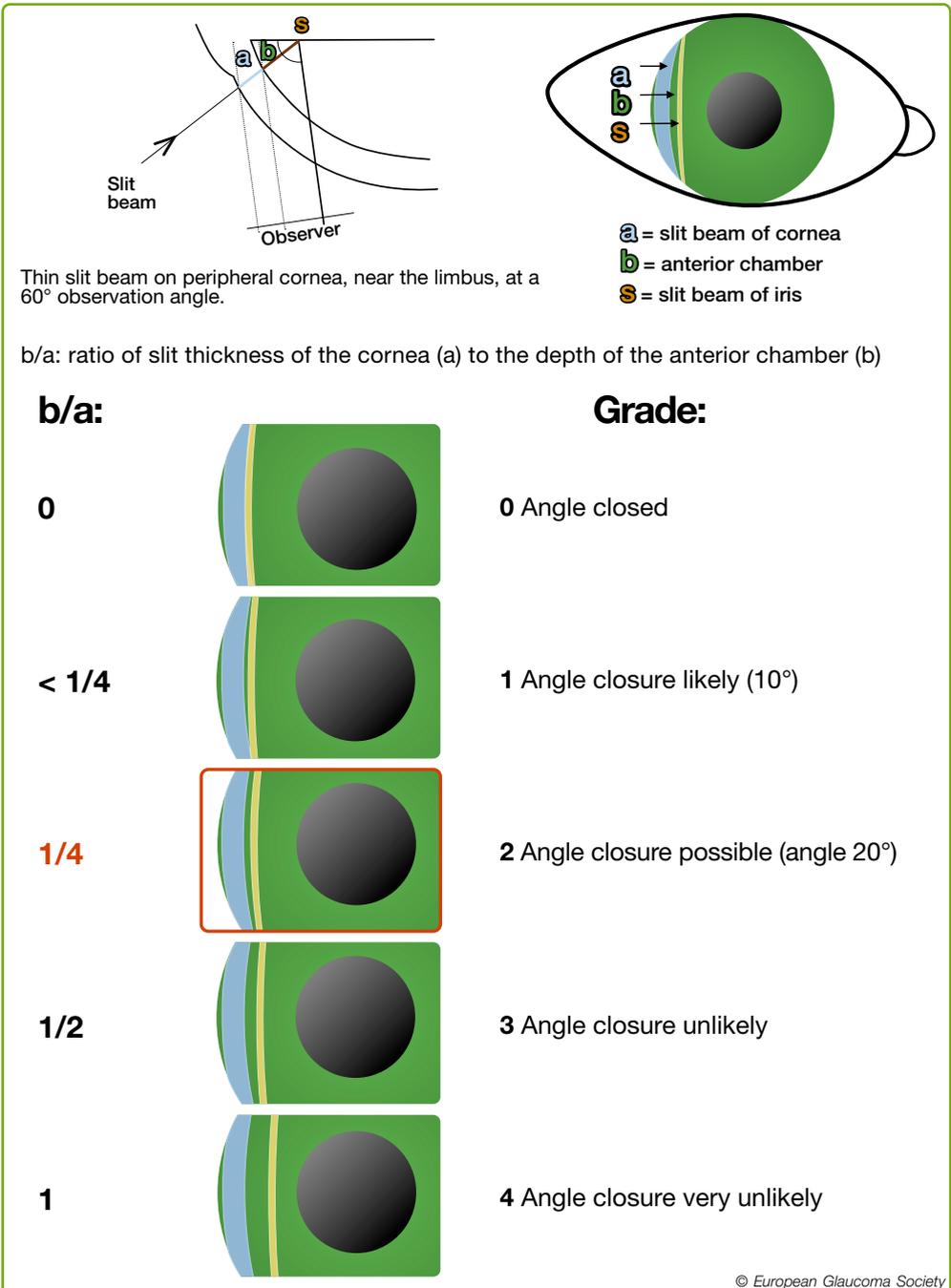


Figure II.1.8 The Van Herick test (see II.1.2.3.1).

II.1.3 Optic nerve head and retinal nerve fibre layer

Glaucoma changes the appearance of the ONH, particularly the neuroretinal rim and vessels, and the RNFL in a characteristic fashion.

Contour changes can best be appreciated with a magnified stereoscopic view preferably through a dilated pupil. Interim examinations, aimed at detecting striking features such as disc haemorrhages, may be performed through an undilated pupil.

Stereoscopic examination of the posterior pole is best performed with:

- Indirect non-contact fundus lens with sufficient magnification at the slit-lamp or
- Direct contact fundus lens at the slit-lamp

The direct ophthalmoscope is also useful for ONH and RNFL examination.

The clinical evaluation of the ONH and RNFL should assess the following features.

II.1.3.1 Clinical examination

II.1.3.1.1 Neuroretinal rim

In a healthy eye, the shape of the rim is influenced by size, shape and tilting of the ONH. The disc is usually slightly vertically oval, often more so in black subjects who may also have larger discs. In medium-size discs, the neuroretinal rim is typically at least as wide at the 12 and 6 o'clock positions as elsewhere and usually widest in the infero-temporal sector, followed by the supero-temporal, nasal and then temporal sectors (see Fig. II.1.9). This pattern, described as ISN'T distribution, is less obvious in larger discs, in which the rim is distributed more evenly and in a smaller discs where cupping may not be evident. Larger and a smaller discs are harder to interpret: e.g., in small discs the changes associated with glaucoma may not result in cupping, but 'saucerization' of the disc surface instead. In large optic discs the normal rim width is relatively narrow and can potentially be misinterpreted as glaucomatous.

The exit of the optic nerve from the eye may be oblique, giving rise to a tilted disc. Tilted discs are more common in myopic eyes, and show a wider, gently sloping rim in one disc sector in the direction of the tilt and a narrower, more sharply-defined rim in the opposite sector. Discs in highly myopic eyes are even harder to interpret.

Glaucoma is characterised by progressive narrowing of the neuroretinal rim. The pattern of rim loss varies and may take the form of diffuse narrowing, localised notching, or both in combination (Fig. II.1.10). Narrowing of the rim, while occurring in all disc sectors, is generally more common and greatest at the inferior and superior poles.

II.1.3.1.2 Retinal nerve fibre layer

The RNFL appearance can be best assessed in the central 60° at the posterior pole with a blue filter photograph. Clinically at the slit lamp, the RNFL is best evaluated with a red-free light and low magnification and/or with a short, narrow beam of bright white light at high magnification around the circumference of the optic disc within about two disc diameters of the disc margin. The RNFL surface is best seen if the focus is adjusted just anterior to the main retinal vessels.

The fibre bundles are seen as radial silver striations around the disc, slit-like, groove-like, or spindle-shaped apparent defects, narrower than the retinal vessels, may be seen in the normal fundus. The RNFL may become less visible with age, and is more difficult to see in less pigmented fundi.

Local (wedge and slit) defects are seen as dark bands, wider than retinal vessels which will extend to the disc margin. These local defects are more easily seen than generalised thinning of the RNFL, which manifests as a loss of brightness and density of striations. When the RNFL is thinned, the blood vessel walls appear sharp against a matt and mottled background. The initial abnormality in glaucoma may be either diffuse thinning or localised defects.

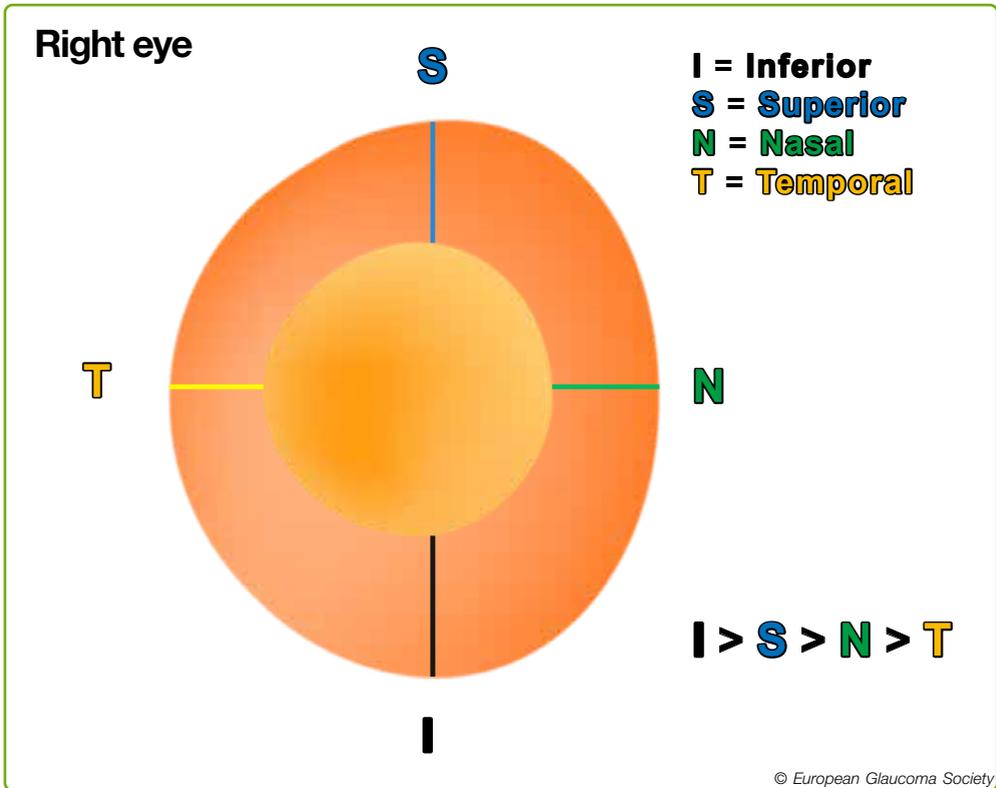


Figure 11.1.9 The ISNT rule.

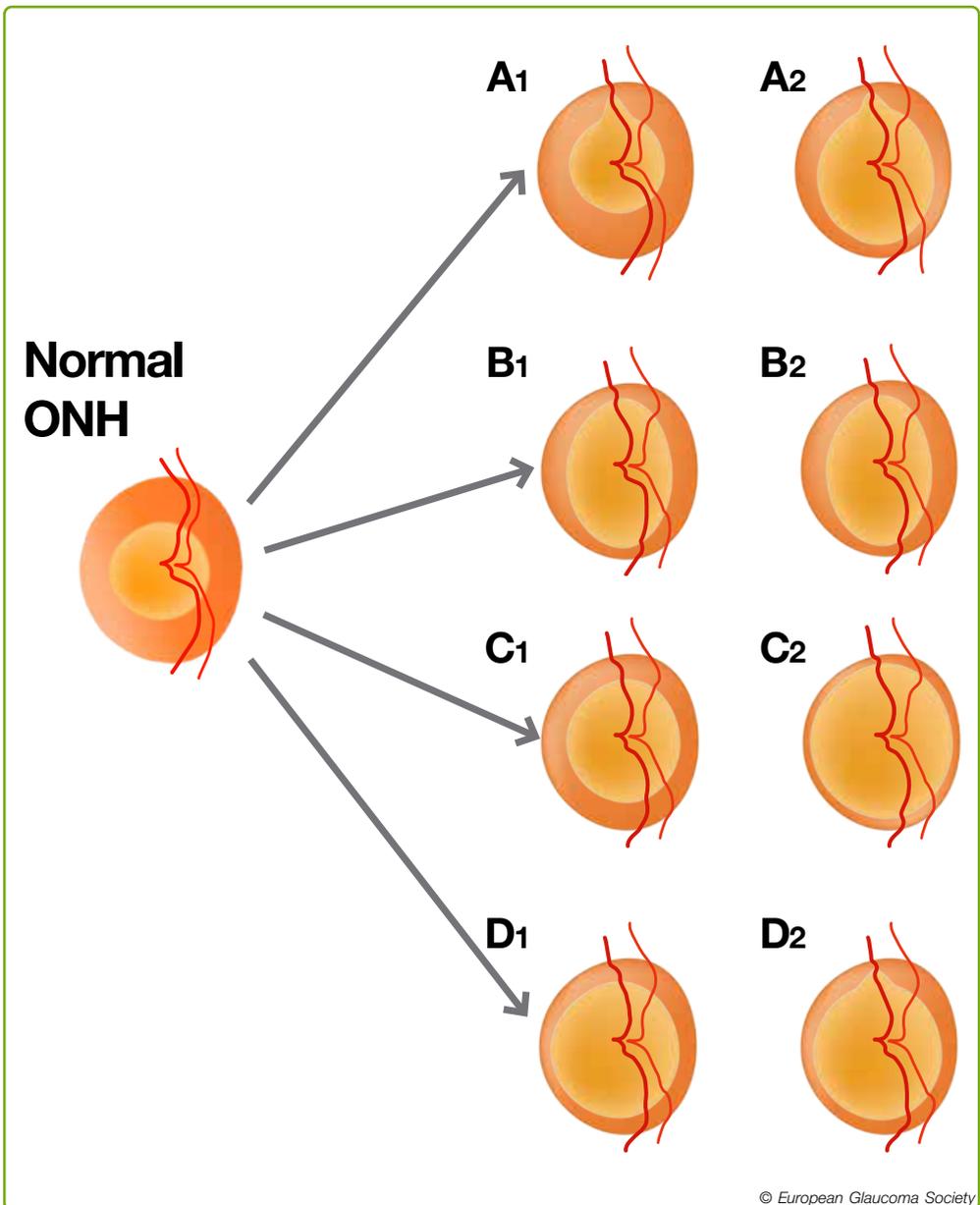


Figure II.1.10 Progression of glaucomatous damage at the optic disc:
 Early localized loss (A1), advancing to localized plus diffuse rim loss (A2).
 Early localized rim loss, polar notches (B1); more advanced polar notches (B2). Diffuse or concentric rim loss, early (C1); advanced (C2).
 Diffuse rim loss (D1), followed by localized rim loss (notch) (D2).

II.1.3.1.3 Optic disc haemorrhages

A large proportion of glaucoma patients have optic disc haemorrhages at one time or another (Fig. II.1.11). They are very often overlooked at clinical examinations, and are easier to find in photographs. The clinical examination should include actively looking for disc haemorrhages. Many studies have shown that optic disc haemorrhages are associated with a higher risk for glaucomatous progression.

II.1.3.1.4 Vessels at the optic disc

Narrowing of the neuroretinal tissue will change the position of the vessels at the optic disc with bending, bayoneting or barring of circumferential vessels. Those positional changes are particularly important to observe when looking for progression, and can be detected with sequential photographs.

II.1.3.1.5 Parapapillary atrophy

Parapapillary atrophy can be differentiated into an alpha zone, which is present in most eyes, and into a beta zone, which is present in some normal eyes and in a high percentage of eyes with glaucoma. Beta parapapillary atrophy is common in myopic and older eyes.

In clinical practice, a large beta zone can be regarded as a clue, and not as a definite sign of glaucoma (Fig. II.1.12).

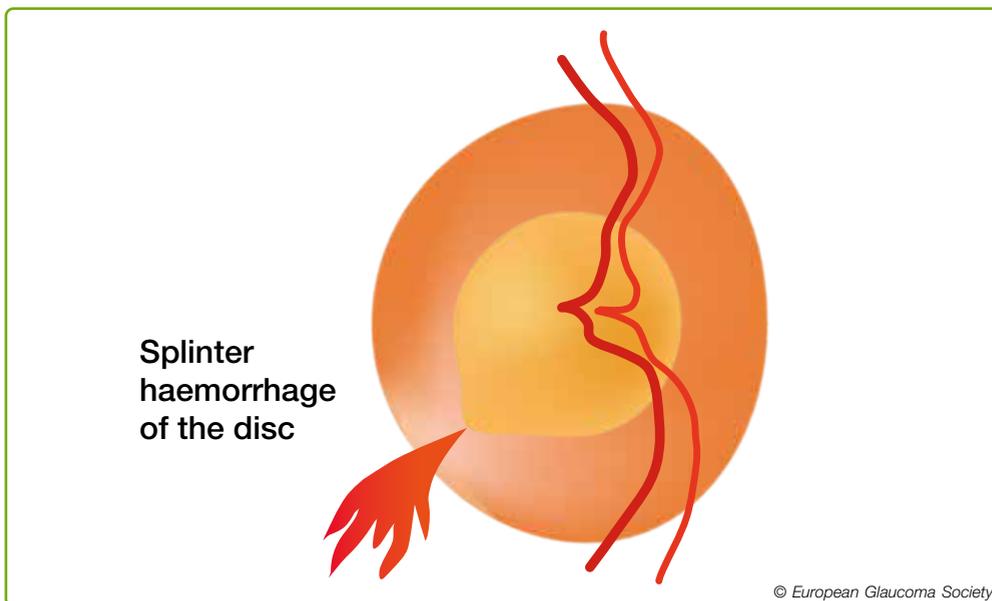


Figure II.1.11 Optic disc haemorrhage.

II.1.3.1.6 Optic disc size (vertical disc diameter)

The optic disc size greatly varies in the population. The width of the rim and the size of the cup vary with the overall size of the disc. The mean vertical disc diameter is approximately 1.9 mm.

The vertical diameter of the optic disc can be measured at the slit lamp using a hand-held high power convex lens. The slit beam should be coaxial with the observation axis; a narrow beam is used to measure the vertical disc diameter using the inner margin of the white Elschnig's ring as the reference. A correction factor needs to be used depending on the magnification of the handheld lens (Fig. II.1.13).

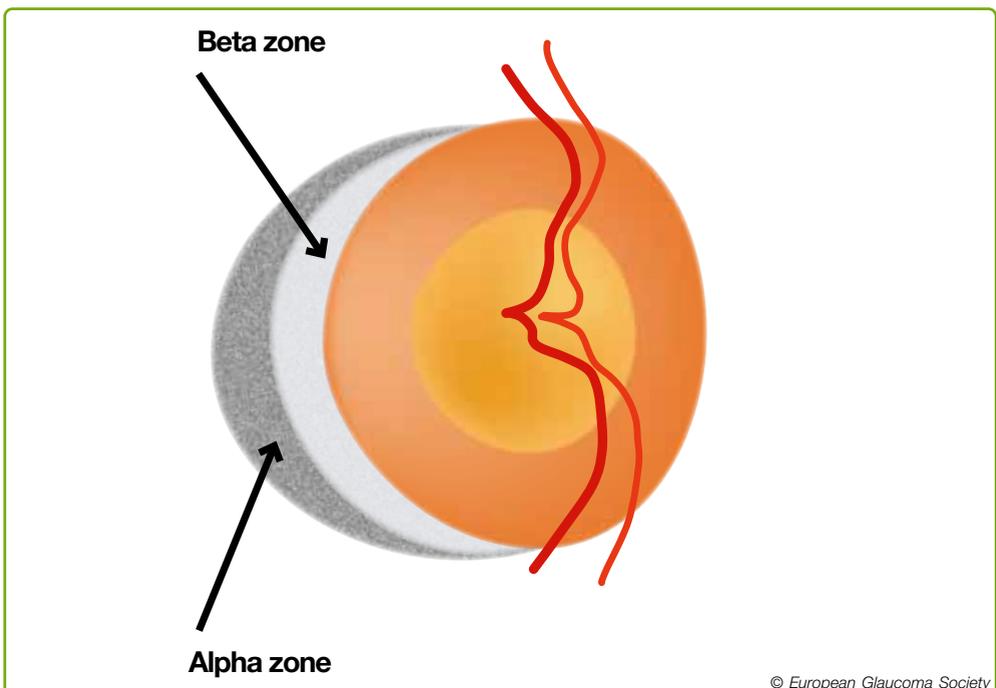
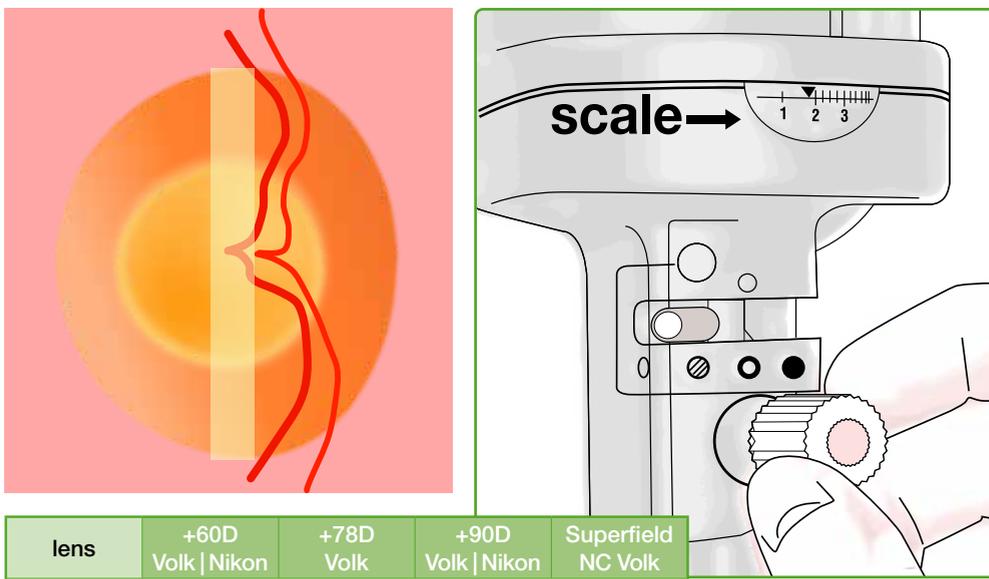


Figure II.1.12 ONH with parapapillary atrophy. The Alpha zone is located peripheral to beta zone, and is characterized by irregular hypo- and hyperpigmentation.

The Beta zone of atrophy is adjacent to the optic disc edge, external to Elschnig's ring (a white circular band that separates the intra- from the peri-papillary area of the optic disc), with visible sclera and large choroidal vessels.

II.1.3.1.7 Rim width and cup to disc ratio (CDR) (see “ Things to avoid - choosing wisely” I.4)

A large CDR has been used as a sign of glaucoma damage. However, the CDR depends mainly on the disc size, and a large CDR in normal large discs may be erroneously considered glaucomatous and a small CDR in glaucomatous small discs may be erroneously considered as normal (Fig. II.1.13). The use of CDR to classify patients is not recommended and the attention should be focused on the neuroretinal rim.



© European Glaucoma Society

lens	+60D Volk Nikon	+78D Volk	+90D Volk Nikon	Superfield NC Volk
correction factor	0.94 1.03	1.13	1.36 1.59	1.50

Measured uncorrected vertical diameter of optic disc			
Disc area	Small (<1.6 mm ²)	Medium (1.6 to 2.8 mm ²)	Large (>2.8 mm ²)
Volk 60 D	<1.65 mm	1.65 to 2.2 mm	>2.2 mm
Volk 78 D	<1.3 mm	1.3 to 1.75 mm	>1.75 mm
Volk 90 D	<1.1 mm	1.1 to 1.45 mm	>1.45 mm
Superfield	<1.15 mm	1.15 to 1.50 mm	>1.5 mm
Digital 1.0x	<1.5 mm	1.5 to 1.95 mm	>1.95 mm
Super 66	<1.45 mm	1.45 to 1.9 mm	>1.9 mm
Nikon 60 D	<1.45 mm	1.45 to 1.9 mm	>1.9 mm
Nikon 90 D	<0.95 mm	0.95 to 1.25 mm	>1.25 mm
Haag-Streit Goldmann	<1.3 mm	1.3 to 1.7 mm	>1.7 mm

Figure II.1.13 Optic disc size assessed at the slit lamp with handheld high power convex lens.

II.1.3.2 Recording of the optic nerve head (ONH) and RNFL features

Some form of photography or imaging is recommended to provide a record of the ONH and RNFL appearance. If photos are not available, a detailed manual drawing is recommended. Even if it is difficult to draw a good picture of the ONH, the act of making a drawing encourages a thorough clinical evaluation of ONH. Document whether or not a disc haemorrhage is present.

Sequential photographs can be used to detect progression of optic disc and RNFL damage.

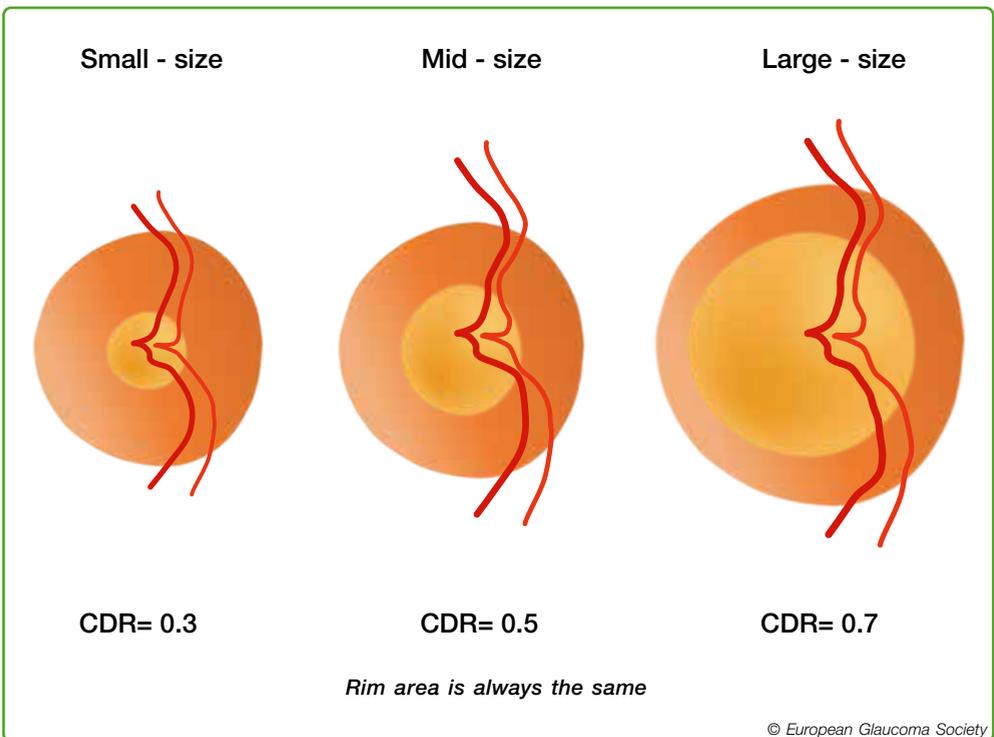


Figure II.1.14 Optic nerve heads with different disc areas but with the same rim area and the same number of retinal nerve fibres: small size disc (disc area less than 2 mm² and CDR=0.3), mid-size disc (disc area between 2 and 3 mm², CDR=0.5) and large disc (disc area more than 3 mm² and CDR=0.7).

II.1.3.2.1 Quantitative imaging (also see I.3)

Quantitative imaging of the ONH, retinal nerve fibre layer and inner macular layers have been used widely to assist glaucoma diagnosis and to detect glaucomatous progression during follow-up. **They should not and cannot replace clinical examination and VF testing. See details about OCT testing and interpretation at the EGS book "Glaucoma Imaging" (2017): <https://www.eugs.org/eng/books.asp>**

Optical coherence tomography

OCT is based on interferometry and is a commonly used test. Current instruments are spectral domain and swept-source OCT systems. Their technical, software and reference database characteristics vary; therefore values measured with different OCT systems are not interchangeable. Three main parameter groups are measured and analysed for classification and detection of progression: ONH, peripapillary retinal nerve fibre layer and macular inner retinal layers.

Interpretation of apparent progression in OCT has to be done with caution due to the possible variability of the measurements and possible non-glaucoma related changes. In cases of advanced loss, progression analysis may be beyond the dynamic range of the instrument.

OCT angiography is a rapidly evolving technology the role of which is not yet defined in glaucoma management.

Confocal Scanning Laser

The HRT (Heidelberg Engineering, Heidelberg, Germany) is used to profile and measure the three-dimensional anatomy of the ONH and surrounding tissues. It can also help detect progressive changes in ONH surface topography but apparent changes need to be interpreted in the clinical context.

II.1.3.2.2 OCT for glaucoma diagnosis (also see I.3)

OCT imaging instruments typically provide three potential outcomes: 'within normal limits', 'borderline' and 'outside normal limits'. No imaging device provides a clinical diagnosis but just a statistical result, based on comparison of the measured parameters with the corresponding reference database of healthy eyes. Therefore an interpretation of the result in the context of all clinical data is mandatory. For instance, imaging artefacts and software errors are quite common and more frequent in eyes that are highly myopic or have tilted nerves. The clinician should assess the quality of the image and segmentation analysis and judge whether the reference database is relevant for the particular patient.

The various imaging technologies have their own advantages and limitations, and their classification shows only partial agreement with clinical exam in diagnosing glaucoma. Agreement between classification with quantitative imaging and VF testing is only moderate. Diagnosis of glaucoma based only on OCT exam should be avoided.

An OCT test “outside normal limits” may be a false positive and can be ignored especially if the clinical examination and VF test are normal and if there are no risk factors for glaucoma.

II.1.3.2.3 Detection of progression with OCT (also see I.3)

Most commercial imaging devices have software for quantifying glaucomatous progression, including the rate of progression. These results may serve as additional tools for the assessment of glaucomatous progression but need careful interpretation in conjunction with other tests and patients circumstances. High quality baselines images are important. The user should assess the test series for the quality of images and software analysis before including the software output in the assessment of the patient. Agreement between structural progression and functional deterioration, over the relatively short duration of reported studies, is only partial or poor because of the measurement variability of both structural and functional tests. Most commercially available software does not compensate for aging, therefore statistically significant slopes do not necessarily mean true glaucomatous progression. Results acquired with different instruments are not interchangeable.

II.1.4 Perimetry

II.1.4.1 Perimetry techniques

VF testing plays a central role in the diagnosis and, more importantly, the management of glaucoma. Loss of visual function is associated with loss of QoL, and it is therefore necessary to monitor each glaucoma patient's VF status.

Static computerised perimetry is preferred in glaucoma management. Kinetic, e.g. Goldmann, perimetry is not suitable for detection of early glaucomatous field loss, since small defects can often be missed between isopters. Computerised perimetry is also less subjective; the results are numerical and tools for computer-assisted interpretation are available. Manual kinetic perimetry may be useful in end-stage disease and in the few patients unable to perform automated perimetry.

II.1.4.1.1 Automated threshold perimetry

The term, standard automated perimetry (SAP), refers to static computerised threshold perimetry performed using standard Goldmann white stimuli on a white background, and is the recommended standard in glaucoma management.

Testing algorithms and programs

Various perimeters attempt to estimate perimetric threshold sensitivity using different testing algorithms and patterns. Commonly used threshold algorithms in the Humphrey perimeter are Swedish interactive threshold algorithm (SITA) Standard, SITA Fast and SITA Faster. In the Octopus perimeter the Dynamic Strategy is often recommended. The Octopus TOP algorithm (tendency-oriented perimetry) is also often used. TOP is a fast strategy, as it exposes only one stimulus at each test point location, interpolating thresholds between several points.

In glaucoma patients and suspects, perimetry is usually performed using a Goldmann size III stimulus in the central 24° or 30° field, where the great majority of retinal ganglion cells are located. The VF outside 30° is seldom tested. In recent years it has sometimes been recommended to perform additional testing focussing on the central 10° of the field, in order to detect more central field loss. EGS does not recommend decreasing the frequency of standard 24° or 30° testing by replacing these tests with 10° tests. Such additional testing may be helpful in patients where structure/function findings do not agree, e.g., in eyes with normal central 24° or 30° VFs but pathological or suspect optic nerve or RNFL findings. Central field loss is very common in glaucoma and such loss even at very central points, often referred to as 'threat to fixation' is clinically worrisome since central VF defects can be symptomatic and compromise the ability to drive.

To the extent possible, it is advantageous to follow patients using a consistent test pattern and strategy, in order to facilitate detection and quantification of progression. In eyes with advanced VF loss, it may become necessary to switch to a larger stimulus size, e.g. to a Goldmann size V stimulus rather than size III, or to a test point

pattern which focuses more closely on the remaining area of functioning vision. In most perimeters one may use test point patterns covering only the central 10° of the field in eyes which have only 'tunnel' fields left.

II.1.4.1.2 Non-conventional perimetry

Some modalities of computerised perimetry use testing stimuli that differ from those used in SAP. Examples include SWAP, frequency doubling technology (FDT), and flicker perimetry. These techniques were developed with the hope that they would be able to recognise glaucomatous field loss earlier than conventional SAP, but lacking such evidence they are not often used today in glaucoma management.

II.1.4.1.3 Patient instructions

The role of the perimetric technician is of greatest importance in patients who are new to automated perimetric testing. Perimetrically inexperienced patients will produce more reliable test results if the operator simply explains what to expect and how to respond to stimuli. It must be pointed out to perimetric novices that most stimuli will be very dim and that even subjects with normal VFs will see only half of the stimuli. A demonstration lasting just a few seconds, in which the novice sees what the stimuli look like, where they will appear and how they change brightness will help the patient understand the test, and will reduce patient anxiety, thus making patients more willing to return for future perimetric testing. Most experienced patients require only minimal re-instruction. However, even with experienced patients, the operator should remain in the vicinity of the perimeter in order to hear and respond to any patient queries. A quiet, dimly lit environment should be ensured. All perimetric technicians should have taken enough threshold perimetry tests themselves to understand first-hand what it is like to take a test.

The learning effect

Many subjects show an improvement in performance reflected as improved reliability and sensitivity over the first few tests.

II.1.4.2 Interpreting test results

Most perimeters provide test results and analyses in paper or electronic reports containing different maps of the VF plus summary indices and other interpretations.

II.1.4.2.1 Test data elements commonly seen in perimetry reports

- The numerical threshold map provides the 'raw' estimated threshold values at each test point location.

- The grey scale maps provide a graphical representation of the numerical threshold map, while the colour-coded maps provide a graphical representation of the deviations from age-corrected normal values.
- The numerical total deviation map shows point-wise differences between the age-corrected normal threshold sensitivity at each test point location and the patient's measured threshold value.
- The numerical pattern deviation map and the corrected deviation map show the same values but after correction for any diffuse loss of sensitivity. Thus, both types of deviation maps highlight localised field loss.
- Probability maps provide the statistical significance of the numerical deviations, compared to age corrected normative data.

II.1.4.2.2 Reliability indices

These indices are meant to estimate the reliability of test results, and were developed in the early days of automated perimetry. Over time it has become clear that these indices are themselves not very reliable. Thus, high frequencies of false negative (FN) responses have been shown to be of relatively little value in the evaluation of glaucomatous VFs, since abnormal fields often have high FN values even in patients who are very attentive and responsive. High rates of fixation losses (FL) assessed using the blind spot technique may indicate poor fixation, but if the blind spot position is erroneously located, a high FL rate will be indicated even if fixation is perfect. It is probably better to rely on the automatic eye/gaze tracker of the perimeter or the judgement of the perimetrist. High frequencies of false positive (FP) answers, may be a sign of poor reliability, but many tests with relatively high FP rates have been found to provide useful information. Most patients will deliver very useful perimetry test results if properly instructed, and one should avoid discarding fields a priori only because one or more reliability parameters has been flagged by the instrument's software.

II.1.4.2.3 Visual field indices

VF indices are numbers summarising perimetric test results. MD (mean deviation in the Humphrey or mean defect in the Octopus) represents the average difference between age-corrected normal sensitivity and measured threshold sensitivity values at all test point locations. The visual field index (VFI - Humphrey) is similar to the MD but more heavily centre-weighted. VFI results are expressed in percent rather than in decibels and are more resistant to cataract effects, compared to MD. The Humphrey PSD and the Octopus loss variance (LV) index are designed to detect localised loss. In general, global indices are not primarily meant for and should not be used alone for diagnosis.

II.1.4.2.4 Interpretation methods and aids

A first-time normal exam can be accepted if reliable, but a first-time apparently abnormal exam should be repeated and confirmed if not consistent with other clinical findings i.e., with the appearance of the optic nerve and RNFL (see FC III).

Analysis of single field test results, based on clustered points

Clusters of test point locations with significantly reduced sensitivity are more reliable indicators of early glaucomatous field loss than are an equal number of significantly depressed points that are randomly scattered about the VF. One rule which is often used to classify a test result as outside normal limits requires a minimum of three clustered points having significantly depressed sensitivity, of which at least one should have a significance of $p < 1\%$.

The Bebié curve

The Bebié curve, which also is known as the cumulative defect curve of the Octopus perimeter is a summary graph of localised and diffuse sensitivity loss. In entirely diffuse loss the overall curve shows reduced sensitivity compared to normal. This is typically associated with media opacities and not with glaucoma. In focal loss, the right part of the curve is depressed as compared to the normal reference curve. Focal loss is much more consistent with a diagnosis of glaucoma than is diffuse loss.

The Glaucoma Hemifield Test (GHT)

The Glaucoma Hemifield Test of the Humphrey perimeter has been developed specifically for glaucoma diagnosis and classifies results as 'within normal limits', 'outside normal limits' or 'borderline'. Other GHT classifications are 'general depression of sensitivity', – typically found in eyes with media opacities but no manifest glaucoma – and 'abnormally high sensitivity' which indicates that the patient has pressed the response button also when not perceiving stimuli.

II.1.4.2.5 Confirmation of classification

Field defects which appear clearly glaucomatous and which are consistent with other clinical findings usually do not need confirmation to support a diagnosis. VFs with subtle defects may require confirmatory tests.

II.1.4.2.6 Detecting and quantifying glaucomatous visual field deterioration

It is important to detect and also to quantify VF deterioration in patients under care for glaucoma (see FC IV).

There are two main approaches to computer-assisted VF progression analyses:

Event analyses

Progression event analyses seek to detect whether or not a statistically significant VF change has occurred. Indices or test points/clusters are flagged if they have deteriorated more than the expected test-retest variation. Event based analyses have been used in all the large randomised controlled glaucoma trials, e.g. EMGT, AGIS, CIGTS and UKGTS. In clinical practice, event analysis is less important than trend analyses. Event analyses usually require confirmation testing.

Trend analyses

Regression analysis to determine the VF rate of progression is widely accepted and used in the management of eyes having glaucomatous field loss. The perimetric rate of progression is the velocity of worsening of the VF, and is usually quantified using linear regression analysis over time of the global indices MD or VFI. Rate of progression is expressed in dB/year or in %/year. Plotting the MD or VFI value of an eye over time can show if the observed rate of progression is likely to lead to loss of QoL during the patient's expected life-time. PSD and LV should not be used for trend analysis, because in early disease they increase as the field worsens, but then peak and start decreasing again as VF damage becomes moderate to advanced.

II.1.4.2.7 Number and frequency of tests

Determining the rate of progression of an individual eye requires a significant time span, typically at least two years, and enough field tests. It has been proposed that newly diagnosed glaucoma patients should be tested with SAP three times per year during the first two years after diagnosis. The other proposal is to cluster tests. In this way rate of progression can be determined early, and rapidly progressing eyes can be revealed with great certainty. Most often, the frequency of testing can then be reduced and tailored to the observed progression rate, and stage of disease. Patients with OHT do not need frequent VF testing.

II.1.4.3 Staging of visual field defects

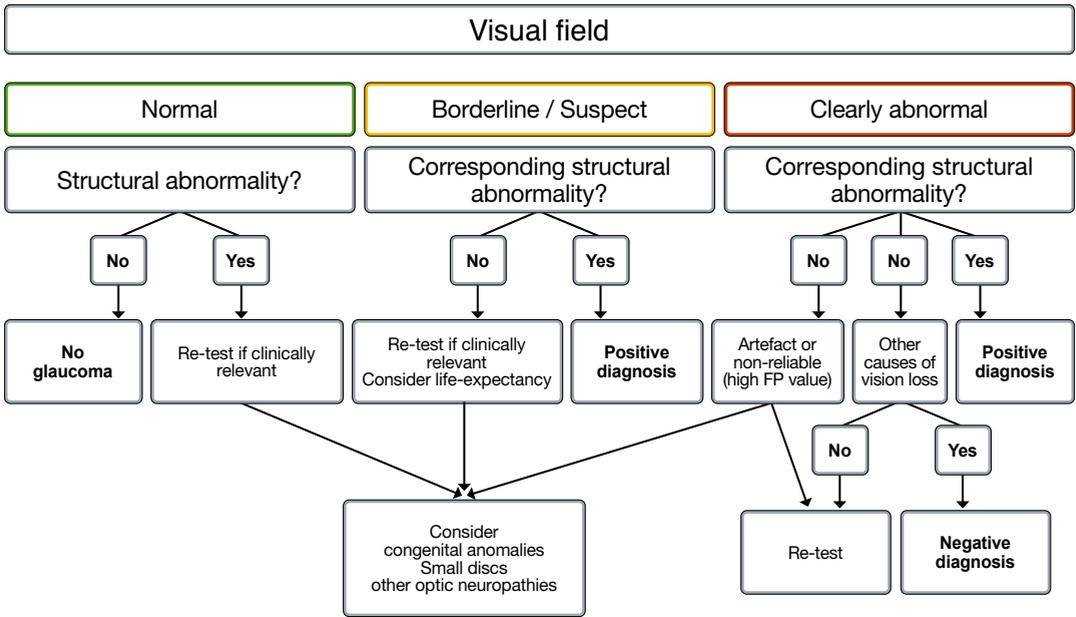
Glaucoma staging is based on the severity of VF damage. Several staging systems have been developed. A simple system based on MD alone is acceptable (see below, simplified from Hodapp's classification). Worse MD values are associated with higher risk of blindness.

Early glaucomatous loss MD \leq 6 dB

Moderate glaucomatous loss 6 > MD \leq 12 dB

Advanced glaucomatous loss MD > 12 dB

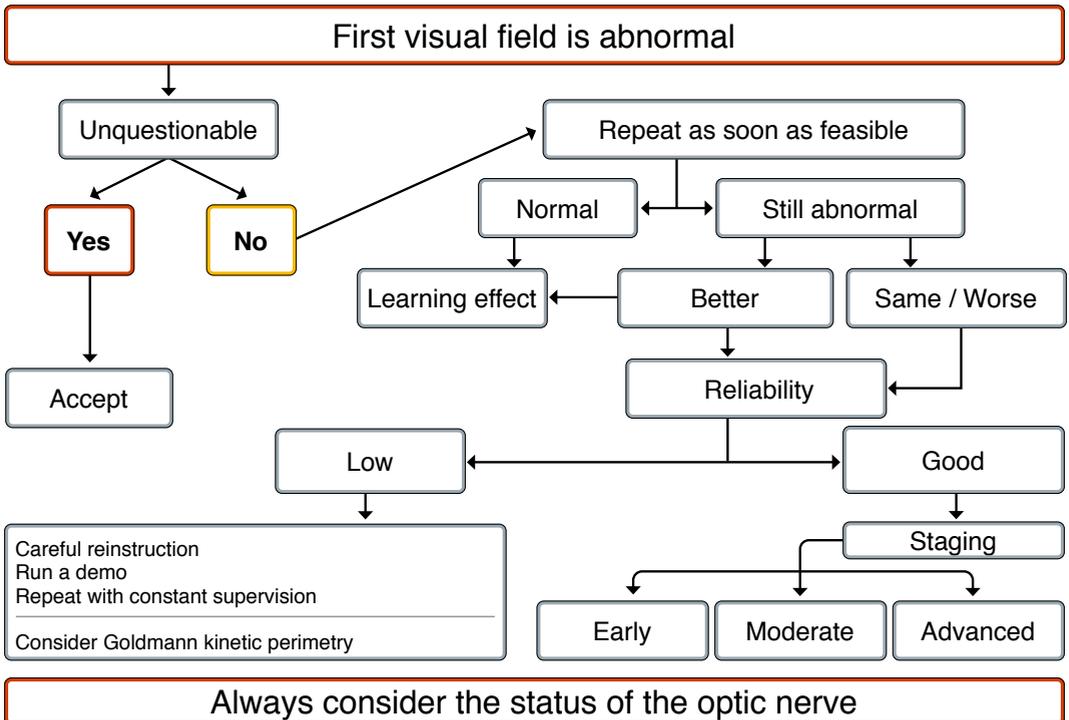
FC III – Initial visual field test interpretation



Consider the reliability of the test before making decisions based on it

© European Glaucoma Society

FC IV – Diagnostic strategy when initial visual field is abnormal



Always consider the status of the optic nerve

© European Glaucoma Society

II.1.5 Artificial intelligence

Artificial intelligence (AI) has been applied to several health areas. In glaucoma AI has been used to interpret fundus photographs, OCTs and VFs. Although AI has huge potential to revolutionise future glaucoma care, a number of challenges need to be overcome. Model generalisability as well as data quality apply to machine learning in general. Other issues such as data quantity and model interpretability (the so-called 'black-box') are more specific for deep learning. Potential solutions to these challenges involve international collaborations for data collection (to enable large-scale and diverse health data collection), tools to improve the quality of the data-collection process, automated integration of data from electronic health record systems, and regulations to ensure security through protection of not only personal data but also analytical models.

II.1.6 Genetics

Many forms of congenital and juvenile glaucoma are linked to specific genetic mutations but management of these conditions is based on the phenotype, i.e. the clinical presentation.

The remainder of this section deals with genetic influences on POAG, since this is responsible for the greatest burden of disease of the glaucomas.

The search for the genetic basis of POAG was prompted by epidemiological findings, for example that first degree relatives of glaucoma patients are at considerably higher risk of developing the condition. The areas of the genome associated with POAG can be divided into Mendelian mutations and complex variants.

II.1.6.1 Mendelian mutations

Mendelian diseases are usually caused by single genetic defects which are rare and strongly linked to the development of disease. Environmental factors and variants elsewhere in the genome apart from the causative mutation do not affect the presence or absence of disease. The most common Mendelian forms of POAG are caused by mutations in the myocilin (MYOC) gene. The prevalence of MYOC mutations has been estimated as 2-4% in POAG patients, but if patients are preferentially selected based on young age of onset, high IOP and strong family history the prevalence rises to 16-40%.

Youngs, currently unaffected members of a family which carries a MYOC mutation may benefit from genetic testing to discover whether they have the mutation or not, because if they do not have it they are at no excess risk for POAG whereas if they do have it then close monitoring and early treatment may preserve vision. However, the advisability of genetic testing will depend on a number of factors such as details about the condition and its prognosis, its inheritance pattern, and risk to children or other family members. Counselling for at-risk but currently unaffected family members should explore the underlying motivation for genetic testing, and explain the testing process and potential impact of the test result.

Recommendation: Individuals from families with multiple members affected with POAG at a relatively young age should be offered the opportunity to undergo genetic testing for MYOC mutations. The discussion and eventual decision should be in liaison with a clinical genetics counselling service.

II.1.6.2 Complex variants

In contrast to Mendelian mutations, variants which contribute to complex disease occur in numerous genes, are more common and have a relatively small effect size. The conceptual framework is that many such variants together with environmental factors coincide to produce disease. With the advent of genome-wide association studies hundreds of such variants associated with POAG, IOP and disc morphology have been discovered. Variants associated with IOP have been incorporated into a genetic prediction model for POAG and a variant in the TMCO1 gene has been

incorporated into the risk calculator for conversion from OHT to POAG in the OHTS. Though the contribution of complex variants to the diagnosis and management of POAG is constantly and rapidly improving it is currently not appropriate to use these variants as a basis for genetic screening.
Recommendation: Do not offer genotyping routinely to POAG patients.

II.1.6.3 Third party genotyping

Individuals may present to healthcare services seeking advice on the results of their genotypes which have been obtained from direct-to-consumer private companies. Such genetic information is usually not subject to the same quality control measures as in clinical genetics services or in clinical research so the results may be misleading. Third party genotyping measures should not currently be used to inform clinical decision making.

Recommendation: Advise individuals presenting with genetic information obtained elsewhere that it may be unreliable and should not be used to guide diagnosis or treatment (see I.4).

For details of diagnosis and treatment options see II.2 and II.3 (see also things to avoid - choosing wisely I.4)





Part II · Chapter 2

Classification and terminology





Part II · Chapter 2

Classification and terminology

II.2.1 Primary childhood glaucomas/ Juvenile glaucomas

Primary congenital glaucoma (PCG) is a rare disease but has a major impact on the child's development and QoL over his/her whole life span. Early diagnosis and appropriate therapy are vital. Surgical treatment is always necessary.

II.2.1.1 Primary congenital glaucoma: from birth to the first years of life

- Neonatal or newborn onset (0-1 month)
- Infantile onset (>1 until 24 months)
- Late onset or late recognised (>2 years), also see II.2.1.2
- Spontaneously non-progressing cases with normal IOP but typical signs of PCG may be classified as self-healed PCG

Epidemiology:

Congenital glaucoma occurs in about 1 in 12-18,000 births among white Europeans. Incidence can be 5 to 10 times higher if consanguinity of parents is present. Severe visual disability is common. PCG is more common in males (65%), and is bilateral in 70% of patients. Isolated trabeculodysgenesis is the most common form of primary congenital glaucoma.

Aetiology and mechanism:

Angle dysgenesis is caused by incomplete development of the TM before and/or after birth. There is a strong monogenetic influence. Heredity shows recessive inheritance with variable penetrance in most cases or is sporadic. Specific chromosomal abnormalities have been identified at chromosomes 1p36 and 2q212. Genetic testing is recommended to rule out other congenital abnormalities that may have impact on family planning. Decreased aqueous outflow causes significant elevation of IOP.

Features:

- Photophobia, tearing, blepharospasm, and eye rubbing are typical early signs
- Not always symptomatic
- Crying, unhappy child during first weeks or year of life may raise suspicion
- Larger corneal diameter (>10.5 mm at birth and >12 mm in the first year of life)
- Increased axial length (>20 mm at birth or >22 mm after 1 year)
- Corneal epithelial (sometimes stromal) oedema
- Ruptures of Descemet's membrane (Haab's striae)
- IOP best measured in the awaked child (hand-held tonometers)
- Under general anesthesia the level of IOP is often artificially lowered by sedation and anesthetic medications
- Diagnostic value of IOP values alone is insufficient
- Disc cupping typically occurs only after some months
- Gonioscopic signs: anterior insertion of the iris, forming a scalloped line with persistent uveal tissue and poorly differentiated structures and/or trabeculodysgenesis often described as Barkan's "membrane"
- The older the age of onset, the fewer the signs and symptoms

Treatment:

Management of these cases is particularly challenging.

Initial surgery is indicated in nearly all cases with primary congenital glaucoma. Medical treatment is usually neither effective nor practicable in long term. Medications, including oral CAIs can be used while decision is made on a surgical approach and in case of failed surgery while awaiting for further options.

Primary surgery: early goniotomy, trabeculotomy, filtration surgery; long-tube drainage devices may be indicated if these are unsuccessful. Repeat surgery is relatively frequent.

Systematic review:

- Ghate D, Wang X. Surgical interventions for primary congenital glaucoma. Cochrane Database Syst Rev. 2015;1:CD008213.

II.2.1.2 Late-onset childhood open angle glaucoma with onset from more than two years of age to puberty

Aetiology and pathophysiology: as in PCG (see II.2.1.1), except:

- No ocular enlargement
- No congenital ocular anomalies or syndromes
- Asymptomatic until field loss advanced

Features:

- Open angle
- Elevated IOP
- Optic nerve and VF damage depending on disease stage

Treatment:

Cases with later manifestation usually do not have enlargement of the globe and may have a more favourable outcome with surgery.

See above II.2.1.1

The treatment of **pediatric glaucoma** cases is particularly challenging due to the nature of the disease and to the intrinsic difficulties in examining patients at this age and operating on them. Treatment has to be adapted to the primary anomaly, and the mechanism of IOP elevation. Whenever possible these cases should be referred to tertiary care centres.

II.2.1.3 Secondary childhood glaucoma

A variety of pathogenetic mechanisms are possible. A complete list and extensive discussion are outside the scope of the guidelines.

Genetic testing should be strongly recommended due to the large overlap of phenotypes.

Treatment of secondary childhood glaucoma

See Treatment for PCG (II.2.1.1)

Management to be adapted to the primary anomaly, the mechanism of IOP elevation and the QoL of the patient. These cases require highly specialised care.

II.2.1.3.1 Glaucoma associated with non-acquired ocular anomalies

- Axenfeld Rieger anomaly (Syndrome if systemic associations)
- Peters anomaly (Syndrome if systemic associations)
- Aniridia
- Ectropion uveae
- Persistent fetal vasculature (if glaucoma present before cataract surgery)
- Oculodermal melanocytosis (Nevus of Ota)
- Posterior polymorphous dystrophy
- Microphthalmos
- Microcornea
- Ectopia lentis
- Nanophthalmos

II.2.1.3.2 Glaucoma associated with non-acquired systemic disease or syndrome

- Chromosomal disorders such as Trisomy 21 (Down syndrome)
- Connective tissue disorders
 - Marfan syndrome
 - Weill-Marchesani syndrome
 - Stickler syndrome
- Metabolic disorders
 - Homocysteinuria
 - Lowe syndrome
 - Mucopolysaccharidoses
- Phacomatoses
 - Neurofibromatosis 1 and 2
 - Sturge-Weber syndrome
 - Klippel-Trenaunay-Weber syndrome
 - Rubinstein-Taybi
 - Congenital rubella

II.2.1.3.3 Glaucoma associated with acquired condition

- Uveitis
- Trauma (hyphaema, angle recession, ectopia lentis)
- Steroid induced
- Tumours (benign/malignant, ocular/orbital)
- Retinopathy of prematurity

II.2.1.3.4 Glaucoma following childhood cataract surgery

Secondary glaucoma is a frequent serious complication after cataract surgery in early infancy. The incidence may increase up to 50% if cataract surgery is performed before the 9th month of life. This secondary glaucoma is difficult to treat and often needs long-tube drainage device surgery for long-term IOP control.

II.2.2 Open angle glaucoma

II.2.2.1 Primary open angle glaucoma (POAG)

Definition: POAG is a chronic, progressive, potentially blinding, irreversible eye disease causing optic nerve rim and RNFL loss with related VF defects. Angle appearance is normal, and major risk factors include the level of IOP and older age. Visual disability is usually prevented by early diagnosis and treatment.

Aetiology and mechanism:

The aetiology remains unclear. Multiple genetic factors and the influence of co-morbidities are likely to play a role. The current concept of how damage is elicited includes deformation of the lamina cribrosa caused by IOP levels that are not tolerated by the individual eye. This is thought to result in axonal damage with consequent apoptotic death of the retinal ganglion cells. Vascular factors also probably play a role.

Any increase in IOP is caused by elevated outflow resistance in the TM outflow pathways.

A substantial proportion of patients develop POAG at IOPs within the normal range.

POAG has been arbitrarily subdivided into 'high pressure' and 'normal-pressure' disease, even though they represent a spectrum of optic neuropathies. It is presumed that risk factors other than IOP have a relatively greater importance if there is glaucoma at the lower pressure levels. The treatment principles are the same, but there may be some differences in clinical features. Glaucoma with lower IOP levels may be more common in women with vascular dysregulation (eg migraine, Raynaud). Disc haemorrhages and paracentral scotomas may be more common. (See FC V)

Epidemiology

Glaucoma is one of the leading causes of irreversible blindness both in Europe and worldwide. POAG is unusual under the age of 40 yrs. Its prevalence increases with age.

Risk factors for the onset of POAG:

- Older age
- Higher IOP
- Race/Ethnicity: The prevalence of glaucoma is highest in people of black race (see glaucoma epidemiology, I.6)
- Family history of glaucoma: the risk of having OAG is higher for individuals with a first-degree relative with confirmed OAG
- Moderate to high myopia
- Low diastolic blood pressure
- Thinner CCT: thinner CCT is not independent prognostic factor for the onset of OAG in univariate analyses

Data from the literature on diabetes, systemic high blood pressure, migraine, Raynaud syndrome and obstructive sleep apnoea are inconsistent

Risk factors for progression of POAG

Early Manifest Glaucoma Trial (EMGT), Advanced Glaucoma Intervention Study (AGIS),

Collaborative Initial Glaucoma Treatment Study (CIGTS), Collaborative Normal Tension Glaucoma Study (CNTGS) have identified the following risk factors for progression (for details on studies see I.7):

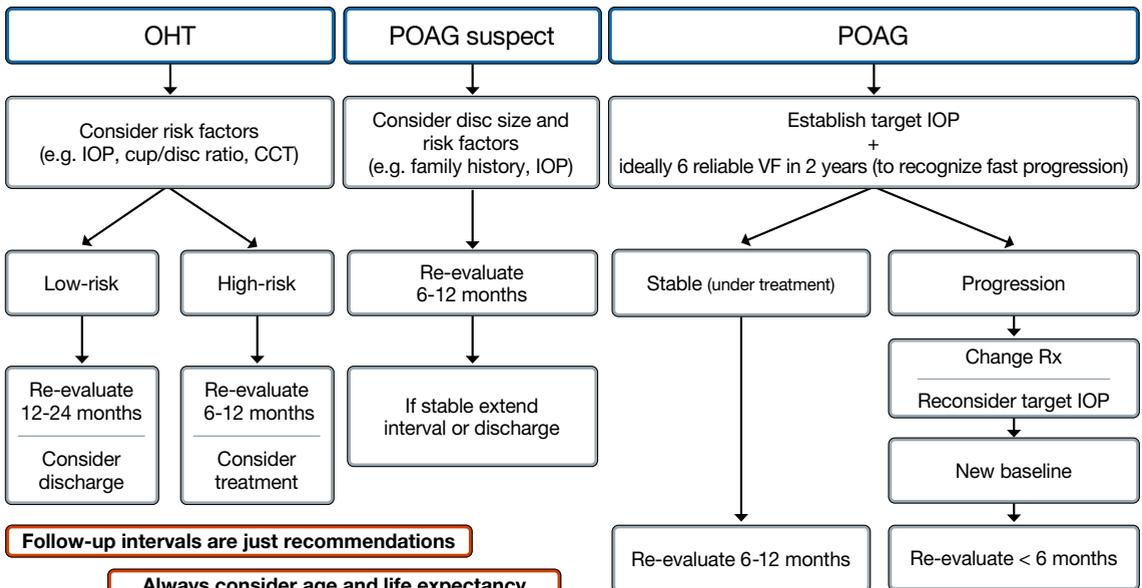
- Older age
- Higher IOP
- Presence of disc haemorrhages
- Thinner CCT: thinner CCT is not independent prognostic factor for progression of OAG in univariate analyses

Treatment:

See part I and chapter II.2

Choice of primary therapeutic modality needs to be made on an individual patient basis.

FC V – Assessment and follow-up Intervals



POAG = primary open-angle glaucoma
 OHT = ocular hypertension
 IOP = intraocular pressure
 CCT = central corneal thickness
 Rx = therapy

Gonioscopy to rule out angle-closure

II.2.2.1.1 Primary late-onset juvenile glaucoma

Aetiology and mechanism: Decreased aqueous outflow

Features:

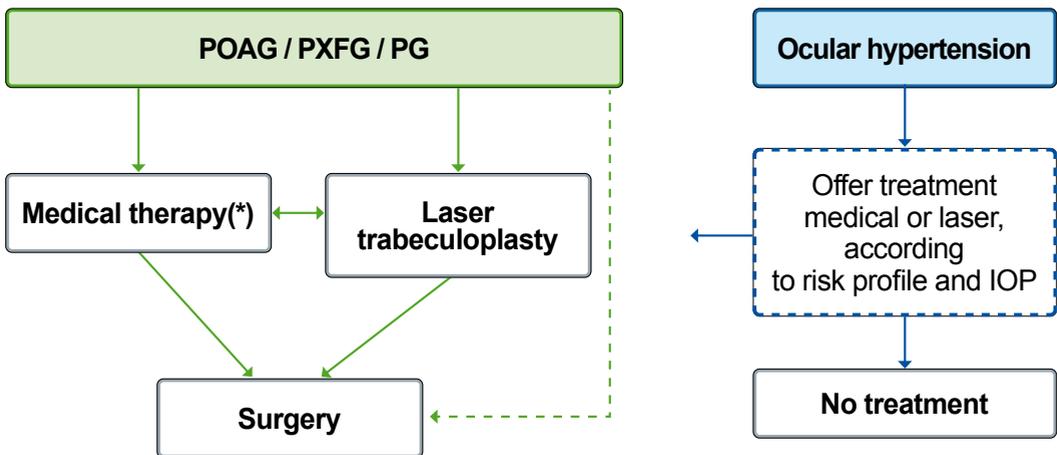
Onset: beyond infancy, usually after puberty or early adulthood. Heredity: if familiar frequently dominant trait. Genes associated with primary juvenile glaucoma have been identified as MYOC.

- Elevated IOP without treatment
- ONH and RNFL: Diffuse damage typical, but any type of glaucomatous damage
- Visual field: glaucomatous defects
- Gonioscopy: wide open anterior chamber angle, often poorly differentiated
- No congenital or developmental anomalies

Treatment (See FC VI):

- a) Medical therapy: any effective and well tolerated topical regimen
- b) Surgery: early surgery often required (filtering procedure or goniotomy/trabeculotomy; consider antimetabolites)
- c) Laser trabeculoplasty: not recommended

FC VI – Treatment options



Consider filtration surgery with anti-metabolites or alternatives (see Part II.3.6.2.4) or long-tube drainage implant/cyclodestructive procedure

(*) Up to 2-3 different drugs. Do not add a medication to a non-effective one; consider switching (see FC XII-XIV)

POAG = primary open-angle glaucoma

PXFG = pseudoexfoliative glaucoma

PG= Pigmentary glaucoma

II.2.2.1.2 Primary open angle glaucoma suspect

Definition: A glaucoma suspect is an individual with clinical findings suggestive but not confirmatory of OAG.

There may be a varying combination of borderline results concerning structural and / or functional tests. Often only time will determine whether a glaucoma suspect has early stages of glaucoma or not (See FC V).

Features:

- Visual field and/or optic disc and/or nerve fibre layer normal or suspicious, with at least one being suspicious
- IOP can be normal or increased

Treatment (See FC VI):

Risks and benefits of treatment need to be weighed against the risk of the development of glaucomatous disc damage. The indication for any form of therapy is relative and may be discussed with the patient. In general, treatment is not necessary if the IOP is not elevated.

Follow-up at intervals of 6-12 months initially, to be prolonged or the patient discharged if all parameters remain unchanged.

II.2.2.1.3 Ocular hypertension (OHT)

Features:

- IOP > 21 mmHg without treatment
- Visual field: normal
- Optic disc and retinal nerve fibre layer: normal
- Gonioscopy: open anterior chamber angle (exclude intermittent angle closure, see II.2.4.1)
- No history or signs of other eye disease or steroid use
- Other risk factors: none

Risk factors for the conversion of OHT to POAG:

The following risk factors and predictive factors were consistently reported in both the Ocular Hypertension Treatment Study OHTS and the European Glaucoma Prevention Study EGPS (for details on the studies see I.7):

- Older age
- Higher IOP
- Higher PSD in the VF
- Thinner CCT

A risk calculator is freely available to estimate the risk of developing glaucoma at 5 years, <http://ohts.wustl.edu/risk/calculator.html>

Treatment:

Treatment may be advisable in people with high risk of conversion to glaucoma. Increased IOP should be confirmed before starting treatment unless very high. In general offer treatment in patients with repeated IOPs in the high twenties, even without additional risk factors.

Treatment principles and choices will be similar to those for POAG. The initial approach is to offer either medical treatment or laser trabeculoplasty.

Follow-up at intervals of 6-12 months initially, to be prolonged if all parameters remain stable.

Assess each patient individually when deciding whether or not to offer treatment.
Involve the patient. Ask their opinion.

II.2.3 Secondary open angle glaucomas

Definition: Secondary open angle glaucomas (OAG) are a heterogeneous group of conditions, in which elevated IOP is the leading pathological factor causing the glaucomatous optic neuropathy. Most forms of secondary glaucoma have complex mechanisms which may range from open angle to closed angle mechanisms.

II.2.3.1 Secondary open angle glaucomas caused by ocular disease

II.2.3.1.1 Pseudoexfoliative or exfoliative glaucoma (PXFG)

Epidemiology: Pseudoexfoliative glaucoma (PXFG) is the most common type of secondary OAG, its prevalence varies considerably across populations. According to population-based data, PXFG develops in approximately 15% to 26% of eyes with pseudoexfoliation syndrome (PXF) over a 5 year period. PXF/PXFG may be associated with systemic diseases (e.g. vascular diseases, inguinal hernia and female's pelvic organ prolapse). Progression of PXFG is approximately 3 times faster than that of POAG.

Aetiology and mechanism:

PXFG develops from PXF, in which an abnormal fibrillo-granular protein (pseudoexfoliation material) is produced in the eye.

Genetics: Development of PXF is strongly associated with certain gene variants including LOXL1. The development of PXFG from PXF is probably influenced by environmental factors.

Features:

- Onset: usually older than 50 years with large between-population variability
- Pseudoexfoliation material accumulates in a characteristic pattern on the anterior lens capsule - better visualised after pupil dilatation, pupillary margin, TM and the zonules
- Pigment loss from the pupil margin is common ("moth eaten pupil")
- On cross sectional assessment one or both eyes may show clinically signs of PXFG; often bilateral and asymmetrical
- IOP is higher than that in POAG, and diurnal IOP fluctuation is high
- At first presentation VF/ONH damage is frequently advanced in the worse eye
- The angle can be wide open, narrow or closed when the lens moves anteriorly due to zonular laxity
- On gonioscopy, Sampaolesi's line (pigment deposition anterior to Schwalbe's line) is common and characteristic for PXFG
- Due to progressive zonular damage, phacodonesis and lens subluxation are not uncommon, and the complication rate of cataract surgery may be increased. Late in-the-bag intraocular lens (IOL) dislocation several years after uncomplicated cataract surgery is not uncommon.

Treatment:

Treatment options of PXFG are similar to those of POAG although there is higher risk of progression in PXFG. Laser trabeculoplasty and medical treatment are equally effective but both lose efficacy after some years. In clinically unilateral PXFG the fellow eye also needs to be regularly checked for IOP elevation and glaucoma since the conversion rate is high. (see II.3)

II.2.3.1.2 Pigmentary glaucoma (PG)

Epidemiology: PG represents 1-1.5% of all glaucoma cases. It is more common in white European myopic men. It is typically diagnosed at the age of 30-50 years. The reported risk of developing glaucoma in patients with pigment dispersion syndrome (PDS) in clinic populations ranges from 10 to 50%, but this may represent a biased population of individuals with PDS and raised IOP.

Pathogenic mechanism:

Melanin pigment is released from the iris pigmented epithelium as the result of rubbing between lens zonules and posterior surface of the iris. Posterior bowing of the iris with “reverse pupillary block” configuration is noted in many eyes with pigment dispersion.

Melanin granules cause an increase of TM outflow resistance and hence an elevation of IOP. The current understanding is that TM cells phagocytise pigment, which subsequently leads to their death.

Two entities can be described:

- PDS: usually bilateral characterised by dispersion of iris pigment, may be associated with elevated IOP
- PG: glaucomatous optic neuropathy and PDS.

Features:

- Midperipheral iris transillumination with a radial spoke like pattern due to pigment loss best visible with retroillumination
- Pigment deposition in the corneal endothelium typically accumulating vertically as a Krukenberg spindle (frequently seen, but not pathognomonic)
- Homogenously dark brown, densely pigmented TM
- Pigment deposition at the insertion of the posterior zonules, known as ‘Scheie stripe’ or ‘Zentmayer’s ring’
- Very deep anterior chamber with backward bowing of the peripheral iris
- Transient blurry vision due to IOP spikes (often after exercise or pupillary dilatation).

Treatment:

Treatment of PG is similar to that of POAG. No PG-specific treatment is available. Laser trabeculoplasty and medical treatment are equally effective, but spikes of IOP are common after laser trabeculoplasty and so should be performed cautiously with low power settings and with prophylactic treatment to prevent IOP spikes. See II.3.

II.2.3.1.3 Lens-induced open angle glaucoma

Aetiology / Pathogenic mechanism:

In lens-induced OAG, TM outflow pathways are obstructed by lens particles and/or inflammatory cells.

- Phacolytic glaucoma: the TM is obstructed by lens material leaking from mature or hypermature cataract
- Traumatic lens injury: the TM is obstructed by lens particles from a traumatically or surgically injured lens
- Phacoanaphylactic glaucoma: lens proteins lead to granulomatous uveitis affecting the TM

Features:

- Unilateral pain with redness and inflammation
- Reduced vision and elevated IOP
- Signs of injured lens and/or mature/hypermature cataract are present, with or without iritis (aqueous flare and keratic precipitates)

Treatment:

Extraction of lens or lens fragments followed by topical anti-inflammatory medication, vitrectomy if needed.

II.2.3.1.4 Glaucoma associated with intraocular haemorrhage

Aetiology / Pathogenic mechanism:

Either acute bleeding in the anterior chamber or long standing blood in the vitreous can cause IOP elevation.

Large quantity of normal red blood cells (hyphaema) or haemoglobin-laden macrophages (haemolytic glaucoma) or degenerated red blood cells (ghost cell glaucoma) obstruct the TM.

Features:

- Pain and eye irritation
- Elevated IOP is more common with larger hyphaemas and is more often due to recurrent haemorrhage or re-bleeding. Re-bleeding can follow traumatic hyphaema, usually after 3-7 days (incidence 5 - 10%)
- In haemolytic glaucoma red-tinged cells in the AH and reddish brown discoloration of the TM are present. "Ghost cells" occur 1 to 4 weeks after vitreous haemorrhage and reach the anterior chamber. Small khaki-coloured cells may be seen circulating in anterior chamber
- Gonioscopic examination may show layering of the ghost cells over the inferior part of TM

Treatment:

- Topical and systemic IOP lowering medication as needed. It is recommended to avoid carbonic anhydrase inhibitors and hyperosmotic agents in patients with sickle cell disease

- Conservative treatment, bed rest, topical cycloplegics and steroids, can be considered for uncomplicated hyphaema. Antifibrinolytic agents such as tranexamic acid can reduce the risk of rebleeding. However it is not clear whether any of the interventions have an effect on visual acuity
- Wash-out through a paracentesis of the anterior chamber and/or vitrectomy to remove RBCs from vitreous if IOP remains high with the risk of corneal blood staining and/or optic neuropathy

II.2.3.1.5 Uveitic glaucoma

Aetiology / Pathogenic mechanism:

Acute IOP elevation is typical in Posner-Schlossman syndrome or in viral infection such as herpes simplex virus and varicella-zoster virus. Chronic IOP elevation is typical for Fuchs' uveitis, juvenile idiopathic arthritis, Behcet disease, pars planitis, sympathetic ophthalmia, sarcoidosis and syphilis.

- Obstruction and oedema of the TM are caused by inflammatory cells, precipitates, debris, secondary scarring and neovascularisation of the chamber angle
- Secondary angle closure may develop due to synechial closure of the chamber angle or seclusio pupillae with subsequent appositional angle closure
- Corticosteroid treatment can also contribute to IOP elevation in some patients

Features:

- Pain, redness, photophobia, decreased vision are possible
- Elevated IOP; some forms are associated with wide oscillations of, or periodic rise in, IOP

Treatment:

- Topical and systemic anti-inflammatory therapy according to the underlying disease
- Topical and systemic IOP lowering medication
- Traditionally topical β -blockers and CAs have been used as first-line treatment
- PGAs can be used therapy in eyes with well controlled uveitis
- Glaucoma surgery suited for the type of inflammatory disease
- Laser trabeculoplasty should be avoided

Acute IOP elevation with corneal oedema but open angle may result from Posner Schlossman syndrome (iridocyclitic crisis), or from endothelitis/trabeculitis as in herpetic eye disease.

II.2.3.1.6 Neovascular glaucoma (see also II.2.5.2.1)

II.2.3.1.7 Glaucoma due to intraocular tumours

Aetiology /Pathogenic mechanism:

Reduced AH outflow due to primary or secondary intraocular tumours, mainly of the anterior segment.

Infiltration of the TM by the tumour or tumour cells floating in the AH. TM obstruction due to tumour related inflammation, tumour debris, haemorrhage or pigment dispersion. Secondary ACG may also develop.

Features:

- Elevated IOP
- A highly variable clinical picture, combining evidence of both tumour and glaucoma

Treatment:

Treatment of underlying tumour (irradiation, surgical tumour excision, enucleation)

Topical and systemic IOP lowering medication; medical therapy is often first-line treatment while awaiting definitive treatment.

Cyclodestructive procedures

Incisional glaucoma surgery indicated only after successful tumour control.

II.2.3.2 Secondary open angle glaucoma due to ocular trauma

Ocular trauma leads to glaucoma by several different mechanisms. The secondary traumatic glaucomas can be caused by both open angle and angle closure mechanisms. In order to identify and treat the causes of IOP elevation; careful evaluation of the ocular damage must be performed.

Aetiology / Pathogenic mechanism:

Blunt non-penetrating or penetrating trauma to the eye can damage intraocular structures.

Any trauma can lead to reduced trabecular outflow due to traumatic changes of the TM. Scarring and inflammation of the TM, obstruction by red blood cells and debris, angle recession, lens-induced glaucoma.

Features:

- Elevated IOP may occur a very long time after the trauma
- Clinical features depend on the aetiology of the trauma

Treatment:

- Anti-inflammatory medication
- Topical and systemic IOP lowering medication
- Long-term IOP lowering and follow up in the presence of permanent anterior segment damage
- Glaucoma surgery

II.2.3.3 Iatrogenic secondary open angle glaucomas

II.2.3.3.1 Glaucoma due to corticosteroid treatment

Aetiology and pathogenic mechanism:

Topical, intravitreal as well as long-term systemic corticosteroid therapy also with nasal sprays, inhalers or skin formulations can induce IOP elevation. The risk of IOP elevation depends on the chemical structure (strength) of the steroid, dose, frequency and duration of therapy, and route of administration.

Corticosteroids induce changes in the trabecular extracellular matrix (glycoproteins) which lead to decreased outflow facility. A TIGR gene may be involved.

Features:

- Elevated IOP usually develops 2 to 6 weeks after initiating corticosteroids, but may occur at any time
- Usually IOP elevation is slowly reversed after stopping the use of corticosteroid

Treatment:

- Discontinuation of corticosteroid therapy is recommended if possible; steroid-sparing therapy of underlying condition should be considered. If this is not possible, consider switching to weaker steroid (e.g. loteprednol, fluorometholone)
- Topical and systemic IOP lowering medication
- Laser trabeculoplasty
- Glaucoma surgery may be performed in intractable cases

II.2.3.3.2 Secondary open angle glaucoma due to ocular surgery and laser

Ocular surgery can cause secondary open angle glaucoma by some of the mechanisms discussed above: intraocular haemorrhage, inflammatory reaction, lens material, pigmentary loss from uveal tissue, or trauma.

Pathogenic mechanism:

Open angle glaucoma following ocular surgery or laser is a result of reduced trabecular outflow.

IOP elevation after intraocular surgery is usually transient. The elevated IOP may be

caused by: viscoelastic material, inflammatory debris, vitreous in the anterior chamber after cataract surgery, lens particles, and prostaglandin release.

Acute onset secondary IOP elevation after neodymium-doped yttrium aluminum garnet (Nd:YAG) LPI, capsulotomy and laser trabeculoplasty. IOP elevation is usually transient, within the first 24 hours, most frequent in the first 4 hours after treatment.

IOP elevation with open angle following vitrectomy with silicon oil implantation develops as a result of:

- Migration of silicon oil into anterior chamber and obstruction of the TM (early post-op IOP increase) usually due to overfill of oil
- Migration of emulsified silicon oil into anterior chamber with obstruction of TM where oil particles are partially phagocytised by macrophages and accumulate in the TM especially in the upper quadrant and can induce trabeculitis (intermediate and late onset IOP increase)
- Prolonged contact of silicon oil with the TM may cause permanent structural changes. Risk factors for developing IOP elevation following vitrectomy with silicon oil implantation include pre-existing OHT or glaucoma, diabetes mellitus, and aphakia (closed angle type)
- Uveitis-glaucoma-hyphema (UGH) syndrome - IOP elevation associated with an anterior chamber IOL due to induced iris root bleeding and anterior uveitis. Modern IOLs pose a significantly lower risk of inducing UGH syndrome

Treatment:

- Topical and systemic IOP-lowering medication
- Anti-inflammatory treatment
- Removal of silicone oil may be considered in eyes with IOP elevation secondary to silicon oil emulsification. However current data suggest that removal of silicon oil is not effective in all cases and the risk of re-detachment increases. Transscleral cyclophotocoagulation and aqueous drainage devices seem to represent more effective options, although the latter are associated with the risk of silicon oil escape into subconjunctival space. Endoscopic cyclophotocoagulation in eyes requiring silicon oil removal and glaucoma treatment is another option. Conventional filtration surgery is associated with poor prognosis.
- Removal of the intraocular lens may be needed in case of UGH syndrome
- Glaucoma surgery according to the specific condition

II.2.3.3.3 Glaucoma associated with vitreoretinal surgery

Aetiology and pathogenic mechanism:

Long standing retinal detachment that leads to ischaemic neovascularisation. Retinal detachment is usually associated with a reduction of IOP. Gas tamponade can elicit significant IOP spikes.

The TM may be obstructed by neovascularisation caused by proliferative retinopathy, or by scarring, pigment dispersion and inflammation, or by cellular debris from retinal cells outer segments (Schwartz's syndrome). Surgery for retinal detachment can also cause glaucoma.

Symptoms and signs:

Elevated IOP and retinal detachment are present. Redness and pain are common features.

Treatment:

- Topical and systemic IOP-lowering medication
- Surgery for retinal detachment
- Consider glaucoma surgery if IOP not controlled

II.2.3.4 Secondary open angle glaucoma caused by extraocular disease

II.2.3.4.1 Glaucoma caused by increased episcleral venous pressure

Aetiology and pathogenic mechanism:

Episcleral, orbital or systemic diseases can cause the elevation of episcleral venous pressure with subsequent reduction of trabecular outflow and IOP elevation. The following disorders can be described:

- Episcleral and orbital causes: chemical burn or radiation damage of the episcleral veins, hemangioma in Sturge-Weber syndrome, Nevus of Ota, endocrine orbitopathy, orbital (retrobulbar) tumor, pseudotumor, orbital phlebitis, orbital or intracranial arteriovenous fistula
- Neurologic conditions: dural shunts, cavernous sinus thrombosis
- Other systemic causes: superior vena cava obstruction, jugular vein obstruction (radical neck dissection), pulmonary venous obstruction
- Idiopathic forms

Features:

IOP elevation can be acute with eye irritation and pain. Dilated, congested episcleral veins, chemosis, facial lymphedema, orbital bruit can be present. Vascular bruits are characteristic signs of A/V fistulae.

Treatment:

- Treatment of the underlying disease
- Topical and systemic IOP-lowering medication
- Glaucoma surgery

II.2.4 Angle closure

Angle closure is defined by the presence of iridotrabecular contact (ITC). Usually it is considered clinically relevant when there is more than 180 degrees of ITC. This can be either appositional (reversible) or synechial (adhesion). Either can be due to any of a number of possible mechanisms. Angle closure may result in raised IOP which may lead to glaucomatous optic neuropathy.

Angle closure is diagnosed by gonioscopy. It is important to rule out secondary causes e.g. phakomorphic, uveitic and neovascular, as management of these cases requires additional treatment of the underlying disease.

Provocative tests for angle closure provide little additional information since even when negative they may not rule out the potential for angle closure. The test does not mimic physiological conditions and may give a false result.

Mechanisms responsible for angle closure may be described by the anatomical factor responsible for the obstruction to aqueous flow: the iris, ciliary body, lens or causes behind the lens. Different mechanisms can co-exist and vary with race.

I. Pupillary block mechanism

Pupillary block is the most common mechanism, involved in half to $\frac{3}{4}$ of cases of PAC. Pupillary block is an exaggeration of a physiological phenomenon in which the flow of aqueous from the posterior chamber through the pupil to the anterior chamber encounters resistance at the pupil, causing pressure to be higher in the posterior than the anterior chamber. As a result, the iris bows forward and the peripheral iris touches the TM. Typically the anterior chamber depth is shallower than average.

II. Anomalies at the level of ciliary body ("plateau iris")

This group of anterior, non-pupillary-block mechanisms, are called "plateau iris". They are usually the result of variations in ciliary processes anatomy which are anteriorly placed, pushing the peripheral iris anteriorly into contact with the TM. The anterior chamber depth is not shallow centrally, and the iris profile is flat. On gonioscopy the double hump sign is observed (see also II.1.2 and Figure II.1.5). Plateau iris "syndrome" may be differentiated from plateau iris "configuration". Anteriorly positioned ciliary body processes can occur in the presence of pupil block which can obscure the iris profile. Relief of pupil block by LPI may be required to identify the plateau iris. Plateau iris "configuration" refers to a situation in which the iris profile angulates sharply in the periphery, but no irido-trabecular contact is present. "Plateau iris syndrome" refers to a post-laser iridotomy condition in which a patent peripheral iridotomy has removed the relative pupillary block, but gonioscopically appositional angle closure persists.

III. Anomalies at the level of the lens

The lens is intimately involved in the pupillary block mechanism of angle closure, but the lens is also directly involved in other processes that contribute to angle closure:

- increase in thickness, e.g., post-traumatic cataract

- subluxation with anterior displacement, e.g. PXF, Marfan syndrome or trauma (see also II.2.5.1, II.2.3.1.1 and II.2.3.2)

The anterior chamber is uniformly shallow and often different from the fellow eye.

IV. Anomalies posterior to the lens

- Aqueous misdirection
 - Aqueous misdirection, also called malignant glaucoma, is an uncommon form of angle closure. (see also II.2.5.3.1).
 - The mechanism is unclear but may involve increased choroidal volume and impaired fluid movement from posterior to anterior segments. The lens/iris diaphragm is pushed forward and occludes the anterior chamber angle. The anterior chamber is very shallow or flat. In early stages the IOP may be normal if it occurs after glaucoma surgery, but it is often very high.
- Other posterior pushing mechanism
 - e.g. tumor, retinal gas or oil tamponade, uveal effusion (spontaneous, drug-induced etc).

These move the lens anteriorly and may generate ITC by increased pupil block or direct lens mechanisms, or often a combination of the two (see below).

Pharmacological mydriasis and systemic drugs with effects on the angle

Systemic drugs and angle closure

Systemic drugs that may induce acute angle closure include: nebulised bronchodilators (ipratropium bromide and/or salbutamol), selective serotonin re-uptake inhibitors, tricyclic antidepressants, muscle relaxants, illegal stimulant drugs, and other agents with a parasympatholytic and sympathomimetic action. Topiramate and sulfonamides can cause acute angle closure due to peripheral uveal effusion.

Acute angle closure can occur, even bilaterally, in patients during or after general anesthesia under curare.

Diagnostic mydriasis is generally safe in the general population and it should be advised in all patients when thorough retinal examination is indicated because of the very low risk of angle closure. The risk of missing sight-threatening retinal conditions because of inadequate fundal examination through undilated pupils far outweighs the risk of precipitating angle closure induced by diagnostic mydriasis. However people undergoing pupil dilatation should be advised to seek eye care urgently in case of symptoms e.g. eye pain or increasing blurring.

Pandit RJ, Taylor R. Diabet Med. 2000 Oct;17(10):693-9. Mydriasis and glaucoma: exploding the myth. A systematic review.

II.2.4.1 Primary angle closure (PAC)

Staging of primary angle closure

- Primary angle closure suspect (PACS)
Two or more quadrants of iridotrabecular contact (ITC), normal IOP, no peripheral anterior synechiae (PAS), no evidence of glaucomatous optic neuropathy.
- Primary angle closure (PAC)
ICT resulting in PAS and/or raised IOP. No evidence of glaucomatous optic neuropathy.
- Primary angle closure glaucoma (PACG)
ITC causing glaucomatous optic neuropathy.
PAS and raised IOP may be absent at the time of initial examination.

Gonioscopy remains the gold standard for confirming ITC and diagnosing angle closure. Angle closure is defined by the presence of appositional or synechial ITC in at least 180 degrees.

Most patients with angle closure are asymptomatic. Although symptoms of pain, redness, blurring of vision or haloes may help identify people with sub-acute episodes of elevation of IOP due to angle closure, the sensitivity and specificity of symptoms for identifying angle closure are very poor.

Angle closure may impair aqueous outflow through simple obstruction of the TM, or by causing irreversible degeneration and damage of the TM. The absence of identifiable causes defines PAC.

Risk factors:

Risk factors for PAC disease include older age, family history, female sex, hypermetropia, and race, being more common in South and East Asians e.g. Chinese. Other factors associated with PAC include a thick peripheral iris, a more anterior iris insertion, and more prominent and anterior lens vault. PXF may also be associated with PAC, probably due to loose zonules. In most cases, the predisposition to pupillary block and angle closure is due to a small anterior segment and to the age-related increased lens volume (see II.2.3).

The prevalence of PACG is approximately 0.4% in white Europeans. Three-quarters of cases occur in female subjects.

II.2.4.1.1 Primary angle closure suspect (PACS) or 'occludable' angle

Aetiology and mechanism:

Features: See II.2.4.1

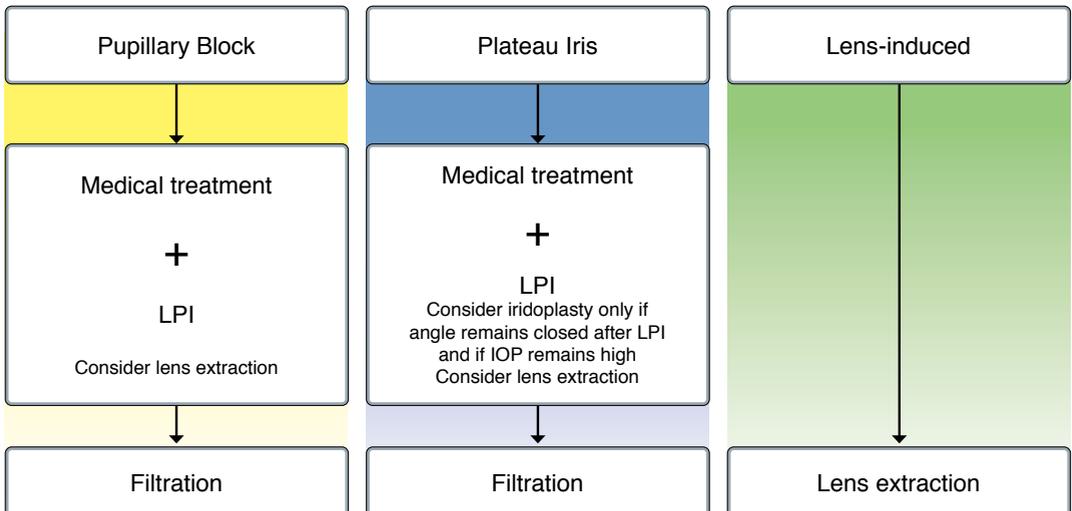
Treatment:

LPI is recommended for PACS in high risk eyes such as those very high hyperopia, family history, or patients requiring pupil dilatation due to retinal disease (see Evidence). If the angle remains appositionally closed after LPI for PACS further interventions are not necessary.

FC VII – Management of chronic angle closure

Identify the pathophysiological mechanism(s) responsible

Make sure a **patent iridotomy** is present/made before considering mechanisms other than pupillary block



II.2.4.1.2 Primary angle closure (PAC) and primary angle closure glaucoma (PACG) (See FC VIII)

Aetiology and mechanism:

Features: See II.2.4.1

Treatment:

Medical treatment must be associated with LPI or lens extraction to widen the anterior chamber angle.

If there is cataract, prompt lens extraction is advisable. If there is no cataract lens removal can be considered at any time.

These eyes are more frequently prone to develop aqueous misdirection and the necessary precautions must be taken when considering glaucoma surgery.

If uncontrolled or in advanced PACG and high presenting IOP (e.g., >35 mmHg), early intraocular surgery (e.g. phaco, trabeculectomy, combined surgery) may be needed to better control IOP. (also see I.3, question 14)

II.2.4.1.3 Acute angle closure (AAC) attack due to pupillary block or mixed mechanisms

Aetiology and mechanism:

In a few cases circumferential iris apposition to the TM and total obstruction of trabecular outflow leads to an acute rise in IOP to very high levels, e.g., up to 50-70 mmHg. Increased resistance to transpupillary aqueous flow due to an increased contact between the iris and the lens probably results from a mid-dilated pupil with co-activation of both sphincter and dilator muscles. This may occur in response to physiological stimuli, e.g. low light levels, or pharmacological.

Typically AAC attacks will not resolve spontaneously. Pupillary block is the most common mechanism but other mechanisms can be involved (e.g., plateau iris, aqueous misdirection, phacomorphic).

Features:

- Ocular pain, frontal headache of variable degree on the side of the affected eye
- Decreased visual acuity, blurred vision, "haloes" around lights
- Variable 'vagal' systemic symptoms (nausea and vomiting, abdominal cramps, bradycardia or arrhythmia)
- High IOP, often above 40 mmHg
- Corneal oedema, initially mostly epithelial. Shallow or flat peripheral anterior chamber
- Peripheral iris pushed forward: gonioscopy shows extensive iridotrabecular contact 360°
- Pupil mid-dilated and reduced or no reactivity to light
- Venous congestion and ciliary injection
- Fundus: the disc may be normal or show glaucomatous excavation; disc oedema, with venous congestion and retinal haemorrhages possible

Treatment options: See also FC VII-VIII

Immediate: medical treatment (topical and systemic) and LPI. Alternative options: anterior chamber paracentesis; thermal laser peripheral iridoplasty (TLPI), cyclodiode.

A: Medical Treatment

Medical treatment serves to lower IOP, to relieve the symptoms and help clear the cornea so that LPI is possible.

All the steps of medical therapy below should be implemented concurrently. Consider possible contraindications to each of the medications to be used.

- Reduction of aqueous production
acetazolamide 10 mg/Kg intravenous (IV). Topical carbonic anhydrase inhibitors (CAIs) are not potent enough. Possible contraindication in people with poor renal function or sulfa allergy

topical beta-blockers and alpha-agonists.
- Dehydration of vitreous body
Hyperosmotics are the effective agents but carry significant systemic risk in some patients: patients must be evaluated for heart or kidney disease because hyperosmotics increase blood volume which increases the load in the heart. Glycerol may alter glucose blood levels and should not be given to diabetics (FC VII)
glycerol 1.0 – 1.5 g/Kg orally
mannitol 1.0 – 2.0 g/Kg IV over 30 minutes (e.g. for a 70 kg patient 350 mL to 700 mL of 20% mannitol IV)
- Pupillary constriction
pilocarpine 1% or 2%.
Note: while the sphincter is ischaemic and the pupil non-reactive to light, topical parasympathomimetics may not be effective initially. Miotics are likely to constrict the pupil only after IOP has been lowered. Miotics in large doses can cause systemic side effects due to trans-nasal absorption leading to abdominal spasms and sweating; therefore intensive topical parasympathomimetics are not indicated
- Reduction of inflammation
Intensive topical steroid, e.g., every 5 minutes for three times, then 4-6 times daily, depending on duration of raised IOP and severity of inflammation.

B: Laser and surgical treatment

- Nd:YAG LPI
LPI should be attempted if the cornea is sufficiently clear. Thermal laser pre-treatment (e.g., argon) of dark irides reduces total Nd:YAG energy required
- Surgical iridectomy may be required when Nd:YAG LPI is not possible

C: Thermal Laser Peripheral Iridoplasty (TLPI)

TLPI can break an attack of acute angle closure as swiftly as medical therapy. Prompt TLPI can be used if topical treatment + acetazolamide have not broken an attack within an hour. TLPI has greater penetration of an oedematous cornea, while LPI requires a relatively clear cornea.

D: Anterior chamber paracentesis can be considered to break the attack and may be particularly useful in cases that are refractory to medical management and when there is no access to laser. Anterior chamber paracentesis can be performed at the slit lamp by an experienced ophthalmologist.

- Rapidly lowers IOP in AAC
- Instantaneous relief of symptoms but high risk procedure in very shallow anterior chambers
- The IOP-lowering benefit may decrease within hours after the procedure
- Anti-glaucoma medications are necessary to maintain IOP control.
- Paracentesis will not directly interrupt the pupillary block but can relieve pain and allow the cornea to clear permitting LPI to be performed
- Possible complications include: excessive shallowing of the anterior chamber; puncture of iris or lens, choroidal effusion, haemorrhage due to the sudden decompression of the globe

E: Lens extraction: See FC VII

After breaking the acute attack, lens extraction within a few days or weeks after the attack is a possible option, particularly in cases of high IOP, and closed anterior chamber angle after LPI.

Phacoemulsification in PACG is generally more challenging and prone to complications than in normal eyes or eyes with POAG because of the shallow AC, larger lens, corneal oedema, poorly dilated or miotic pupil, extensive posterior synechiae, lower endothelial cell count, and weaker zonules, especially after an AAC.

See I.3, question 14

F: Trabeculectomy

See I.3, question 16

II.2.4.1.4 Status post-acute angle closure attack

Aetiology and mechanism:

Previous episode of acute angle closure attack

Features:

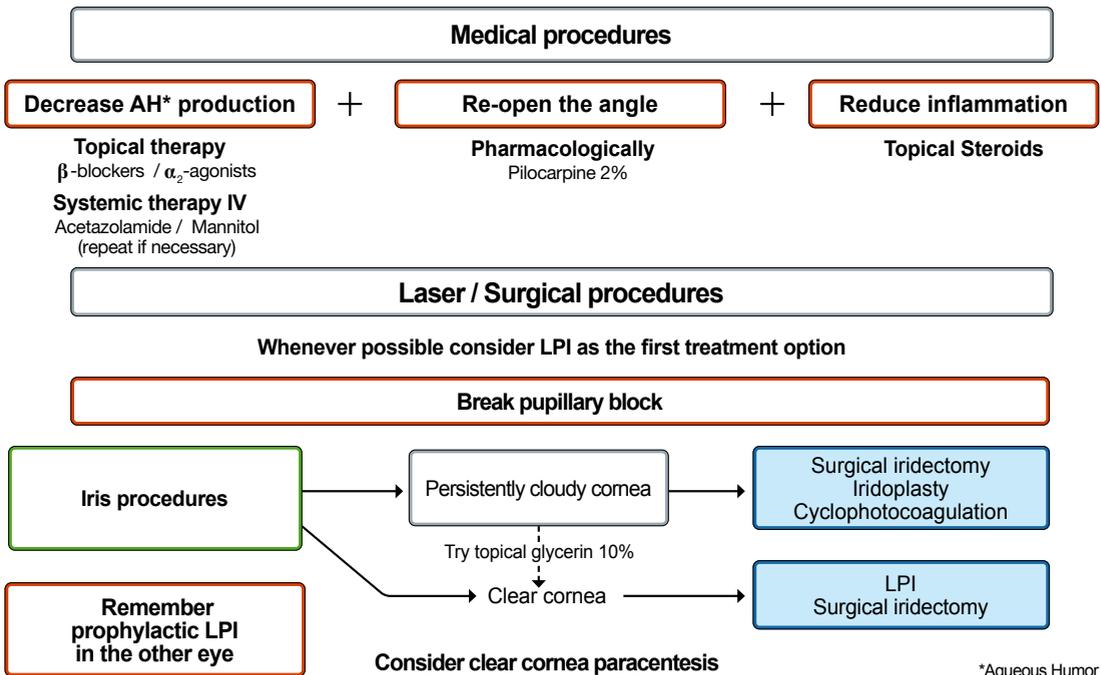
- Patchy iris atrophy
- Iris torsion/spiralling
- posterior synechiae
- Pupil either poorly reactive or non-reactive
- "Glaukomflecken" (epithelial and anterior cortical lens opacities)
- PAS

- Even without synechia, the TM can be damaged with reduced outflow
- Endothelial cell count can be decreased
- Zonules are often weak
- The disc may become pale but flat, suggesting an anterior ischaemic optic neuropathy, or it can show the typical glaucomatous optic disc cupping

Therapy:

Management according to angle, lens, IOP and disc/visual field. In case of cataract surgery a non-dilatable pupil, low endothelial cell count and loose zonules are of concern.

FC VIII – Management of acute primary angle closure attack



II.2.5 Secondary angle closure

There are many different causes of secondary angle closure and the clinical signs vary according to the underlying condition.

A complete discussion of these topics is outside the scope of this text.

II.2.5.1 Secondary angle closure with pupillary block

Aetiology and mechanism:

Pupillary block pushes the iris forward to occlude the angle. In iritis or iridocyclitis, the development of posterior synechiae may lead to seclusion of the pupil and absolute pupillary block with consequent forward bowing of the iris or 'iris bombé'. Acute secondary angle closure glaucoma may result.

The following is a limited list of other aetiologies for relative or absolute pupillary block:

- Enlarged, swollen lens (cataract, traumatic cataract)
- Anterior lens dislocation (trauma, zonular laxity; Weill-Marchesani's syndrome, Marfan's syndrome etc.)
- Protruding vitreous face or intravitreal silicone oil in aphakia
- Microspherophakia
- Miotic-induced pupillary block (also the lens moves forward)
- IOL-induced pupillary block; anterior chamber IOL, phakic intraocular lens, anteriorly dislocated posterior chamber IOL.

Features:

- IOP > 21 mmHg
- Appositional or synechial angle closure on gonioscopy."

Treatment:

- Several steps may be considered, according to the clinical picture of causative mechanisms
- Topical and systemic IOP lowering medication (not sufficient on its own)
- Nd:YAG LPI
- Peripheral surgical iridectomy
- Lens extraction, vitrectomy
- Discontinuing miotics in miotic-induced pupillary block
- Pupillary dilatation
- Nd:YAG laser synechiolysis of posterior synechiae

II.2.5.2 Secondary angle closure with anterior 'pulling' mechanism synechial closure without pupillary block

Aetiology and mechanism:

The TM is obstructed by iris tissue or a membrane. The iris and/or a membrane are progressively pulled forward to occlude the angle.

Features:

- IOP > 21 mmHg
- Appositional or synechial angle closure
- Disc features compatible with glaucoma may be present

II.2.5.2.1 Neovascular glaucoma

The iridotrabecular fibrovascular membrane is induced by ocular microvascular disease with retinal ischemia; initially the neovascular membrane covers the angle, causing a secondary form of OAG, then it contracts, causing synechial angle closure.

Treatment:

For the underlying disease / retinal ischemia

- Anti-vascular endothelial growth factor (VEGF)
- Retinal ablation with laser or cryoprobe

For the glaucoma

- Topical steroid initially
- Topical and systemic IOP lowering medication as needed
- Filtering procedure with antimetabolites, with relatively good prognosis if neovascularisation process is successfully treated and quiescent
- Aqueous drainage devices
- Cyclodestructive procedures
- Miotics are contraindicated

Systematic review:

- Simha A, Aziz K, Braganza A, et Al. Anti-vascular endothelial growth factor for neovascular glaucoma. Cochrane Database of Syst Rev 2020 Feb 6;2(2):CD007920.

II.2.5.2.2 Iridocorneal endothelial syndrome

Iridocorneal endothelial (ICE) syndrome, with progressive endothelial membrane formation and progressive iridotrabecular adhesion. Typically the PAS are patchy, very anterior, with areas of TM apparently normal. There are different presentations of ICE syndrome according to the involvement of the anterior segment structures. ICE syndrome is unilateral, more common in middle-aged women.

Treatment

- Topical and systemic IOP lowering medications as needed
- Filtering procedure, with antimetabolite, has limited success
- Aqueous drainage device

II.2.5.2.3 Epithelial and fibrous ingrowth after anterior segment surgery or penetrating trauma

Epithelial and fibrous ingrowth after anterior segment surgery or penetrating trauma
Inflammatory membrane.

Treatment:

- Topical and systemic IOP lowering medication as needed
- Excision, destruction of the immigrated tissue
- Filtering procedure, with antimetabolite, has limited success
- Aqueous drainage device
- Cyclodestruction

II.2.5.3 Secondary angle closure with posterior 'pushing' mechanism without pupillary block

II.2.5.3.1 Aqueous misdirection or malignant glaucoma

Aetiology and mechanism: Aqueous misdirection, is a rare type of secondary angle closure most commonly encountered after filtering surgery in eyes with PACG. It may occur after any type of intraocular surgery. Typically it occurs after surgery involving shallowing of the anterior chamber in eyes at risk, e.g. after trabeculectomy or lens extraction. Forward movement of the lens iris diaphragm causes angle closure resulting in IOP elevation. Risk factors include small eyes (axial length < 21 mm), higher hypermetropic refraction (> +6 D) and PACG.

Choroidal expansion and resistance to flow of fluid from the posterior to the anterior segment leads to forward displacement of the irido-lens diaphragm and closure of the anterior chamber angle.

Treatment:

- Medical treatment
 - Parasympatholytics (atropine or cyclopentolate)
 - Aqueous production suppressants given orally and/or topically
 - Hyperosmotics (see II.2.4.1.2)
 - Miotics are contraindicated!
- Surgical treatment
 - A patent peripheral iridotomy must be present or, if not present, LPI should be performed
 - Phakic: pars plana vitrectomy with or without lens extraction
 - Pseudophakic: Nd:YAG laser vitreolysis/capsulotomy may be tried
 - Pseudophakic: zonulo-hyaloido-vitreotomy via anterior chamber, through a peripheral iridectomy or iridotomy via the anterior chamber

Diode laser cyclophotocoagulation can be considered at any time.

II.2.5.3.2 Iris and ciliary body cysts, intraocular tumors

Treatment:

- Tumour irradiation or excision
- Filtering surgery only after the tumor is controlled
- Cyclodestruction

II.2.5.3.3 Silicon oil or other tamponading fluids or gas implanted in the vitreous cavity

Treatment:

- Topical/systemic IOP lowering medications as needed
- Inferior iridectomy
- Silicon oil or gas aspiration
- Filtering surgery
- Long – tube drainage device
- Cyclodestruction

II.2.5.3.4 Uveal effusion treatment

Aetiology and mechanism:

- 1) Inflammation as in scleritis, uveitis, human immunodeficiency virus infection
- 2) Increased choroidal venous pressure as in nanophthalmos, scleral buckling, panretinal photocoagulation, central retinal vein occlusion, arterio-venous communication
- 3) Tumor
- 4) Drug-induced

Treatment:

- Anti-inflammatory medication (for 1)
- Topical and systemic IOP lowering medication as needed
Relaxation of scleral buckling; vitrectomy, sclerectomy in nanophthalmus
- Tumor excision or irradiation (for 3)
- Attempt to address the underlying mechanism

II.2.5.3.5 Retinopathy of prematurity (stage V)

Features:

- Discomfort, pain, redness
- Corneal oedema
- IOP \geq 21 mmHg
- Axially shallow anterior chamber

Treatment:

- Topical and systemic IOP lowering medications
- Filtering procedure with or without antimetabolite
- Drainage devices

II.2.5.3.6 Congenital anomalies that can be associated with secondary angle closure glaucoma

These conditions are extremely variable in pathogenesis, clinical presentation and required management; an extensive discussion is outside the scope of this chapter.

Aetiology and mechanism:

Angle closure is caused by pushing forward the ciliary body and iris. Increase of volume of the posterior segment of the eye.

Examples are familial iris hypoplasia, anomalous superficial iris vessels, aniridia, Sturge-Weber syndrome, neurofibromatosis, Marfan's syndrome, Pierre Robin syndrome, homocystinuria, goniodysgenesis, Lowe's syndrome, microcornea, microspherophakia, rubella, broad thumb syndrome, persistent hyperplastic primary vitreous.

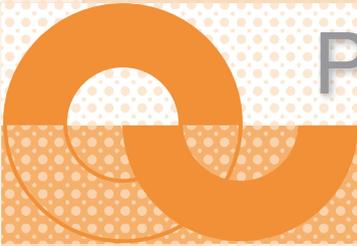
Features:

- IOP > 21 mmHg
- Corneal oedema
- Axially shallow anterior chamber

Treatment:

Treatment to be adapted to the primary anomaly. LPI and surgical iridectomy are not effective.





Part II · Chapter 3

Treatment options



Part II · Chapter 3

Treatment options

II.3.1 General principles of glaucoma treatment

The goal of care for people with, or at risk of, glaucoma is to promote their well-being and quality of life within a sustainable health care system. Well-being and quality of life are influenced by a person's visual function, the psychological impact of having a chronic progressive sight-threatening condition and the costs and side-effects of treatments. Costs include inconveniences to the individual and their care givers as well as the financial cost of examinations, diagnostic procedures and therapies, both to the individual and society. The effect of visual function on well-being and quality of life is variable; in general, early to moderate glaucoma has only a modest influence, whereas advanced visual function loss in both eyes may considerably reduce quality of life.

Glaucoma is still the second leading cause of blindness in Europe. In most Western countries at least half of patients with manifest glaucoma are undiagnosed and glaucoma is often diagnosed late. A considerable percentage of glaucoma patients (over 10%) become blind in both eyes or encounter serious field loss in both eyes within their lifetime. Major risk factors for glaucoma blindness are the severity of the disease at presentation, bilateral disease, and age. A young patient with mild bilateral damage is at much larger risk of disability in his lifetime than an 80-year-old patient with moderate unilateral disease. Thus, treatment must be individualised to the needs and rate of progression of each patient (see also I.3, question 3, Figure II.3.1).

The risk of encountering loss of QoL from glaucoma should determine target pressure, intensity of treatment, and frequency of follow-up.

For instance, patients with severe functional loss or younger patients with manifest disease should have more aggressive treatment and closer follow-up than patients with little or no risk, e.g., very old patients with early field loss or unilateral disease. Glaucoma suspects have an even smaller risk of visual impairment.

In most patients with advanced glaucoma and reasonable life expectancy, aggressive IOP lowering treatment is recommended. Elderly patients with significant health problems and mild glaucoma with relatively low IOP might prefer being followed without treatment. When treatment options are discussed with a patient, general health status and personal preferences must be considered and respected. It is also important to ensure that patients are able to comply and persist with therapy.

Disease progression rates differ very much between patients and types of glaucoma, from rapid to very slow. Many patients with glaucoma show no or only small deterioration despite years of follow-up, while rapid progression may occur in others, e.g. in PXFG.

The likely or observed rate of progression should determine target pressure and treatment intensity (see also II.3.3).

Determining the rate of progression is the standard in glaucoma care. In patients at high risk of losing vision related QoL, a sufficient number of VFs is required to estimate the rate of progression. Frequent VF testing, e.g., three VF tests per year for the first two years after diagnosis, may be valuable for patients with significant disease to make it possible to identify rapidly progressing glaucoma. If progression has not been identified in the first two years, the frequency of tests may be reduced. Such frequent testing is not required for all patients with glaucoma, e.g., elderly with mild disease in one eye and low untreated IOP.

Once the progression rate has been determined, the target pressure should be re-evaluated and based on the measured rate of progression and IOP values measured during the follow-up time.

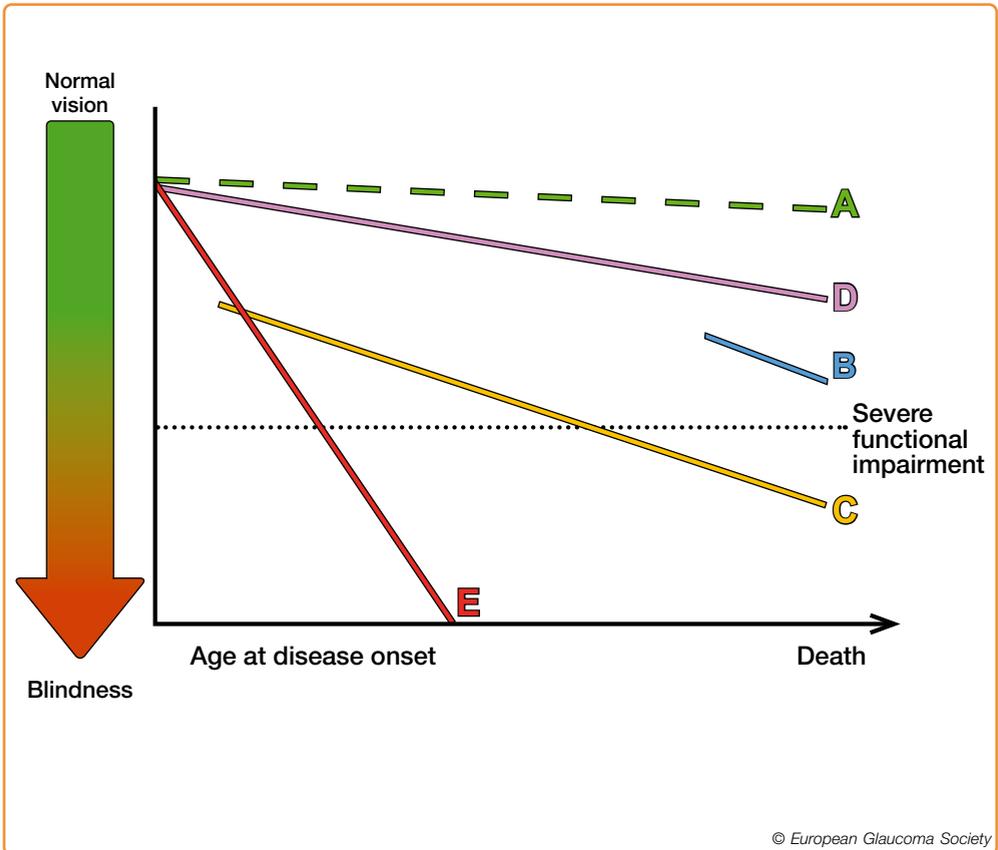


Figure II.3.1. The whom-to-treat graph

The rate of ganglion cell loss and resulting functional decay is very different among different glaucoma eyes. QoL is reduced when VFs defects become severe. Line A represents the effect of ageing alone. In glaucoma, loss of visual function is often much more rapid. An older patient, diagnosed late in life, with a moderate rate of progression (B) has a much lower risk of developing severe functional impairment than a younger patient with the same amount of field loss and rate of progression at diagnosis (C). A very slow rate of progression may be inconsequential by the patient and treatment may be left unchanged (D), while a rapid rate of progression (E) needs a considerably lower target pressure. It is the extent of binocular VF or the VF of the better eye that largely determines the patient's QoL, while the rates of progression of each eye separately are needed to determine treatment

Currently, the only approach proven to be effective in preserving visual function is lowering IOP (See Part I and FC IX to XIII). However, some patients may be more susceptible to the level of IOP than others.

The need for effective non-IOP related treatments has been acknowledged. Blood pressure may also be important in glaucoma. There is some evidence that some patients overtreated for systemic hypertension may be at increased risk of VF loss. However, there is no conclusive evidence to support the idea that ocular blood flow can be improved and can improve the outcome in glaucoma patients. Neuroprotection can be defined as a 'therapeutic approach' aiming to directly prevent neuronal damage. Several compounds have been shown to be neuroprotective in animal models of experimental glaucoma. So far, no compound has reached a sufficient level of evidence to be considered effective in glaucoma patients.

The goal of glaucoma management is to promote the best possible well-being and quality of life with minimal glaucoma induced visual disability in individuals with glaucoma within a sustainable health care system.

Overview of strategies to achieve our goal.

- Identification of patients with glaucoma and especially those at risk of severe visual loss.
- Identification of patients at risk of developing glaucoma.
- Identification of the type and mechanism of glaucoma (see II.2).
- Management and treatment according to the expected rate of disease progression and risk of loss of quality of life.
- Decreasing the risk of disease progression.
- Determine the target IOP for the individual. In general, when there is more advanced damage, lower IOPs are needed to prevent further progression.

IOP lowering with medication/laser/surgery.

- Verify the efficacy of treatment and reassess target IOP (see II.3).
- Monitor the Rate of Progression (Field and Disc).
- Adjust management according to rate of progression.
- Consider always adherence to treatment and assiduity of follow-up.
- Audit outcomes e.g. efficacy, safety, use of resources (see I.8).
- Failures include patients suffering from the consequences of insufficient IOP lowering, side effect of medications and surgical complications.

II.3.2 Treatment options

The benefits of IOP reduction in managing POAG irrespective of the level of untreated IOP, as well as reducing the conversion of OHT to POAG have been well established. Most forms of open angle glaucoma may be initially treated with topical medications or laser trabeculoplasty. Initial surgery may be considered in patients with advanced VF loss at presentation.

For OHT and if possible for those glaucoma patients without very high IOP and without severe damage, it is useful to measure IOP more than once before initiating IOP-lowering therapy.

Systematic review:

- Burr J, Azuara-Blanco A, Avenell A, Tuulonen A. Medical versus surgical interventions for open angle glaucoma. Cochrane Database Syst Rev. 2012;(9):CD004399.

II.3.3 Target IOP

Therapy in glaucoma management aims to lower IOP to slow the rate of VF deterioration sufficient to maintain the patient's QoL.

Target IOP is the upper limit of IOP judged to be compatible with this treatment goal. It should be re-evaluated regularly and, additionally, when progression of the disease is identified or when ocular or systemic comorbidities develop.

There is no single target IOP level that is appropriate for every patient, so the target IOP needs to be estimated for each eye of every patient.

II.3.3.1 Setting the target IOP

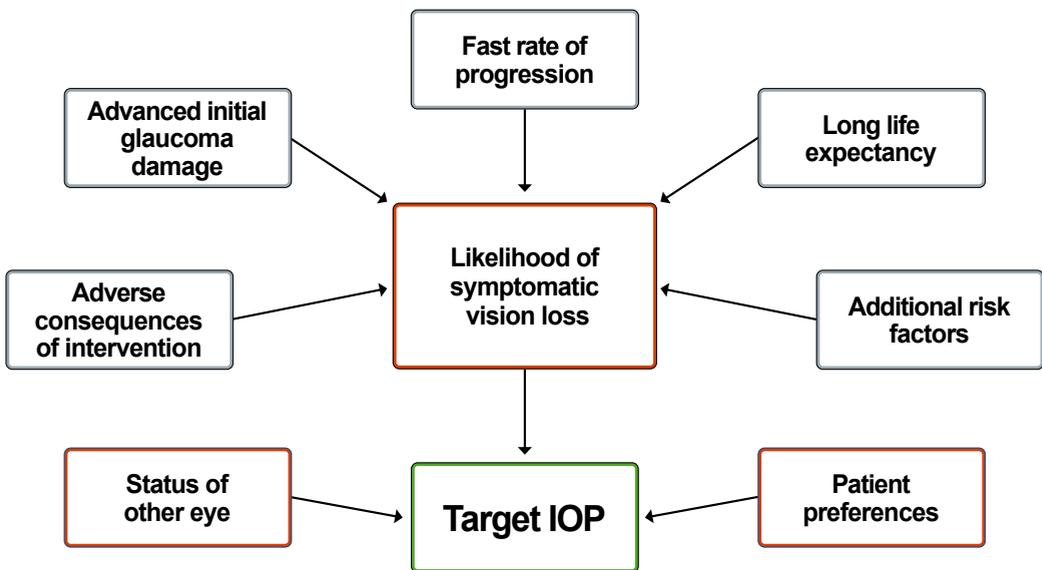
There is little evidence to support any particular algorithm to set the target IOP.

In newly diagnosed patients, the target IOP is initially determined according to stage of disease and the baseline IOP. The treatment goal is typically estimated as a specific pressure level or a percentage reduction. For instance, in early glaucoma, an IOP of 18 to 20 mmHg with a reduction of at least 20% may be sufficient. In moderate glaucoma, an IOP of 15 to 17 mmHg with a reduction of at least 30% may be required. Lower target IOP, e.g., 10 to 12 mmHg may be needed in more advanced disease. (See FC X).

Factors to consider when setting the target IOP include:

- Stage of glaucoma
The greater the pre-existing glaucoma damage, the lower the target IOP should be
- Age and life expectancy
Whilst younger age implies greater life expectancy and, therefore, a lower Target IOP, older age is a risk factor for more rapid progression
- Untreated IOP
The lower the untreated IOP levels, the lower the Target IOP should be
- Goldmann IOP is underestimated if the cornea is thin
- Additional risk factors, e.g., PXF (see II.2.3.1.1)
- Rate of progression during follow-up
The faster the rate of progression, the lower the Target IOP should be
- Other factors to consider: adverse consequences of intervention, patient preference, family history, status of the other eye

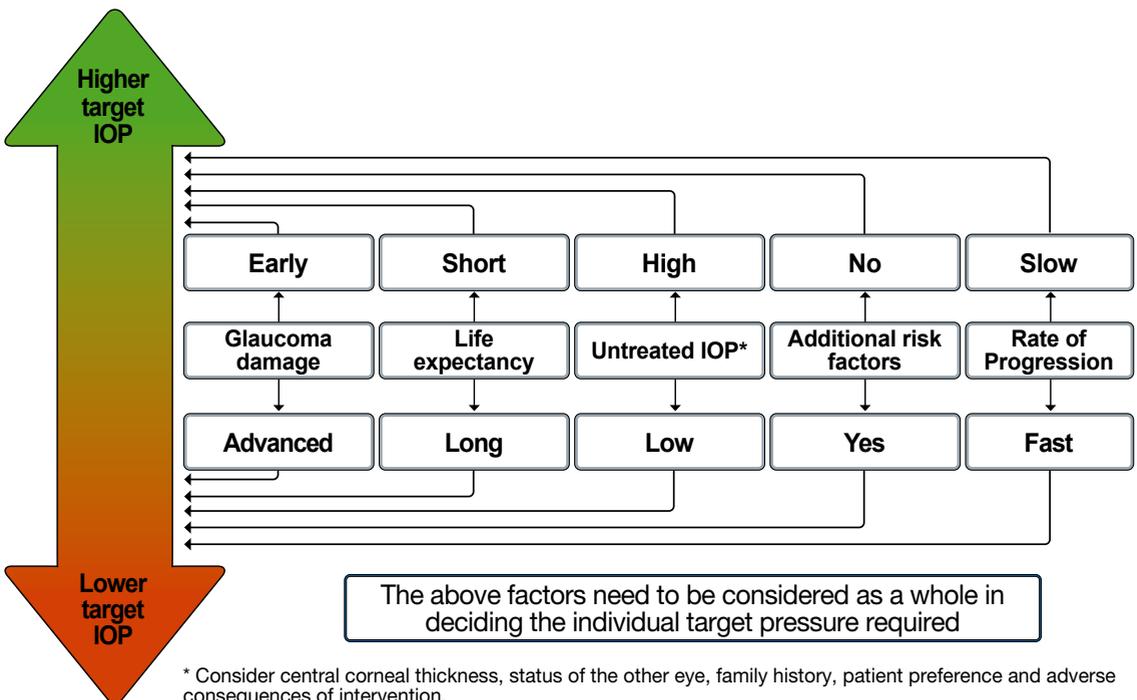
FC IX – Considerations on target IOP



The treatment target is a compromise between reducing the risk of symptomatic vision loss and the consequences of therapy. Patient preferences should be taken into account.

Greater initial VF loss is the most important predictor of blindness from glaucoma. In a newly-diagnosed patient, the RoP is unknown and Target IOP is based on risk factors for progression (see II.2.2.1). After sufficient follow-up and with sufficient VF tests to reliably determine the progression status, usually 2-3 years, the importance of the risk factors for decision-making decreases and importance of the measured rate of progression increases; the RoP should be used to adjust the target IOP, taking into account IOP levels over the observation period, life expectancy, and current levels of visual function damage (See FC X).

FC X – Setting the target IOP



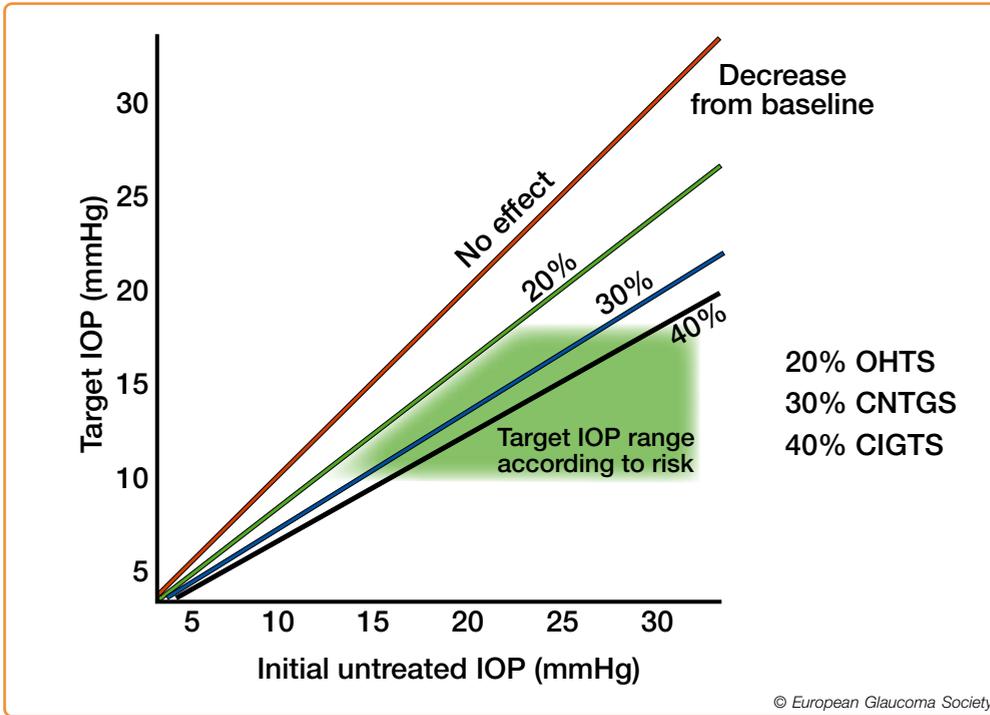


Figure II.3.2. Diagrammatic evaluation of target IOP. The target IOP is frequently situated within the shaded area. The percentage IOP reduction targeted (i.e. 20%, 30%, 40%) depends mainly on VF damage at diagnosis and on rate of progression. (see also FC X)

II.3.3.2 Achieving and re-evaluating the target IOP

The principles of adjusting therapy to achieve treatment targets are shown in FCs XI to XIV.

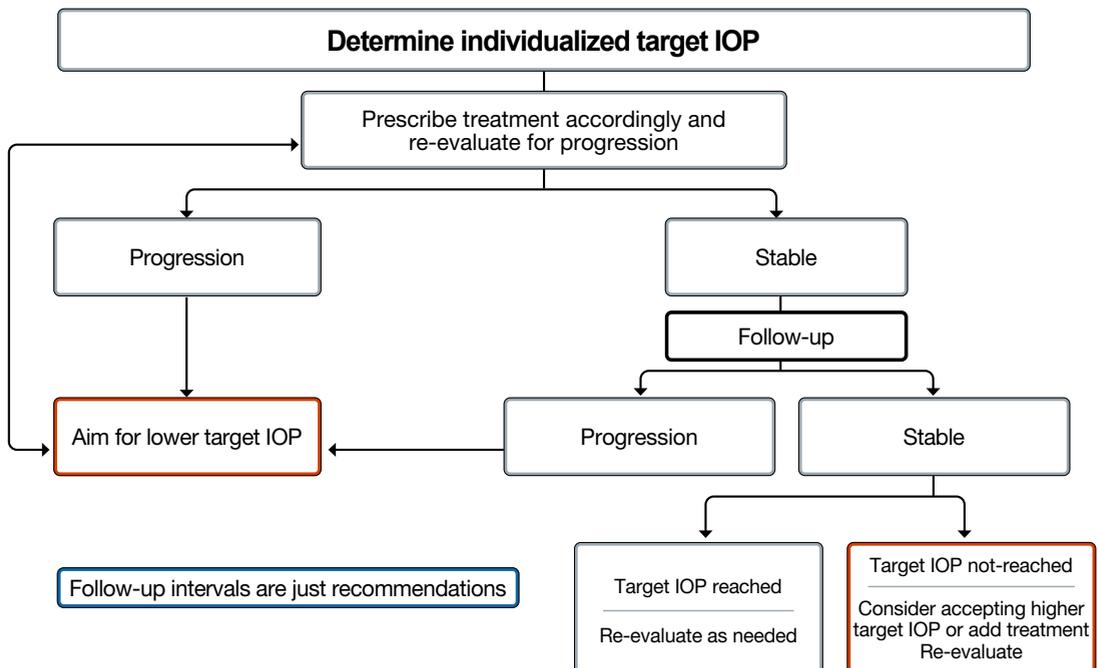
If the VF is worsening at a rate that may threaten QoL during the patient's expected lifetime, then the Target IOP should be lowered further and treatment changed.

In consultation with the patient the risks and benefits of the additional intervention should be weighed. (See FC XI)

If there are sufficient VFs to judge the rate of progression, and this rate is sufficiently slow not to impact on the patient's QoL, then the Target IOP may be revised upward if the Target IOP has not been met or if the patient is on excessive therapy or is experiencing side effects.

If there are insufficient VFs to judge the rate of progression and the Target IOP has not been met, then additional therapy should be considered, as above.

FC XI – Adjustment of target IOP

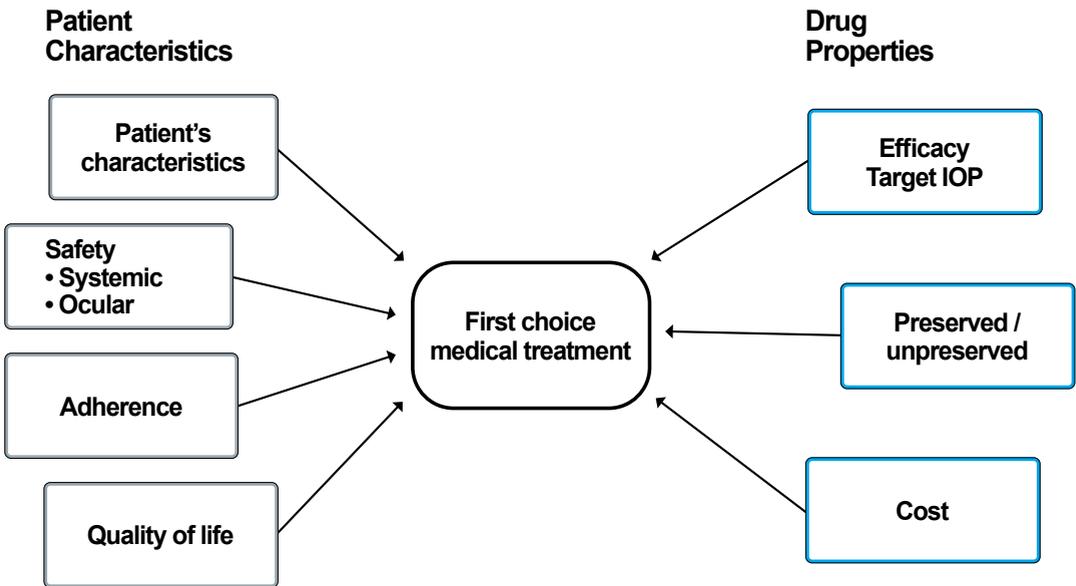


II.3.4 General principles of medical management

II.3.4.1 Start with monotherapy

To minimize side effects, the least amount of medication required to achieve the desired therapeutic response should be given. It is recommended to initiate the treatment with monotherapy (See FC XII, XIII and XIV), except in cases with very high IOP and severe disease. Treatment is considered “effective” when the IOP reduction on treatment is comparable to the published range for that drug in a similar population. The highest reduction of IOP is obtained with PGAs, followed by non-selective β -blockers, Rho kinase inhibitors, alpha-adrenergic agonists, selective β -blockers and at last topical carbonic anhydrase inhibitors. IOP-lowering treatment efficacy depends on untreated IOP, with larger reductions in patients with higher untreated IOP levels. Uniocular drug trial may be useful to evaluate the efficacy of therapy.

FC XII – Considerations on first choice medical treatment

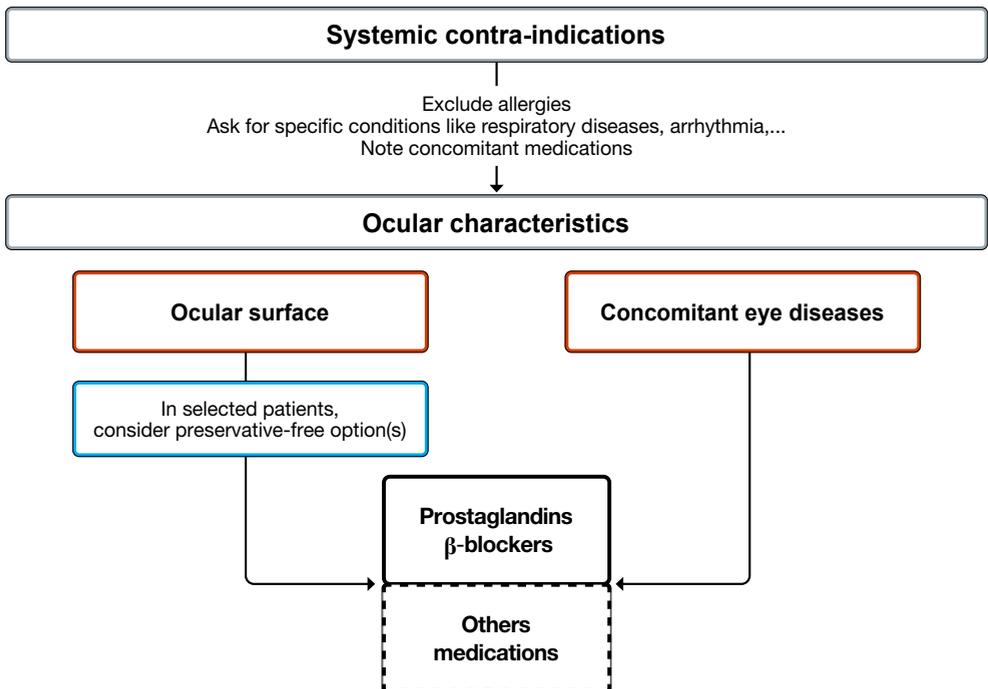


A first choice medical treatment is considered a drug that the treating physician prefers to use as initial IOP lowering therapy as opposed to the first line treatment, which is one that has been approved by policymakers.

Systematic review:

- Li T, Lindsley K, Rouse B, et al. Comparative Effectiveness of First-Line Medications for Primary Open Angle Glaucoma: A Systematic Review and Network Meta-analysis. Ophthalmology. 2016;123(1):129-140.

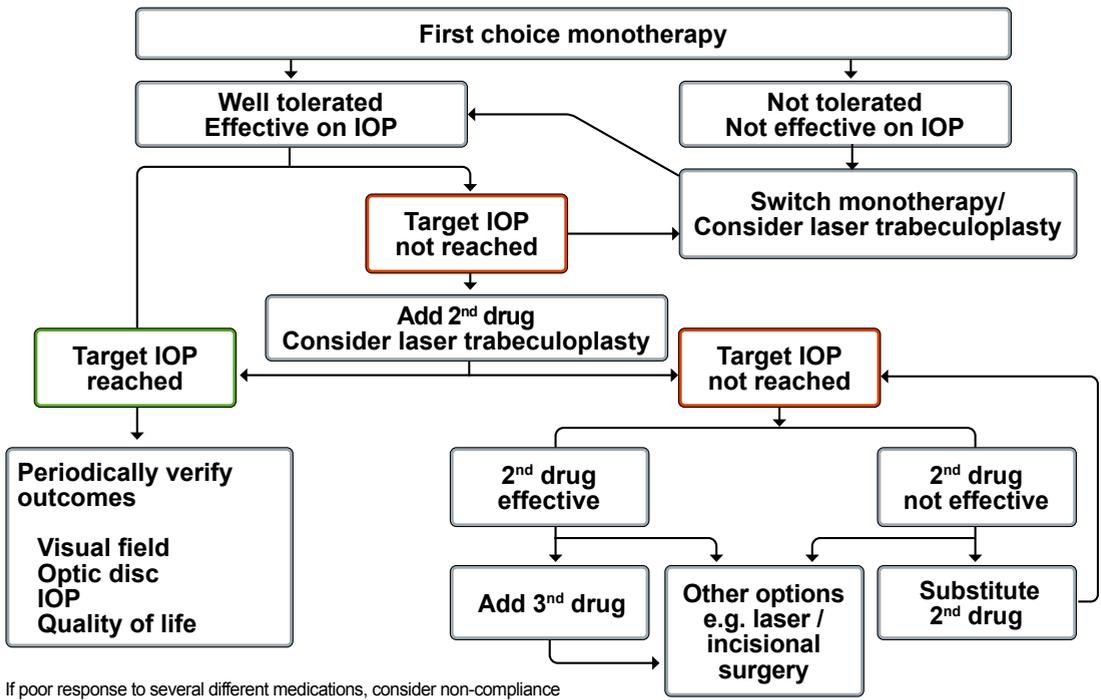
FC XIII – Medical management – choosing therapy



II.3.4.2 Switch to another monotherapy

If the initial therapy is not effective or the drug is not tolerated, one should switch to another monotherapy (in the same or another class) rather than adding a second drug. Laser trabeculoplasty is an option (See FC XIV).

FC XIV – Therapeutical algorithm in glaucoma topical therapy



II.3.4.3 Add second drug / combination therapy

If monotherapy is well tolerated and effective, but has not lowered IOP to the target pressure, an additional drug of a different class should be considered. (see Tables 3.1 to 3.6). Multiple topical treatments may reduce adherence and increase exposure to preservatives. Therefore, fixed combination therapy, when available, is preferable to two separate instillations of agents.

Most fixed combinations available in Europe contain a β -blocker. β -blockers may improve local tolerability of the other agent but can be associated with systemic side effects and need to be used cautiously in patients with relevant contraindications. The most frequently used combination is a PGA with a β -blocker. Other combinations include CAI with α -2 agonist and PGA with Rho kinase inhibitor.

Fixed combinations usually have clinical equivalence to unfixed combinations.

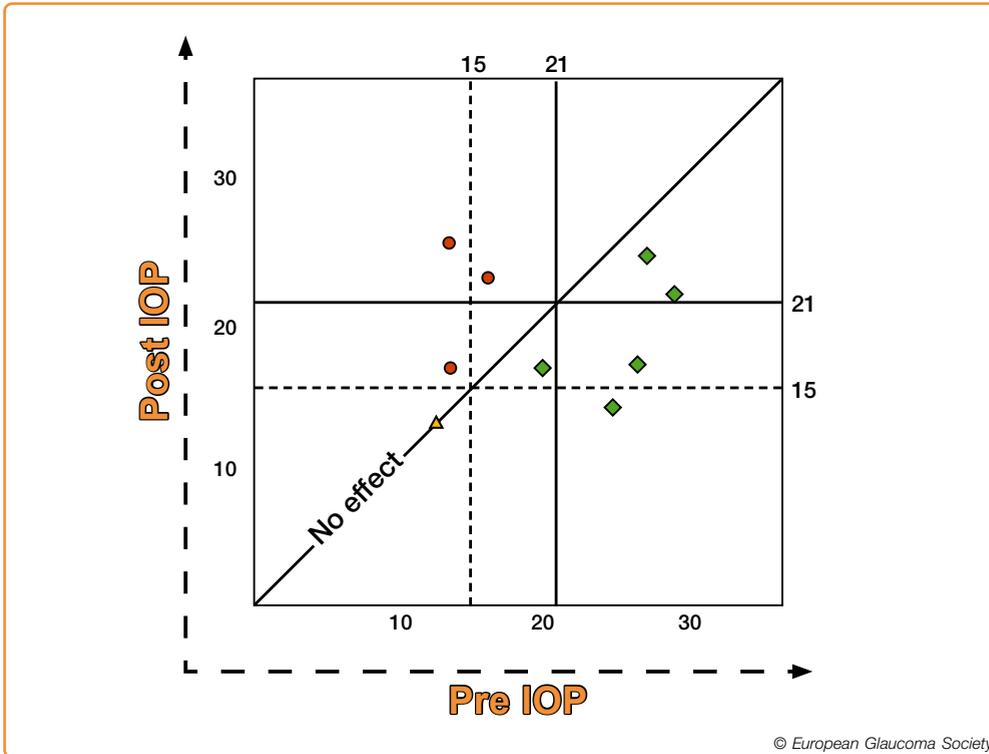
Combination therapy is not recommended as first choice treatment. However, in selected cases, such as advanced glaucoma and/or very high IOP, the target pressure is unlikely to be achieved by a single agent and combination therapy may be advisable.

Occasionally, in case of uncertainty about the efficacy, consider temporarily stopping IOP lowering medication to re-evaluate untreated IOP.

If a patient is insufficiently controlled with two agents then a third agent, laser or incisional surgery may be considered. (see FC XIV)

It is essential to involve patients in decisions regarding the management of their condition.

To use the least amount of medication (and consequent inconvenience, costs and side effects) to achieve the therapeutic response should be a consistent goal.



© European Glaucoma Society

Figure II.3.3. The pre - post IOP graph. Circles in red here represent an increase of IOP from baseline. Green diamonds represent a decrease of IOP from baseline. The yellow triangle is on the 'no effect line'

The Following pages outline the most frequently used anti-glaucoma medications, and emphasize their mode of action, dosage and side effects. A complete list of all possible medications is beyond the scope of the Guidelines.

Antiglaucoma drugs have been available since 1875. The following diagram shows the chronology of the introduction of topical IOP-lowering medications (Fig. 3.3).

The text should be considered as a general guide, and cannot be all-inclusive. Only latanoprost has been tested in a trial on children.

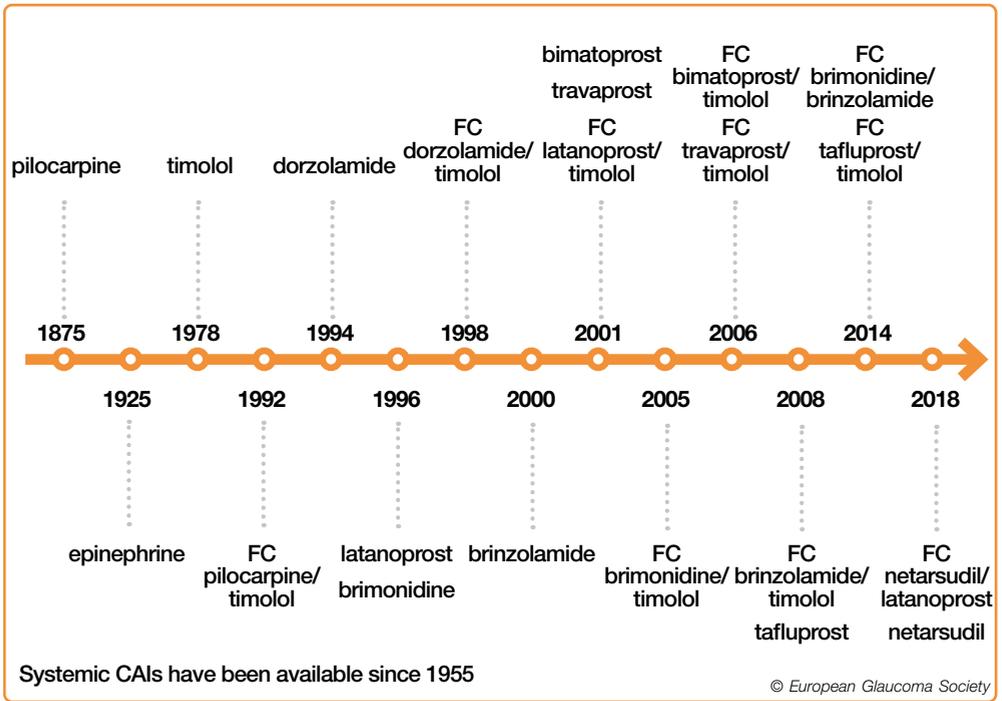


Figure II.3.4. IOP lowering molecules and year of first clinical use. FC: fixed combination

II.3.5 IOP-lowering drugs

Some of the listed molecules are not yet available in Europe

Table 3.1 Class: Prostaglandin analogues

	Compound	Mode of action	IOP reduction	Side effects
Prostaglandin analogues	Latanoprost 0.005% Tafluprost 0.0015% Travoprost 0.003% - 0.004% Latanoprost bunod 0.024%	Increase of in uveo-scleral outflow	25-35%	Local: Conjunctival hyperaemia, burning stinging, foreign body sensation, itching, increased pigmentation of periocular skin, periorbital fat atrophy, eyelash changes. Increased iris pigmentation, (in green-brown, blue/ grey-brown or yellow-brown irides). Cystoid macular oedema (aphakic/pseudophakic patients) with posterior lens capsule rupture or in eyes with known risk factors for macular oedema, reactivation of herpes keratitis, uveitis
Prostamide	Bimatoprost 0.03% Bimatoprost 0.01%	Increase of in uveo-scleral outflow	25-35%	Systemic: Dyspnea, chest pain/ angina, muscle-back pain, exacerbation of asthma.

Table 3.2 Class: β -receptor Antagonists

	Compound	Mode of action	IOP reduction	Contra-indications	Side effects
Nonselective	Timolol 0.1-0.25-0.5% Levobunolol 0.25% Metipranolol 0.1-0.3% Carteolol 0.5-2.0%	Decreases aqueous humour production	20-25%	Asthma, history of chronic obstructive pulmonary disease, sinus bradycardia (< 60 beats/min), heart block, or cardiac failure	Local: Conjunctiva hyperaemia, superficial punctate keratitis, dry eye, corneal anesthesia, allergic blepharo-conjunctivitis Systemic: Bradycardia, arrhythmia, heart failure, syncope, bronchospasm, airways obstruction, distal oedema, hypotension, Hypoglycemia may be masked in Insulin dependent Diabetes Mellitus (IDDM), nocturnal systemic hypotension, depression, Erectile dysfunction
Beta-1-selective	Betaxolol 0.25 -0.5%	Decreases aqueous humour production	\pm 20%	Asthma, history of chronic obstructive pulmonary disease, sinus bradycardia, heart block, or cardiac- coronary failure	Local: Burning, stinging more pronounced than with non-selective compounds Systemic: Cardiac and respiratory side effects less pronounced than with non-selective compounds, depression, erectile dysfunction

Table 3.3 Class: Carbonic anhydrase inhibitors

	Compound	Mode of action	IOP reduction	Contra-indications	Side effects
Topical	Brinzolamide 1% Dorzolamide 2%	Decreases aqueous humour production	20%	Patients with low corneal endothelial cell count, due to increased risk of corneal oedema	Local: Burning, stinging, bitter taste, superficial punctate keratitis, blurred vision, tearing Systemic: Headache, urticaria, angioedema, pruritus, asthenia, dizziness, paresthesia and transient myopia.
Systemic	Acetazolamide	Decreases aqueous humour production	30-40%	Depressed sodium and/or potassium blood levels, cases of kidney and liver disease or dysfunction, suprarenal gland failure, hyperchloremic acidosis. Allergy to sulfamides.	Systemic: Paresthesias, hearing dysfunction, tinnitus, loss of appetite, taste alteration, nausea, vomiting, diarrhoea, depression, decreased libido, kidney stones, blood dyscrasias, metabolic acidosis, electrolyte imbalance

Table 3.4 Class: Alpha-2 selective adrenergic agonists

	Compound	Mode of action	IOP reduction	Contra-indications	Side effects
Alpha-2-selective	Apraclonidine 0.5-1.0%	Decreases aqueous humour production	25-35%	Oral monoamine oxidase (MAO) inhibitor users Pediatric age Very low body weight in adults	<p>Local: Lid retraction, conjunctival blanching, limited mydriasis (apraclonidine), allergic blepharoconjunctivitis, periocular contact dermatitis, allergy or delayed hypersensitivity (apraclonidine and clonidine >brimonidine)</p> <p>Systemic: Dry mouth and nose (apraclonidine), fatigue, sleepiness (brimonidine)</p>
	Brimonidine 0.2%	Decreases aqueous humour production and increases uveo-scleral outflow	18-25%		

Table 3.5 Class: Rho kinase inhibitors

Compound	Mode of action	IOP reduction	Side effects
Netarsudil 0.02%	Increase trabecular outflow Reduce episcleral venous pressure	20% - 25%	<p>Local: conjunctival hyperaemia, cornea verticillata, instillation site pain, conjunctival haemorrhage, instillation site erythema, corneal staining, blurred vision, increased lacrimation and erythema of eyelid</p> <p>Systemic: headache, nasal discomfort, rhinalgia, dermatitis allergic, dermatitis contact, lichenification, petechiae, polycondritis, escoriation</p>
Ripasudil 0.4%	Increase trabecular outflow	20%	<p>Local: Conjunctival hyperaemia, conjunctivitis, blepharitis, eye irritation, corneal epithelial disorder, eye pruritus, abnormal sensation in eye, eye discharge, eye pain, conjunctival follicles, intraocular pressure increased, contact dermatitis</p> <p>Systemic: gastro-intestinal disorders, dizziness, headache, nasal congestion, allergic rhinitis</p>

Table 3.6 Class: Parasympathomimetics (cholinergic drugs)

	Compound	Mode of action	IOP reduction	Contra-indications	Side effects
Direct-acting	Pilocarpine 0.5-4%	Facilitates aqueous outflow by contraction of the ciliary muscle, tension on the scleral spur and traction on the TM	20-25%	20-25% Post-operative inflammation, uveitis neovascular glaucoma. Patient at risk for retinal detachment, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia, hypotension, recent myocardial infarction, epilepsy, Parkinsonism	<p>Local: Reduced vision due to miosis and accommodative myopia, conjunctival, hyperaemia, retinal detachment, lens opacities, precipitation of angle closure, iris cysts</p> <p>Systemic: Intestinal cramps, bronchospasm, headache</p>
Indirect-acting	Ecothiophate iodide 0.03%		15-25%		<p>Local and systemic: Side effects are similar but more pronounced than with direct acting compounds</p>

Table 3.7 Class: Osmotics

	Compound	Mode of action	IOP reduction	Contra-indications	Side effects
Oral	Glycerol Isosorbide	Dehydration and reduction in vitreous volume resulting in posterior movement of the iris-lens plane with deepening of the AC	15-20%	Cardiac or renal failure	Nausea, vomiting, dehydration (special caution in diabetic patients), increased diuresis, hyponatremia when severe may lead to lethargy, obtundation, seizure, coma, possible increase of glycemia, acute oliguric renal failure, hypersensitivity reaction
Intravenous	Mannitol		15-30%		

II.3.5.1 Prostaglandin analogues (PGAs)

PGAs have become the first-choice therapy largely on the basis of their efficacy, once-daily dosing and safety profile.

The primary mechanism of action of PGAs is to increase uveoscleral outflow. Reduction of IOP starts approximately 2-4 h after the first administration, with the peak effect within approximately 8-12 h PGAs may reduce short-term IOP variability compared to other classes of drugs.

Differences in efficacy within the class are not clinically significant. When combined with most of the other IOP-lowering drugs, PGAs provide additive IOP lowering, but two different PGAs should not be combined. Conjunctival hyperaemia, generally mild, is a common finding with difference in frequency and level among PGAs. Hyperaemia may decrease over time. Other PGA side effects are reported in Table 3.1.

Latanoprost is the only IOP-lowering agent studied in children and was shown to have a good safety profile.

Details on the mode of action, IOP lowering effect, contraindications and side effects of other first line drugs (β -blockers, carbonic anhydrase inhibitors, alpha-2 selective adrenergic agonists, Rho kinase inhibitors) and second line drugs are listed in Tables 3.2-3.7.

II.3.5.2 Local toxicity of topical treatment: the role of preservatives

Preserved topical glaucoma medications may cause and/or exacerbate pre-existing ocular surface disease (OSD), such as dry eye and Meibomian gland dysfunction, which has a high prevalence in adults. Benzalkonium chloride (BAC) is the most common preservative in glaucoma medications. Symptoms of OSD often diminish if BAC-preserved drops are substituted with non-preserved drops. A possible unwanted effect of long-term BAC use is a reduction in the success rate of filtering surgery.

Therapeutic options to reduce OSD include preservative-free or BAC-free medication, decreasing the number of eye drops (i.e. by using fixed combinations), treating the ocular surface with unpreserved tear substitutes and performing earlier laser or surgery. Regarding OSD, several factors have to be considered: e.g. the active compound, the specific preservative and other excipients, the ability of the patient to use single-dose preparations and the patient's ocular surface.

The European Medicines Agency (EMA) has suggested that the use of preservatives should be avoided in patients who do not tolerate eye drops with preservatives and in those on long-term treatment, or to use concentration at the minimum level consistent with satisfactory antimicrobial function in each individual preparation, with a specific indication to avoid mercury containing preparations.

Not all patients are sensitive to preservatives and not all the local side effects observed with topical IOP-lowering medications are induced by preservatives.

Particular attention should be paid to glaucoma patients with pre-existing OSD or to those developing dry eye or ocular irritation over time. This can be done by assessment of the redness of the eyelid margin, positive corneal and conjunctival fluorescein staining or reduced tear break-up time.

II.3.5.3 Generic IOP-lowering topical medications

By definition a generic drug is identical to a brand name drug in dosage, strength, route of administration, performance characteristics and intended use. For the purposes of drug approval, the interchangeability of a generic drug and the corresponding brand-name drug is based on the criterion of 'essential similarity'. With systemic drugs, bioequivalence studies are performed using blood samples to determine whether the plasma concentration within certain limits equals the branded drug. Clinical studies are usually not required for generic approval in ophthalmology, and a $\pm 10\%$ difference between the concentration of the active compound between the generic and the branded products is considered acceptable by the EMA. Whereas the active compound is assumed to be equal, the excipients can vary considerably. This is an important issue because different adjuvants may alter the viscosity, osmolarity and pH of the eye drops and therefore have an impact on tolerability and corneal penetration. Many drugs are now off-patent and generic alternatives abound. The extent to which these generics are similar in efficacy and tolerability to the branded alternative is not well studied, but there are differences concerning the drop size, the body of the bottle and the bottle tips. Closer monitoring of patients may be required after switching.

Systematic reviews:

- Hedengran A, Steensberg AT, Virgili G, et al. Efficacy and safety evaluation of benzalkonium chloride preserved eye-drops compared with alternatively preserved and preservative-free eye-drops in the treatment of glaucoma: a systematic review and meta-analysis. *Br J Ophthalmol* 2020.
- Steensberg AT, Müllertz OO, Virgili G, et al. Evaluation of Generic versus Original Prostaglandin Analogues in the Treatment of Glaucoma: A Systematic Review and Meta-Analysis. *Ophthalmology Glaucoma* 2020;3:51–59.

II.3.6 Dietary supplementation and alternative therapies and glaucoma

At the present time there is no evidence to support that dietary supplementation or cannabinoids have a positive effect on glaucoma management.

Systematic review:

- Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA* 2015;313:2456–2473.

II.3.7 Management of glaucoma during pregnancy and breast-feeding

Regarding glaucoma treatment, the most sensitive period is the first trimester due to concerns relating to teratogenicity. Therefore, for a woman with glaucoma who is of childbearing age, who might wish to conceive, the treatment strategy before and during pregnancy should be discussed. (See table 3.8 and 3.9) and alternative options (e.g., laser or surgery) explored.

The potential risks to the fetus (and neonate) of continuing glaucoma medications must be balanced against the risk of vision loss in the mother. As IOP levels may decrease during pregnancy, temporary treatment discontinuation can be considered under strict follow-up in some patients. However, if medical treatment is necessary, the lowest effective dosage of medication should be used. With medical therapy, systemic absorption should be reduced by punctal occlusion and eyelid closure. No IOP-lowering medications have been labelled for use during pregnancy and/or breast feeding. Some glaucoma treatments are contraindicated such as CAs, particularly in the first trimester as they may be teratogenic. Brimonidine that may induce apnea in infants and, therefore, should be avoided in late pregnancy and during breast feeding.

Although results from animal studies of IOP-lowering medications have reported adverse effects, the overall level of evidence for the risk to pregnant women and fetus/infants is low. For beta-blockers and pilocarpine there is considerable experience and they are generally considered safe.

During breast-feeding, PGAs may be acceptable. Also, CAs and beta-blockers may be used in nursing mothers as suggested by the American Academy of Pediatricians. These are also the first line choices in infants with congenital glaucoma when medical therapy is being considered.

There is a lack of well-controlled human studies during pregnancy. Therefore it is not possible to accurately determine the real incidence of the adverse effects, or to exclude the existence of any additional unforeseen adverse effects on the fetus.

Table 3.8 Communication of risks related to pregnancy on the product label

Pregnancy Pregnancy exposure registry	Risk summary	Provides "risk statements" that describe for the drug the risk of adverse developmental outcomes based on all relevant human data (literature, trials), animal data, and the drug's pharmacology. Should be an integrated summary, in some cases multiple risk statements may be needed. Information included here should be interpretable by health care providers.
	Clinical considerations	<ul style="list-style-type: none"> - Disease-associated maternal and/or embryo/foetal risk - Dose adjustment during pregnancy and postpartum - Maternal adverse reactions - Fetal/neonatal adverse reactions - Labor or delivery
	Data	<ul style="list-style-type: none"> - Human - Animal
Lactation	Risk summary	Summarize information of the presence of a drug and/or its active metabolite(s) in human milk, effects on the breast-fed child and also on milk production
	Clinical considerations	Risk benefit counselling Data
Females and males of reproductive potential	Includes information for these populations when there are recommendations for pregnancy testing and/or contraception before, during, after drug therapy. Also if there are human or animal data suggesting effects related to fertility (e.g., testicular or ovarian histological findings), following headings should be included: <ul style="list-style-type: none"> a) Pregnancy testing b) Contraception c) Infertility 	

Adapted from Reproductive and Developmental Toxicology 2nd Edition, Elsevier 2017. Based on FDA Pregnancy, Lactation, and Reproductive Potential Guidance, 2014.
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pregnancy-lactation-and-reproductive-potential-labeling-human-prescription-drug-and-biological>
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-assessment-medicinal-products-human-reproduction-lactation-data-labelling_en.pdf

Table 3.9 Class: Adverse effects of IOP-lowering medications during pregnancy/ breast-feeding

	Pregnancy			Breast-feeding
	Animal Studies	Human		
		Theoretical risk	Reported cases	
Parasympathetic agents	Teratogenic	Teratogenicity Dysregulation of placental perfusion	Meningism in newborn	Seizures, fever, diaphoresis
Sympathetic agents • brimonidine	No significant effect	Delay in labor/uterine hypotony	No reported side-effects	Central nervous system depression, hypotension and apnea
Prostaglandin analogues	High incidence of miscarriage	Uterine contractions	One case of miscarriage	No reported side-effects
β-blockers	Delayed fetal ossification, fetal resorption	Cardiac rhythm changes Respiratory	Arrhythmia and bradycardia Impaired respiratory control in newborns	Controversy over concentrations in breast milk. Apnea and bradycardia
Carbonic anhydrase inhibitors Topical		Teratogenicity (1st trimester)		
	Decreased weight gain Vertebral body malformation	Lower fetal weight	No reported side-effects	No reported side-effects
Oral	Forelimb anomalies	Limb malformations	One case of teratoma	No reported side-effects

II.3.8 Neuroprotection and glaucoma treatment

Neuroprotection can be defined as a 'therapeutic approach' aiming to directly prevent or significantly hinder neuronal cell damage.

There is no evidence yet to support the use of neuroprotective agents in glaucoma. Citicoline oral solution is registered for glaucoma in 4 European countries. Gingko Biloba is used occasionally by some clinicians.

Systematic review:

- Sena DF, Lindsley K. Neuroprotection for treatment of glaucoma in adults. Cochrane Database Syst Rev 2017;1:CD006539.

II.3.9 Practical considerations related to topical medical treatment

Once the medication is instilled into the conjunctival sac, the spontaneous tear flow will cause complete washout within 5 minutes.

When two drops are prescribed a minimum interval of two minutes between instillations is recommended. Blinking also may influence washout.

As drugs are absorbed through the highly vascularised nasal mucosa avoid hepatic first-pass metabolism, this might lead to systemic side effects, particularly with beta-blockers. Punctal obstruction may not increase the efficacy of a topical drug however it will likely reduce systemic side effects.

If the medication is a suspension patients should be advised to shake the bottle before use.

II.3.10 Adherence in glaucoma

Glaucoma is a chronic progressive disease that requires continuous long-term engagement of the patient with the recommendations proposed by the doctor.

II.3.10.1 Terminology

The commonly used term 'compliance' has been increasingly replaced in recent times by the term 'adherence'. Both are defined as the 'cooperation of the patient with the recommendations given by the doctor'.

The former is more passive while the latter implies the active part of the patient. 'Persistence' is defined as the length of time during which the patient is taking the medication as prescribed.

II.3.10.2 Factors associated with non-adherence

The following factors encountered as common obstacles to glaucoma medication adherence have been described:

- Medication (for example costs of the drugs, side effects, complicated dosing regimen)
- Individual
 - Situational / environmental (for example a major event in the patients life, unsteady life-style with many travels)
 - Forgetfulness, comorbidity, poor understanding of the disease
 - Gender (men are more likely to be non-adherent)
 - Stage of the disease (patients with a less advanced disease tend to be less adherent)
- Clinician (for example lacking communication with the doctor)

II.3.10.3 Identifying non-adherence

Clinicians are unable to detect non-adherence, unless volunteered by patients.

Non-adherence is best identified by asking how and who administers the eye drops, taking an empathetic approach and asking open-ended questions, e.g., have you forgotten to use your eye drops during the last week? If yes, how many times?. Sometimes asking the patient to demonstrate their drop instillation technique is useful.

II.3.10.4 Improving adherence

Adherence may be improved by simplifying the drop regime, patient education, improving communication and setting alarms/messages.

Systematic review:

- Waterman H, Evans JR, Gray TA, et al. Interventions for improving adherence to ocular hypotensive therapy. Cochrane Database Syst Rev 2013:CD006132.

The patient's cooperation, described as adherence and persistence with the prescribed glaucoma management, is necessary to obtain IOP-lowering and to prevent glaucoma progression.

II.3.11 Laser surgery

II.3.11.1 Laser peripheral iridotomy (LPI)

Indications:

Angle closure disease (high risk PACs, PAC, PACG)
Treatment of AAC with suspected pupillary block or plateau iris mechanism
(See FC VII and VIII).

Preoperative preparation:

Instil topical pilocarpine. If the cornea is edematous, use topical glycerin 10% if available. Systemic acetazolamide, IV mannitol or oral hyperosmotic agents (See FC XI) may be needed to clear the cornea in cases of AAC. For prevention of IOP spikes use topical alpha 2 agonist 1 hour prior to the procedure and immediately afterwards.

Procedure:

After instillation of topical anesthetic an iridotomy contact lens with contact lens fluid is placed onto the cornea. The lens keeps the eyelids open, stabilises the eye, provides additional magnification, focuses the laser beam and acts as a heat sink.

Iridotomy site is usually chosen in the superior quadrants of the iris well covered by the upper eyelid (to reduce visual symptoms), in a thin looking area or a crypt in the iris periphery. Whole thickness perforation of the iris is assumed when pigment, mixed with aqueous, flows from the posterior into the anterior chamber. Once a full thickness hole has been made, it should be enlarged horizontally to achieve an adequate size (200 microns). Iridotomy size should be sufficient for patency in spite of iris oedema, pigment epithelial proliferation and pupil dilatation. Transillumination through the peripheral iridotomy is not a reliable indicator of success.

Lasers parameters for Nd:YAG LPI

Power	1-6 mJ
Spot size	50-70 μm (constant for each laser model)
Pulses per burst	1-3
Recommendations	<p>Focus the beam within the iris stroma rather than on the surface of the iris*</p> <p>Avoid any apparent iris vessels</p> <p>Use the least amount of energy that is effective</p> <p>Lens capsule damage is possible above 2 mJ energy</p> <p>With most lasers less than 5 mJ per pulse is required</p>

* Pretreatment with argon laser to minimize bleeding by coagulating iris vessels is optional (spot size 400 μm , duration 0.2 sec, energy approximately 200-300 mW).

In case of thick dark irides, to reduce total Nd:YAG energy, pretreatment with argon laser in 2 stages may be considered. In the first stage a low power argon of 90-250 mW, duration 0.05 sec, spot size 50mm is applied, followed by the high power argon of 700 mW, duration 0.1 sec, spot size 50 mm to create a punched-out crater appearance. LPI is completed with Nd:YAG laser.

Complications:

- Intraoperative complications
 - Bleeding from the iridotomy site can usually be stopped by gentle pressure applied to the eye with the contact lens.
- Postoperative
 - Visual disturbances, e.g. glare, blurring, ghost images, halo, crescent are less likely to occur when the peripheral iridotomy is completely covered by the eyelid.

Transient IOP elevation a few hours after the procedure is the most frequent early complication.

Postoperative inflammation is transient and mild, rarely resulting in posterior synechiae. Rare complications include cystoid macular oedema and aqueous misdirection.

Postoperative management:

- Check the patency of the peripheral iridotomy immediately after treatment.
- Check the IOP after 1-3 hours and treat accordingly.
- Topical anti-inflammatory drops during the first week.
- Check the angle with gonioscopy.

I.3.11.2 Laser trabeculoplasty

Indications:

Lowering of IOP in POAG, PXFG and PDG, high risk OHT:

- As initial treatment (See FC VI)
- As an add-on or replacement treatment (e.g. for reasons of efficacy, tolerability and adherence) (See FC XIV)

Contraindications:

- Angle closure
- Neovascular glaucoma
- Uveitic glaucoma
- Post-traumatic glaucoma with angle recession
- Angle dysgenesis

Preoperative preparation:

Use topical anesthesia. For prevention of IOP spikes, medications to lower the IOP are recommended. Options include topical alpha-2 agonist, pilocarpine or acetazolamide prior to or immediately after the procedure.

Systematic review:

- Zhang L, Weizer JS, Musch DC. Perioperative medications for preventing temporarily increased IOP after laser trabeculoplasty. Cochrane Database Syst Rev 2017;2:CD010746.

Procedure:

Most frequently used lasers are:

- Q-switched, short pulsed, frequency-doubled Nd:YAG (532 nm) laser – SLT
- Argon continuous-wave laser (green or blue/green) - ALT.

Lenses:

Goldmann type gonioscopy lens, Ritch trabeculoplasty lens©, CGA©, Meridian©, Latina© (SLT), Magnaview©.

Identify angle landmarks and place the laser spots at the pigmented TM over 360° (in eyes with highly pigmented TM, 180° initial treatment may be preferred).

Laser parameters for laser trabeculoplasty

Laser parameters	ALT	SLT
Spot size	50 µm	400 µm
Exposure	0.1 sec	3 nsec (fixed)
Power	500-1200 mW according to the reaction on the TM; with heavily pigmented TM low power is sufficient	0.4 to 1.2 mJ according to the desired reaction; in heavily pigmented TM start with low levels e.g. 0.4 mJ
Optimal reaction	Transient bleaching or small gas bubble formation	The power is titrated until the appearance of tiny air bubbles, »champagne bubbles«, at the site of the laser burn, then the power is reduced by increments of 0.1 mJ until there are no visible bubbles*
Number of spots	50-100 evenly spaced spots over 180-360°	50-100 non-overlapping spots spaced over 180 -360°

* some prefer to continue with the power that causes champagne bubble formation

Complications:

- Transient elevation of IOP
- Inflammation (mild)
- PAS (after ALT)
- Corneal endothelial damage

Post-operative management:

Consider checking IOP within 24hours or after 1 hour in high risk patients (e.g. with advanced glaucomatous damage). Topical corticosteroids or non-steroidal anti-inflammatory medication may be prescribed for 4-7 days, but often is not needed. Efficacy of the treatment may be evaluated 4-8 weeks later.

Effectiveness of laser trabeculoplasty:

ALT and SLT have the same efficacy.

Laser trabeculoplasty is initially effective in 80 to 85% of treated eyes with a mean IOP reduction of 20 to 25% (of 6 to 9 mmHg). The effect wears off over time, for both ALT and SLT.

Repeat treatment:

If the first complete treatment is effective but the target pressure is not reached or if the effect wears off after a period of control, a retreatment may be effective. Evidence for further retreatments is lacking.

Predictors of efficacy:

Higher baseline IOP is associated with greater IOP reduction after SLT and ALT.

ALT is less successful in eyes with no pigmentation of TM. SLT seems to be independent of the pigmentation of TM.

II.3.11.3 Thermal laser peripheral iridoplasty (TLPI)

Indication:

It may be helpful in plateau iris syndrome with remaining angle closure despite a patent peripheral iridotomy and elevated IOP, although the efficacy in reducing IOP is limited. (See FC VIII)

Lasers:

Different types of continuous wave lasers can be used for photocoagulation.

Preoperative preparation:

Instillation of pilocarpine. For prevention of IOP spikes use topical alpha 2 agonist prior to the procedure and immediately afterwards.

Lens:

Contact TLPI lenses.

Laser parameters for laser iridoplasty

Laser parameters [II,D]	Contraction burns (long duration-low power-large spot size)
Spot size	200-500 μm
Exposure	0.3-0.6 sec
Power	200-400 mW
Location	Aiming beam should be directed at the most peripheral part of the iris
Optimal reaction	Visible contraction of the peripheral iris with flattening of the iris curvature (without bubble formation or pigment release)
Number of spots	20-24 spots over 360° leaving 2 beam diameters between each spot and avoiding visible radial vessels

Complications:

- Mild iritis
- Corneal endothelial burns
- Transient elevation of IOP
- Post-operative synechiae of the pupil
- Permanent pupil dilatation
- Peripheral iris atrophy

Post-operative management:

- Anti-inflammatory medication instilled for the first week.
- Prevention of IOP spike
- Gonioscopy

II.3.12 Cyclodestructive procedures

Indications:

- When filtration surgery or glaucoma drainage devices are likely to fail, have failed, or are not feasible
- Refractory glaucomas

Available technologies:

- Lasers
 - Laser delivery modes are: transscleral, endoscopic and transpupillary
 - Each technique requires the appropriate probe
 - Transscleral diode cyclophotocoagulation
 - Micropulse laser cyclophotocoagulation
 - Direct and endoscopic cyclophotocoagulation
- Ultrasound
 - High intensity focused ultrasound circular cyclocoagulation
- Cryoprobe

Technique:

Anesthesia	Retrobulbar or peribulbar injection
Scleral transillumination	The light source is directed posterior to the limbus to identify ciliary body by transillumination. The dark demarcation line indicates the anterior margin of the ciliary body
Probe positioning, settings, applications	According to the manufacturer recommendations

Endoscopic cyclophotocoagulation:

Endoscopic techniques combined with laser technology allow the photocoagulation of ciliary processes. The approach can be limbal or through pars plana.

Transpupillary cyclophotocoagulation:

This procedure is limited to cases of aniridia, through a large surgical iridectomy or when broad anterior synechiae cause anterior displacement of the iris.

Complications:

- Persistent inflammation
- Hyphaema
- Corneal decompensation
- Vision loss
- Hypotony and phthisis

Post-operative management:

Consider pain control. Topical corticosteroids and atropine instillation as needed. In the immediate postoperative period, IOP should be monitored and the anti-glaucoma medication tapered accordingly.

Systematic reviews:

- Michelessi M, Bicket AK, Lindsley K. Cyclodestructive procedures for non-refractory glaucoma. Cochrane Database Syst Rev. 2018;4(4):CD009313.
- Chen MF, Kim CH, Coleman AL. Cyclodestructive procedures for refractory glaucoma. Cochrane Database Syst Rev. 2019;3(3):CD012223.
- Tóth M, Shah A, Hu K, Bunce C, Gazzard G. Endoscopic cyclophotocoagulation (ECP) for open angle glaucoma and primary angle closure. Cochrane Database Syst Rev. 2019;2(2):CD012741.

II.3.13 Incisional surgery

II.3.13.1 General principles

Indications for different techniques of incisional surgery depend on:

- the type of glaucoma
- the target IOP
- the previous history (e.g. surgery, medications, degree of VF loss)
- the risk profile (e.g. single eye, occupation, refractive status)
- the preferences and experience of the surgeon
- the patient preference, expectation and postoperative compliance

Surgery should be considered whenever medical or laser treatment is unlikely to maintain sight in the glaucomatous eye. It should not be left as a last resort (see II.3.1).

The ophthalmologist must assess the risks and benefits of early surgery in each individual case.

The primary goal of surgery is to reduce the IOP, ideally achieving a target IOP without additional medication. Additional medications can be used if a target IOP is not reached by surgery alone. Success rates of a surgical method in terms of IOP lowering can be best evaluated in the absence of additional IOP-lowering medical treatment. Also, it is useful to count the percentage of “successes” below a defined IOP level as in Fig. II.3.3. It is important to consider not just IOP but complication rates and functional outcomes. Filtration surgery is a generic term used for procedures where the IOP-lowering effect is obtained by creating a way for the aqueous to drain in the episcleral/subconjunctival space. PCG is usually treated with surgery, likely trabeculotomy or goniotomy, or filtration surgery with antifibrotic agents (see II.2.1).

Complicated glaucoma cases such as those that have failed previous surgery, many secondary glaucomas, and congenital glaucomas, require specialist treatment. In addition to trabeculectomy, other forms of therapy may be necessary.

For repeated surgery, cyclodestructive procedures and long-tube implants are more commonly used (See FC VI).

II.3.13.2 Techniques

Glaucoma surgery is successfully practiced in many ways. A detailed description of surgical techniques is not within the scope of this text.

II.3.13.2.1 Penetrating glaucoma surgery

II.3.13.2.1.1 Trabeculectomy

The most widely used surgical procedure in glaucoma is trabeculectomy, which produces a 'guarded' fistula between the anterior chamber and the subconjunctival space. Modifications have been developed including changes in size, shape and thickness of the scleral flap, limbal or fornix based conjunctival flaps, fixed, releasable or adjustable sutures and the use of antifibrotics and other anti-scarring agents delivered in different ways to reduce wound healing.

The long-term success rate of filtering surgery by experienced surgeons in an unoperated eye has been reported to be very high. Long-term IOP control is achieved in many cases, although some patients do require further therapy or repeat surgery.

However, there are large differences in the criteria used for the definition of success and in the final success rates observed.

The use of implants for performing filtration surgery should be weighed against the cost of the devices and the expected benefits.

Risk factors for filtration surgery failure:

- Young age
- African ancestry
- Inflammatory eye disease
- Long-term multiple topical medical therapy
- Aphakia
- Complicated cataract surgery
- Recent intraocular surgery (<3 months)
- Conjunctival incisional surgery
- Failed glaucoma filtration surgery
- Neovascular glaucoma

Indications:

- Other forms of therapy, such as medications or laser, have failed to control the disease, or are not suitable (e.g. due to non-compliance or side-effects)
- Where a target pressure is unlikely to be achievable with topical medications and/or laser, e.g. patients with advanced glaucoma and high IOP at presentation.

VF preservation is not significantly different whether initial treatment is with medication or laser or trabeculectomy in mild disease. In advanced glaucoma initial surgery may be more effective.

Long-term risks of trabeculectomy:

Accelerated progression of cataract is frequently seen after filtration surgery. Patients undergoing trabeculectomy should be advised on the symptoms of a developing blebitis/endophthalmitis including red eye, tearing, discharge or decreased vision, and should be warned to immediately seek the help of an ophthalmologist if any of these symptoms develop in the operated eye. Endophthalmitis is more common if the bleb is thin and cystic or leaking. A long-tube drainage device should be used if filtration surgery cannot be performed in the upper quadrants. Clinically significant vision threatening consequences of hypotony may develop at any time post-operatively e.g. macular folds, epiretinal gliosis, chronic choroidal detachment.

II.3.13.2.1.2 Trabeculotomy and goniotomy

Trabeculotomy, alone or combined with trabeculectomy, is generally used for paediatric glaucoma and is less effective in adults. Trabeculotomy may also be performed ab-interno, gonioscopy assisted transluminal trabeculotomy. Goniotomy is a viable alternative for pediatric glaucoma if the cornea is clear. (see also II.2.1)

II.3.13.2.2 Non-penetrating glaucoma surgery

These techniques were developed to lower IOP in OAG with less risk. In a number of cases a filtration bleb may form. Long-term pressure lowering by non-penetrating glaucoma surgery is less than with trabeculectomy.

The techniques are deep sclerectomy, canaloplasty and viscocanalostomy.

Systematic reviews:

- Eldaly MA, Bunce C, Elsheikha OZ, Wormald R. Non-penetrating filtration surgery versus trabeculectomy for open angle glaucoma. Cochrane Database Syst Rev. 2014;(2):CD007059.
- Gabai A, Cimarosti R, Battistella C, Isola M, Lanzetta P. Efficacy and Safety of Trabeculectomy Versus Nonpenetrating Surgeries in Open angle Glaucoma: A Meta-analysis. J Glaucoma. 2019;28(9):823-833.

Arguments in favour of trabeculectomy:

lower long-term postoperative IOP
fewer postoperative IOP-lowering medications

Arguments against trabeculectomy:

possible higher rate of cataract formation
postoperative bleb complications
higher risk of complications from postoperative hypotony eg choroidal detachment

Arguments in favour of non-penetrating glaucoma surgery:

fewer intraoperative complications eg iris prolapse, expulsive haemorrhage
less demanding postoperative care eg bleb management
fewer hypotony-related complications
possible lower rate of cataract formation

Arguments against non-penetrating glaucoma surgery:

less IOP reduction
technically demanding procedures
goniopuncture often needed
anatomical unpredictability

II.3.13.2.3 Long-tube glaucoma drainage devices

Long-tube glaucoma drainage devices e.g. Molteno©, Baerveldt©, Ahmed© are generally reserved for patients with risk factors for a poor result with trabeculectomy with antifibrotics (see II.3.13.3.1). Recent trials established their potential role as a primary surgical procedure in selected cases.

Systematic review:

- Tseng VL, Coleman AL, Chang MY, Caprioli J. Aqueous shunts for glaucoma. Cochrane Database Syst Rev. 2017;7(7):CD004918.

II.3.13.2.4 Additional/alternative surgical techniques

Surgical procedures that entail less tissue manipulation with the expectation of a better safety profile and quicker recovery as compared to conventional filtration surgery have been developed and called minimally invasive or micro incisional glaucoma surgery.

These procedures are classified as ab externo or ab interno. However, only the ab interno non-bleb forming procedures can be defined as “Minimally Invasive Glaucoma Surgery”. MIGS tend to have a modest IOP-lowering effect but can reduce the burden

of medication. However, the aim of decreasing medication burden as reported in some studies, rather than absolute IOP-lowering, is not in line with the traditional aim of glaucoma surgery. MIGS could be suitable for patients with mild to moderate glaucoma.

All these procedures can be combined with phacoemulsification, but it is difficult to separate the IOP lowering effect of MIGS from that of phacoemulsification alone.

Currently there is not sufficient evidence to support the superiority or equivalence in efficacy between any of these procedures nor versus trabeculectomy. The available data are limited and/or insufficient on long term safety, cost effectiveness, medication independency or on the ideal patient profile to allow comparison to conventional surgery. Finally, as the methodologies used to report results have not been uniform, difficulties remain when comparing these different outcomes.

Systematic reviews:

- Hu K, Gazzard G, Bunce C, Wormald R. Ab interno trabecular bypass surgery with Trabectome for open angle glaucoma. *Cochrane Database Syst Rev.* 2016;(8):CD011693.
- King AJ, Shah A, Nikita E, et al. Subconjunctival draining minimally-invasive glaucoma devices for medically uncontrolled glaucoma. *Cochrane Database Syst Rev.* 2018;12(12):CD012742.
- Le JT, Bicket AK, Wang L, Li T. Ab interno trabecular bypass surgery with iStent for open angle glaucoma. *Cochrane Database Syst Rev.* 2019;3(3):CD012743.

Additional/alternative surgical techniques (*)

Based on subconjunctival/transcleral filtration:

ab-interno device

ab-externo device

Based on suprachoroidal drainage:

ab-interno device

ab-externo device

Based on Schlemm's canal drainage/bypass/expansion:

trabecular bypass stents/canal expanders

ab-Interno trabeculectomy

ab-externo canaloplasty/trabeculotomy

(*) This list is not all inclusive. The EGS does not endorse any product or procedure.

II.3.13.3 Methods of preventing filtering bleb scarring

II.3.13.3.1 Antifibrotic agents

Wound healing is one of the main determinants of the long-term IOP control after filtering surgery. Risk factors for conjunctival scarring are young age, African-African heritage race, inflammatory eye disease, long-term multiple topical medical therapy, aphakia, complicated cataract surgery, recent intraocular surgery (< 3 months), previous conjunctival incisional surgery, previous failed glaucoma filtration surgery, neovascular glaucoma. (see text box above).

Antifibrotics such as 5-fluorouracil (5-FU) and mitomycin-C (MMC) are routinely used in patients undergoing glaucoma filtration surgery in order to reduce postoperative conjunctival scarring and improve drainage.

Although 5-FU and MMC are not officially approved for ocular surgery, their off-label use in filtration surgery has become standard clinical practice and there is evidence supporting their use.

Systematic reviews:

- Wormald R, Wilkins MR, Bunce C. Post-operative 5-Fluorouracil for glaucoma surgery. Cochrane Database Syst Rev. 2001;(3):CD001132.
- Wilkins M, Indar A, Wormald R. Intra-operative mitomycin C for glaucoma surgery. Cochrane Database Syst Rev. 2005;(4):CD002897. Green E, Wilkins M, Bunce C, Wormald R. 5-Fluorouracil for glaucoma surgery. Cochrane Database Syst Rev. 2014;(2):CD001132.
- Cabourne E, Clarke JC, Schlottmann PG, Evans JR. Mitomycin C versus 5-Fluorouracil for wound healing in glaucoma surgery. Cochrane Database Syst Rev. 2015;(11):CD006259.
- Foo VHX, Htoon HM, Welsbie DS, Perera SA. Aqueous shunts with mitomycin C versus aqueous shunts alone for glaucoma. Cochrane Database Syst Rev. 2019;4(4):CD011875.

II.3.13.3.1.1 General precautions for the use of antifibrotics

The use of antifibrotics is potentially hazardous, and requires careful surgical technique to prevent complications. Early and late over drainage and hypotony, or a thin focal drainage bleb that is associated with a higher risk of infection, are more common with antifibrotics. The use of larger antifibrotic treatment areas and a fornix-based conjunctival flap may minimize the occurrence of thin cystic blebs. It is important to assess each individual case for risk factors, and/or for the need of low target IOP and choose the substance, concentration, volume and duration of exposure used. The use of antifibrotics will enhance the unfavourable effect of any imprecision during surgery.

Strategies to increase control of flow should be considered, such as smaller sclerostomies, larger and/or thicker scleral flaps, tighter suturing of the scleral flap, and releasable or adjustable sutures.

A large surface area of cytotoxic treatment together with large scleral flaps and accurately sutured fornix-based conjunctival flaps lead to more diffuse, posteriorly extended non-cystic blebs giving a considerable reduction in bleb-related complications such as blebitis and endophthalmitis.

Antimetabolites should not enter the eye. Contact with the cut edge of conjunctival flap should be avoided. Precautions for use and disposal of cytotoxic substances should be observed.

II.3.13.3.1.2 Administration

5-Fluorouracil:

- Intraoperative use
 - Concentration: 25 or 50 mg/ml undiluted solution. Administration: on a filter paper or a sponge or by subconjunctival injection.
 - Time of exposure: usually 5 minutes. Rinse: with at least 20 ml of balanced salt solution.

- Postoperative use
 - Relative contraindication if epithelial problems present. Concentration: 0.1 ml injection of 50 mg/ml undiluted solution.
 - Administration: subconjunctival injection adjacent to but not into bleb (pH 9), with a small caliber needle (e.g. 30 G needle on insulin syringe). Reflux from the injection site over the ocular surface should be prevented by pressing with a dry sponge or Q-tip.
 - Repeated injections are often necessary.

Mitomycin C:

- Intraoperative use
 - Concentration: 0.1-0.5 mg/ml
 - Administration: intraoperatively on a filter paper or a sponge or by subconjunctival injection.
 - Time of exposure: 1-5 minutes if on a filter paper or sponge.
 - Rinse: with at least 10-20 ml of balanced salt solution.

- Postoperative use
 - Concentration: 0.1 ml injection of 0.1 - 0.5 mg/ml solution.
 - Administration: adjacent to but not into bleb, with a small calibre needle (e.g. 30 G needle on insulin syringe). Reflux from the injection site over the ocular surface should be prevented. A very small amount of MMC entering the eye will irreversibly damage the endothelium.

II.3.13.3.2 Alternative methods of preventing filtering bleb scarring

Beta-radiation was shown to be effective in clinical trials.

II.3.14 Cataract and glaucoma surgery

When glaucoma surgery is indicated and there is a visually significant cataract, the two procedures can be combined or performed sequentially. Uncomplicated phacoemulsification with clear cornea incisions may affect subsequent glaucoma surgical procedures only if done soon after cataract surgery. The development or worsening of a visually significant cataract is common after glaucoma surgery. Cataract surgery performed after trabeculectomy can affect the IOP control.

Cataract surgery alone is of limited benefit in lowering the IOP in OAG and is not recommended as an intervention to control glaucoma.

In PAC disease clear lens extraction is an option in PACG and PAC with high IOP (see II.2.4 and I.3, question 14).

Combining glaucoma procedures with phacoemulsification allows for greater IOP reduction than phacoemulsification alone. The success rate of combined phacoemulsification and filtration surgery is less than filtration surgery alone.

With appropriate techniques, phacoemulsification is safely applicable in cases with small pupil, shallow AC or pre-existing filtering blebs.

There is insufficient evidence comparing outcomes of sequential versus combined cataract and glaucoma surgery to inform our choice.

Note

A series of horizontal dotted lines for writing notes.

