How to interpret evidence in everyday practice: The Finnish Current Care Guideline for open-angle glaucoma

Running title: Translation of the Finnish Current Care Guideline for Glaucoma

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This guideline contains evidence summaries on a separate document named Glaucoma Current Care Evidence summaries 2014. All evidence summaries are numbered individually in the guideline text, e.g. [E1] (B) and can be found on the evidence summary document with that same number.

Abstract
The key points of the Guideline

The up-date of the guideline for glaucoma is based primarily on published systematic reviews searched up by March 2014. The recommendations for everyday practice are presented in nine tables, which are based on 95 graded statements with evidence summaries. The online availability of the evidence summaries enables the verification of the evidence and consequent recommendations.

In most patients, chronic open-angle glaucoma is a slowly progressive disease. However, some patients may have aggressive disease with very high intraocular pressure (IOP) ≥30 mmHg, or the disease progresses rapidly regardless of IOP. These patients should be treated and followed up intensively.

Although the primary goal of treatment is to prevent glaucoma-induced visual disability, no randomized trials with visual disability as the end point have been published. Instead, the majority of studies report the efficacy of lowering IOP, which is the only means of treating glaucoma. When planning treatment, side effects should also to be considered.

In addition to lowering of IOP, the effectiveness of treatment should be monitored with optic disc and retinal nerve fiber layer imaging and visual field examinations. If the glaucomatous changes show progression, treatment should be intensified while taking into account the patient's age and systemic diseases.

There is no solid evidence for either the most clinically effective or the most cost-effective tests and technologies to be used for the diagnosis and detection of progression to prevent visual disability. In addition, the optimum testing frequency and timing of control visits is unclear.

During follow up, structural and functional changes appear and progress at different time points, with a delay of up to several years. Different tests and technologies give variable results in diagnostics and follow up, and their sensitivity and specificity values indicate a large range depending of the selected reference standard. The value of diagnostic and follow up tests is hampered by a missing gold standard, and the risk of bias in study designs is significant. Although progression is included in the definition of glaucoma, long-term follow up could serve as the most appropriate reference standard.

The most important risk factors for the development of glaucoma are elevated IOP (even though in half of glaucoma patients the IOP is within the normal range), age, exfoliation together with increased IOP, diabetes and hemorrhage at the optic nerve head. In addition, myopia, positive family history, ethnicity and reduced perfusion pressure may increase the risk for glaucoma. Factors associated with visual field progression are age, disc hemorrhage (in normal-tension glaucoma), baseline visual field loss, baseline intraocular pressure, exfoliation and the length of follow up.

The key questions and the consensus of the recommendations (based on the graded body of evidence) for everyday practice are presented in nine tables. It is crucial to constantly and consciously consider sufficiency of care: this applies to under-testing, under-diagnosing and under-treatment as well as over-testing, over-diagnosis and over-treatment. Depending on the operational environment, culture and politics, different conclusions may be drawn from the same evidence, especially when the evidence is inconsistent or missing.

Key words:
evidence-based medicine (EBM), guidelines, glaucoma, ocular hypertension, recommendation

Core summary:

The update of the Guideline for glaucoma is based primarily on published systematic reviews searched up to March 2014. The online availability of the 95 graded evidence summaries enables the verification of the evidence and the consequent recommendations for everyday practice, which are presented in nine tables. Depending on the operational environment and culture, different conclusions may be drawn from the same evidence, especially if the evidence is inconsistent or missing.

Ten external stakeholders gave a mean value of 1.8 (range of 1 = completely agree to 4 = completely disagree) for the structured questions (e.g. definitions, goals, questions, target users) and judged the systematics of the evidence and the presentation of the recommendations. In the period 2010–2013, Current Care Guideline for Glaucoma was accessed 27,600 times.

Introduction

Quality of care consists of scientific knowledge (evidence), measurements of health care performance (statistics) and experience (successes and mistakes). Without good research evidence, clinical decision-making in diagnosis and treatment may be on unsound grounds.[1] It has been estimated that only 10–20% of health care decisions are based on high grade of evidence. However, high quality evidence may not necessarily correlate with clinical importance.[1] Depending on the operational environment, culture and politics, different conclusions may be drawn from the same evidence, especially if the evidence is inconsistent or missing.

In 1994, a national evidence-based Current Care Guidelines program was established in Finland under the auspices of the Finnish Medical Society Duodecim (http://www.kaypahoito.fi/web/english/home). National Access to Care legislation is based on the Current Care Guidelines. Thus, the Guidelines have an important role in everyday practice. From the beginning, a Guideline Developer's Handbook has been available to promote proper methodology. In January 2014, the Current Care collection included 101 Guidelines covering a wide variety of clinical topics. Current Care Guideline working groups in different specialties have produced over 3,800 evidence summaries and recommendations, which were read 1.4 million times in 2013.

The process is described in detail at http://www.terveysportti.fi/xmedia/ccs/process/Suositus.html. In summary, the process consists of 1) formulating clinically relevant key questions, 2) trying to answer the key questions by creating Evidence Summaries based on a systematic literature search, and 3) finally making practical evidence-based recommendations for everyday practice. The evidence of key statements is graded from A to D:

- Level A (expressed with the verb *is* better/the same as, etc.) refers to strong research based evidence, e.g. homogenous results from high-quality systematic review(s), or multiple, relevant, high-quality studies (e.g. two or more randomized controlled trials);
- Level B (expressed with the verb *"seem"* to be better/the same as, etc.) refers to moderate evidence, e.g. one randomized controlled trial, or multiple adequate studies;
- Level C (expressed with the verb *"may"* be better/the same as, etc.) refers to limited research-based evidence, e.g. controlled prospective studies, or studies where there is considerable incongruity among outcomes;
- Level D, (expressed as "no, or unclear evidence") refers to retrospective studies, or the consensus reached by the group in the absence of good quality evidence.

The Current Care consensus process is informal; the working group discusses the evidence in the context of the Finnish health care system. When grading the evidence, the applicability of results of the study population is considered, especially when evidence in the Finnish population is not available.

If consensus is not reached through informal discussions, a formal process for consensus has been recently developed. When there is lack of grade A or B evidence, and especially in the case of grade D evidence, this process can be time-consuming. As an example, the details of the recommendation for the follow up protocol of glaucoma (presented in Table 7) generated the longest discussions and comments due to the lack evidence and the impact of follow up policies in everyday practice. The discussion is an iterative process; at the end of this process, the actual practical recommendations are carefully worded based on the overall body of evidence.[1]

The first (of four) Current Care Guidelines within ophthalmology was published in 2002 and dealt with open-angle glaucoma. It was translated into English,[2] although its 50 Evidence Summaries were available only in Finnish on the Current Care website. The first update was published online in 2007. The present review is an English translation of the second update of the Finnish Current Care Guideline for glaucoma; it

[1] These stakeholders included the Finnish Ophthalmological Society, the Finnish Glaucoma Society, the Finnish Patient Association for Glaucoma, the Society for Visually Disabled Patients, the Association of Ophthalmic Surgeons, the Association of Clinical Pharmacology, three university eye departments, three eye departments of central hospitals, two associations representing general practitioners, the Finnish Insurance Institution, the Finnish Medicines Agency (Fimea), and the National Supervisory Authority for Welfare and Health (Valvira).

[2] Two respondents represented patient organizations, two represented ophthalmic associations, two represented university eye departments, two represented the eye departments of central hospitals and two represented associations for general practitioners.

is based primarily on published systematic literature reviews searched up to March 2014. This Current Care Guideline, based on 95 Evidence Summaries, has created graded (A to D) statements, marked as *[E],* including the evidence summaries produced in English (56 of 95, 59%). Thus, only the minority of references *without* Evidence Summaries and grading of evidence (marked in superscript, e.g.[1]) are listed at the end of the Guideline.The Finnish version (www.kaypahoito.fi, published October 24, 2014) also contains additional informative material without the grading of evidence on 20 topics (e.g. exfoliation, quality of life, tonometers, study design of RCTs, etc.).

The update process of Current Care Guideline for glaucoma culminated in the circulation of all the material to 26 stakeholders in Finland for comments.[1] Ten stakeholders responded[2] and graded the eight structured questions with a mean value of 1.8 (range 1–4, 1 = agree and 4 = completely disagree). The eight structured questions were adopted from the AGREE II criteria[3] regarding definitions of the overall goals of the Current Care and key clinical questions. The process involved the views of patient groups, target users of the Current Care Guideline; it included their judgment on the systematics of the evidence, the presentation of the information and its adequate considerations of health benefits, plus the side effects and risks in the formulation of the practical recommendations. The stakeholders presented 23 suggestions for improvement; these were formally reviewed by the team by April 29, 2014 and considered in the Guideline. The Current Care Guideline for Glaucoma was accessed 27,600 times in the period 2010–13. The previous update in 2007 increased the yearly access rate by 28%.

Goals and limits of the Guideline

The purpose of this Guideline is to unify care processes of glaucoma patients in Finland by providing evidence-based knowledge on key clinical questions (Table 1).

Table 1.
The purpose of this treatment Guideline is to provide answers to the following questions:

1. Which factors increase the risk of glaucoma?
2. Which examinations are required for the diagnosis of glaucoma?
3. Is screening for glaucoma worthwhile?
4. What is the effect of lowering intraocular pressure (IOP) in patients with glaucoma and ocular hypertension? Can progression and glaucoma-induced visual disability be prevented?
5. Which treatment forms lower IOP and what are their side effects?
6. What is the treatment goal and which treatment plan should be followed?
7. During glaucoma follow up, which examinations should be prescribed and how often?
8. How should patients with an aggressive form of the disease be treated and followed up?

This Current Care Guideline is aimed at both public and private healthcare in Finland. The recommended practice policies represent the consensus of the Current Care Guideline team group, and these recommended practice policies are presented in 8 Tables. Thus, the recommendations (Tables 2-9) are clearly separated from the graded statements of evidence (as presented in the text).

In this Guideline, the term chronic open-angle glaucoma refers to primary open-angle glaucoma, exfoliative glaucoma and normal-tension glaucoma. In addition, the Guideline also includes ocular hypertension (OHT), i.e. elevated intraocular pressure (IOP) without structural and functional abnormalities. The Guideline does not deal with closed-angle glaucoma, other secondary glaucomas (except for exfoliation), or congenital or juvenile glaucoma.

Epidemiology

Glaucoma is a progressive neuropathy of the optic nerve with typical structural and functional abnormalities in the retinal nerve fiber layer, optic disc and visual field. In the majority of patients, the glaucomatous abnormalities progress slowly over a period of years. However, in some patients the disease may lead to serious optic nerve damage in a period as short as a few months. It is essential to organize care for the proper identification of these high-risk patients in particular. They are therefore dealt with as a separate group in the Current Care Guideline.

The risk of glaucoma increases with age. Among individuals over the age of 50 years, the prevalence of glaucoma is ca 2% *[E1]* (B), increasing to >3% in the over-75-year age group. Even in the developed world,

more than half of patients go undiagnosed *[E2]* (B). The incidence of glaucoma ranges from 30 and 181 per 100,000 person-years for ages 50 years and 70 years, respectively *[E1] (B).*

After age-related macular degeneration, chronic open-angle glaucoma is the second most prevalent cause of registered visual handicap in Finland.[4] In 2013, over 84,000 subjects in a population of 5.4 million were entitled to special refunds on medicines for glaucoma,[5] which roughly approximates to 100 million glaucoma patients globally. The incidence of glaucoma-induced visual disability in Europe has been estimated at 560,000 subjects, with 220,000 being blind *[E3]* (C). In Finland, respectively, these estimates would correspond to 3500 visually disabled patients (4.7% of those using glaucoma medications) and 1300 blind patients (1.6% of those using medications).

In Finland, 80% of subjects on glaucoma medications are ≥65 years old.[5–6] While the increase of treated glaucoma patients prior to 2004 was 3% per year, the figure for the period 2004–2012 was 2.5% per year.[6] If this rate continues, there will be over 100,000 glaucoma patients in Finland by 2020. There is an even larger group of subjects with risk factors who are suspected of having glaucoma. These patients may also require follow up because of the possible development of glaucomatous abnormalities later on.

Risk factors

Although in half of the patients with glaucoma, the intraocular pressure is within the statistically determined "normal" range (10–21 mmHg), the risk of developing glaucomatous damage rises when the intraocular pressure increases (particularly with IOP levels >30 mmHg) *[E4]* (A). With lower intraocular pressure levels (<30 mmHg) the conversion of ocular hypertension into glaucoma is, in addition to IOP level, best predicted by the age of the patient *[E5]* (A). Risk factors for glaucoma reported in population-based studies are presented in Table 2.

Table 2. Which factors increase the risk of glaucoma?

Risk factors	Risk	Evidence	
Age	Doubles every 10 years	(A)	*[E5][E6]*
IOP 22–29 mmHg	10–13-fold	(A)	*[E4]*
>30–35 mmHg	40-fold		
Exfoliation with increased IOP	5–10-fold	(B)	*[E7]*
Disc hemorrhage	12-fold	(B)	*[E8]*
Diabetes	2–3-fold	(B)	*[E9]*
Myopia	2–4-fold	(C)	*[E10]*
Family history	3-fold	(C)	*[E11]*
Decreased perfusion pressure together with age	3-fold	(C)	*[E12]*
Black ethnicity		(C)	*[E13]*

Glaucoma diagnostics

The diagnosis of glaucoma is based on the examination of the optic nerve head, nerve fiber layer, visual fields, intraocular pressure level, and on gonioscopy. There is, however, no consistent or generally approved definition of the diagnostic tests nor their criteria in the scientific literature *[E14]* (D). Table 3 presents a recommendation for the basis of diagnosis and screening.

Table 3.
Which examinations are required for the diagnosis of glaucoma? Is screening worthwhile?

When prescribing examinations consider:
- patients' age
- severity of glaucoma
- other ocular and systemic diseases

Level					
Very good	IOP	Gonioscopy	Visual field	Disc imaging[1]	Nerve fiber imaging[1]
Good	IOP	Gonioscopy	Visual field	Imaging disc *or* nerve fibre[1]	
Satisfactory	IOP	Gonioscopy	Visual field		
Insufficient	IOP				

[1] If automated imaging technology is used, conventional imaging is also necessary.

Due to lack of evidence, systematic screening is not recommended.

Intraocular pressure (IOP)

All tonometers may induce considerable variation in measurements of IOP, including the Goldmann applanation tonometer, even though it is regarded as the gold standard. *[E15]* (C). The uncertainty of reporting confounds the evaluation of measurements. The significance of diurnal variation and its measurement of the progression of glaucoma is uncertain *[E16]* (D).

Although a thin cornea may result in lower IOP readings than a thick cornea, no reliable conversion equation exists to correct the IOP readings *[E17]* (D). Devices for measuring the central corneal thickness yield variable results and may not give comparable measurements *[E18]* (C). There is no evidence that IOP readings corrected for central corneal thickness improve the risk prediction of the development of glaucoma in ocular hypertensive patients, or reduce glaucoma-induced visual disability *[E19]* (D). Although measurement of corneal thickness does not reduce visual disability, it may aid clinical decision-making in selected cases (D). The association between corneal thickness as an independent risk factor in glaucoma is unclear *[E20]* (D).

Gonioscopy

Examination of anterior chamber angle is ***critical*** for the classification of open-angle and closed-angle glaucoma. Of the several chamber angle classifications, the Schaffer classification is used in Finland. The results of the new devices imaging the chamber angle are variable *[E21]* (C) and the evidence of their effectiveness in everyday clinics on top of gonioscopy is inadequate *[E22]* (D).

Diagnostics of the structural and functional abnormalities

No randomized screening or diagnostic trials of examination tests reporting their clinical effectiveness or cost-effectiveness in preventing glaucoma-induced visual disability have been published. Although there are numerous comparative diagnostic studies, there is no evidence of which test or combination of tests improve patient outcomes *[E14]* (D). There is a high degree of variability in the design and conduct of largely cross-sectional studies of the diagnostic accuracy of technologies for glaucoma.

Diagnostic studies typically compare the performance of a small number of technologies, and indirect comparisons with other tests must be interpreted with caution (e.g., because of differences in population, study definitions, reference standard, etc.). The risk of bias in diagnostic study designs is an additional concern. One of the major challenges in evaluating a diagnostic test for glaucoma is the lack of a perfect

reference standard. Although progression is included in the definition of glaucoma, long-term follow up could serve as the most appropriate reference standard.

There is much variation in the parameters measuring ocular structure and function. The variation depends on the examination method, the examinee and the examiner, and the severity of the disease. Although the accuracy of diagnostics may increase when the results of different examination methods are combined, evidence for an optimal test combination is missing. The following evidence indicates the need to combine different clinical information:

- No distinct parameters of the optic nerve head (e.g. cup/disc ratio) seem to separate glaucoma subjects from healthy individuals *[E23]* (B).
- The inter-observer congruency (kappa statistics) in evaluating disc images in cross-sectional studies may vary between 0.5 and 0.9 (on average 0.7) *[E24]* (C).
- The evaluation of *progression* from disc images shows large variability (agreement between 54–92%, on average 72%) *[E25]* (D).
- During follow up, the clinically detectable changes in the optic nerve head, retinal nerve fiber layer and visual field may typically appear and progress at different time points (with a delay of 1–6 years). Their correlation at any time point seems poor.[e.g. 7-10]
- The visual field may appear normal despite structural damage to the optic nerve head and retinal nerve fiber layer.[e.g.11-15]
- The variation in the beginning and length of follow up window in clinical studies and everyday clinics may define which abnormalities are detected “first”.
- The clinical assessment of abnormalities depends on the examination method and requires a lot of experience of the examiner.
- The results and agreement of imaging instruments may differ from each other both in diagnostics and follow up *[E21]* (C), *[E26]* (D).
- There may be large variations in the sensitivity and specificity of the clinical and digital structural and functional examinations that depend on the comparison test. The risk of bias in study designs is significant *[E26]* (D), *[E27]* (D).
- If the diagnosis of glaucoma is defined only by the visual field examination, the clinical significance of a single abnormal visual field may be small *[E28] (*C).

The guideline for the principles of combining glaucoma diagnostic tests is presented in Table 4.

Table 4. The guideline for diagnosis of glaucoma (the "2 out of 3" rule)

Abnormal	Normal	Diagnosis	Comment	Procedure
Nerve fiber layer Optic nerve head Visual field		Glaucoma	Clear diagnosis	
Nerve fiber layer Visual field	Optic nerve head	Glaucoma	Small disc?	Initiate (consider initiating) therapy
Nerve fiber layer Optic nerve head	Visual field	Preperimetric glaucoma	10˚-field may be abnormal	
Optic nerve head Visual field	Nerve fiber layer	Other diagnosis than glaucoma? E.g. neurologic disease	If the imaging quality of nerve fibers is high, uncommon in glaucoma	
Nerve fiber layer	Optic nerve head Visual field	Preperimetric glaucoma?	Wait and see if there is progression. 10˚ visual field may be abnormal.	Follow up without treatment (unless IOP ≥30 mmHg)
Optic nerve head	Nerve fiber layer Visual field	Suspicion of glaucoma	Large disc, or disc anomaly? Wait and see.	
Visual field	Nerve fiber layer Optic nerve head	Suspicion of glaucoma	Retest visual field. Other cause for field defect?	

Structural abnormalities

There are large variations in the sensitivity and specificity of structural examinations that depend on the comparison test. The high risk of bias in study designs is also of concern *[E26]* (D).

Optic disc

In clinical diagnostics and follow up, descriptions of the optic disc, estimations of the cup/disc ratio, and drawings are not as accurate as optic disc photography; for example, over 80% of disc hemorrhages may be missed during clinical examination *[E29]* (C). Although extensive experience and skills are required in the optimum evaluation of fundus images, the interpretation of reports of automated imaging instruments may also be demanding. The reports cannot replace evaluation of fundus images e.g. because missed disc hemorrhages [17].

The appearance of a healthy optic disc varies greatly due to varying optic disc size among healthy individuals, the cup/disc ratio may vary from 0 to 0.9, limiting its capacity to separate the healthy from the sick. A large cup in a large disc raises suspicion of glaucoma even if the IOP is not elevated. A small optic nerve head is more insidious because early disc abnormalities may go unnoticed.[e.g. 17-19]

A splinter hemorrhage in the nerve head may foretell and precede glaucomatous damage and its progression both in the optic disc, nerve fiber layer and visual fields. Optic disc hemorrhages appear to be

more prevalent in low-tension glaucoma than in high-tension glaucoma.[e.g.20-22] Intraocular pressure lowering treatment may not prevent the incidence of disc hemorrhages in normal-tension glaucoma.[e.g. 23-24]

Peripapillary atrophy may be more prevalent in glaucoma than in the healthy population, but its significance for the etiology and progression of the disease abnormalities is unclear and it cannot sufficiently separate the healthy from the sick.[e.g. 25-27]

Photography of the retinal nerve fiber layer

Although photography of the nerve fiber layer may support clinical glaucoma diagnostics *[E30] (*C), in particular with unusually small or large optic discs, [e.g. 12,28] the evidence of its sensitivity and specificity is insufficient *[E26]* (D). There is limited evidence of its feasibility in screening selected populations but there is insufficient experience on its use in population-based screening studies *[E31]* (D). It may be possible to observe glaucomatous abnormalities in the nerve fiber layer already before abnormalities can be detected in the optic disc and/or the visual field.[e.g. 11-12]

Automated imaging instruments

No randomized screening or diagnostic trials using automated imaging instruments have been published reporting their clinical effectiveness or cost-effectiveness in preventing glaucoma-induced visual disability *[E14] (D).* Although evidence is lacking, the currently available instruments (optical coherence tomography, scanning laser polarimeter and confocal scanning laser ophthalmoscope) may offer additional support for diagnostics and follow up *[E14] (*D).

The desired benefit of automated imaging instruments compared with visual field examination would be independent from the responses of the patient as well as from the expertise required of the clinician evaluating structural abnormalities. However, perfecting clinical evaluation skills is still mandatory as evaluation of the changing digital reports may also be demanding; glaucoma is not a “red disease”, i.e. the diagnosis cannot be based only on the red color of the print out. The clinician needs to be able to differentiate artefacts from clinically significant abnormalities.[29]

The normative databases of the imaging instruments are not comprehensive. In addition, the reproducibility of measurements may not be sufficient to separate true progression from variability induced by the patient and the instrument, i.e. which measurement represents clinically significant diagnosis and progression of disease *[E21] (*C).

Visual field examination

There are large variations in the sensitivity and specificity of the functional examinations that depend on the comparison test. The risk of bias in study designs is significant *[E27]* (D). The largest number of scientific reports has been published using the Humphrey and Octopus automated perimeters. The literature reports numerous definitions for visual field abnormality and progression with large variability *[E32]* (D), *[E33]* (C).

For diagnosis and evaluation of progression, the visual field examination should be reliable and repeatable. A visual field examination is dependent on the patient’s response, which shows variation both during and between the tests *[E34] (*B). As the visual field test strategy affects the results, it is advisable to follow patients using the same instrument and the same examination protocol. Earlier randomized studies (e.g. EMGT, OHTS) used traditional threshold strategies.[30-31] The evidence of the shortened testing times (e.g. SITA) on the number of visual fields needed for verification of the visual field progression has not been verified.

The kinetic visual field examination may be useful for the examination of the peripheral visual field, e.g. for the issuing of driving licenses (II/4 isopter), in far advanced glaucoma (in addition to a central 10-degree program) and in cases where automated perimetry is unreliable (D).

Glaucoma screening

With screening of a symptom-free population, one attempts to find a disease in its early phase in order for the treatment to be as effective as possible, or in order to identify individuals with the greatest susceptibility to the disease.

There are no systematic reviews or studies that provide evidence for direct or indirect links between glaucoma screening and visual field loss, visual impairment, optic nerve damage, intraocular pressure, or patient-reported outcomes *[E35]* (D). In addition, economic simulation models of the cost-effectiveness of

screening report inconclusive results with large uncertainties. Although training and guidelines are expected to improve diagnostics, the evidence is inconclusive *[E35]* (D).

The lack of appropriate tests for screening is the main challenge due to high variability of the sensitivity and specificity of the structural and functional examinations *[E26]* (D), *[E27]* (D). Due to a lack of evidence *[E35]* (D), systematic screening is not recommended.

Intraocular pressure in screening

Measurement of the intraocular pressure is insufficient for glaucoma screening *[E36]* (A). In screening studies of the adult population, more than half of individuals with glaucoma have had IOP within the normal range *[E36]* (A).

Clinical examination of ocular fundus in screening

In mass screening studies, ophthalmoscopy of the fundus has proven to be unreliable. There may be considerable variation in the evaluation of glaucomatous abnormalities even among experienced ophthalmologists *[E24]* (C). The majority of hemorrhages at the optic nerve head may be missed *[E29]* (C).

Optic nerve head in screening

There are no distinct parameters of the optic nerve head (e.g. cup/disc ratio) that could separate glaucoma subjects from healthy individuals *[E23]* (B)**.**

Retinal nerve fiber layer photography in screening

There is insufficient experience on the use of nerve fiber layer photography in population-based screening studies, although clinically useful experiences have been reported when screening and diagnosing selected populations *[E30]* (D).

Imaging instruments in screening

No randomized screening or diagnostic trials using automated imaging instruments have been published that report clinical effectiveness or cost-effectiveness in preventing glaucoma-induced visual disability *[E14]* (D).

Visual field examination

There are large variations in the sensitivity and specificity of structural examinations that depend on the comparison test. The risk of bias in study designs is significant *[E27]* (D). Frequency Doubling Technology (FDT) may be useful in screening for glaucoma *[E37]* (C).

The clinical-effectiveness and cost-effectiveness of glaucoma treatment

Although there is high-level evidence that treatment (medicines, laser, and surgery) decrease intraocular pressure and reduce the risk of development and deterioration structural a functional abnormalities *[E38]* (B), *[E39]* (B), the *direct* effects of treatments on *visual impairment* and the comparative efficacy of different treatments as well as which treatments improve patient-reported outcomes is unclear *[E40] (*D). So far the evidence is based on some country-specific economic *simulation* models*,* e.g. in the US, UK, Holland, and China, treating glaucoma appears to be cost effective compared to 'no treatment' *[E40] (*D).

Conversely, the results of *simulation* models vary as to whether to treat none, some or all patients with ocular hypertension, and they depend on different estimates used for the prevalence of glaucoma and visual disability as well as on the country *[E40]* (D). The cost-effectiveness models of different therapeutic interventions give also variable results.

All published *simulation* models are based on the characteristics of the participants enrolled in relatively small and limited randomized controlled trials (RCTs), which may not include all important predictors in the general population and everyday practice. In addition, RCTs may give an optimistic impression of outcomes compared with "real life" where there is a poorer compliance and adherence to care protocols both by the patients and clinicians in implementing the guidelines. For example, the OHTS-EGPS (Ocular Hypertension

Treatment Study – European Glaucoma Prevention Study) prediction equation generally overestimated the 5-year risk of OAG in four cohorts with OHT in different geographical locations and settings *[E40]* (D). In addition, in published RCTs, data has been reported for one eye only (not always reporting whether it is the worst or the better eye of the patient), i.e. the data of the other eye are simulated with no published evidence.

As the evidence on glaucoma-induced visual disability is limited, the blindness rates in the modeling studies have used different estimates. Similarly, the data on utility values and the influence of glaucoma severity on health status are limited. Retrospective observational data is also incomplete and selective. Reliable and "realistic" data (preferably from large randomized trials or prospective cohorts of 'everyday patients') are not available so far *[E40]* (D).

Visual disability

The purpose of the treatment is to prevent glaucoma-induced visual disability. However, no treatment RCTs have been published in which prevention of visual disability was the end point of the study. In population-based cross-sectional studies, the prevalence of visual disability or blindness in one or both eyes varies between 3 and 12%. The prevalence of visual disability among screened populations varies from 0.03 to 2.4% *[E41]* (C). In most screening reports, the prevalence of visual disability among new and already diagnosed patients is not reported separately. Due to uncertainties in reporting and variable definitions, the prevalence data of visual disability should be considered cautiously. Patients already within health care systems are reported to suffer from the disease more severely than the screened population. Some registry-based retrospective studies report clearly higher prevalence rates compared with cross-sectional screening studies (visual disability in both eyes in 15% within 15 years and 22% in 20 years, visual disability in one eye in 9% in 10 years and 54% in 20 years) *[E41]* (C).

Treatment of glaucoma

The goal of treatment is presented in Table 5. The majority of the studies are concentrated on the IOP-lowering effect of the treatment because lowering IOP is so far the only treatment modality for glaucoma.

The efficacy of treatment in ocular hypertension

Lowering of intraocular pressure seems to reduce the risk of the development of structural and functional abnormalities in patients with ocular hypertension *[E38]* (B). Only one RCT (the European Glaucoma Prevention Study) had a placebo-treated control group in which a dorzolamide-treated group was compared with placebo *[E38] (B).* Variation in IOP may not increase risk of progression in ocular hypertensive patients *[E42]* (C).

The efficacy of treatment in glaucoma

Lowering intraocular pressure seems to reduce the risk of the deterioration of structural and functional abnormalities in glaucoma *[E39]* (B).

Table 5. What is the goal of glaucoma treatment?

The goal of treatment is to prevent glaucoma-induced visual disability.

The goal of lowering IOP

The target IOP level is the level where damage does not develop or already existing damage does not progress. Progression may be slow, however, and it may take 3–5 years to find a safe IOP level for an individual. Target IOP must be updated during check-ups by monitoring the progression of structural and visual field abnormalities (Table 7).

IOP reduction

If treatment is initiated, the IOP should be lowered by **at least 25%**[1] of the untreated level.

Initial IOP mmHg	Target IOP ≤-25% mmHg
>12	9
14	11
16	12
18	14
20	15
22	17
24	18
>26	20

The target IOP level should be lower, especially if the patient has, e.g.

Far advanced glaucoma
Aggressive glaucoma
Several risk factors
Long life expectancy

[1] *[E38 (B), [E39] (B)*

Methods for lowering intraocular pressure

Medical treatment

Lowering intraocular pressure is currently the only form of treatment for glaucoma. Although some medications have also been suggested to have a beneficial effect on the survival of the ganglion cells (neuroprotection), adequate evidence for neuroprotection is missing *[E43]* (D).

According to systematic reviews, prostaglandin analogs lower IOP more than other medical monotherapies *[E44]* (B). The IOP-lowering efficacy of different prostaglandin analogs may differ from each other slightly, but their clinical significance is small or non-existent:

- Prostaglandins – travoprost *[E45]* (C), latanoprost *[E46]* (C) and tafluprost *[E47]* (C) – with or without preservatives seem to lower IOP similarly.
- Latanoprost and tafluprost seem to lower IOP equally effectively *[E48]* (B).
- Bimatoprost may lower IOP somewhat more than tafluprost *[E49]* (C), travoprost *[E50]* (C) and latanoprost *[E50]* (C).
- Travoprost may lower IOP somewhat more than tafluprost *[E51]* (C).

Brimonidine seems to lower IOP somewhat less than timolol within 12 months *[E52]* (B). Topical carboanhydrase inhibitors seem to lower IOP less than timolol *[E53]* (B).

Combination drugs

Differences between various combination drugs are so small that recommendations are not appropriate. The combination of prostaglandin and timolol lower IOP on average by 2 mmHg more than timolol alone, and by 1 mmHg more than prostaglandin alone *[E54]* (A).

The combination drugs seem to have a somewhat lower efficacy than the same drugs in different bottles, but the clinical difference is small *[E55]* (C). The combination of prostaglandin and timolol seems to be somewhat more effective dosed in the evening than in the morning *[E56]* (B). A dortzolamide-timolol combination seems to lower IOP as much as a brinzolamide-timolol combination *[E57]* (C). A brimonidine-timolol combination seems to lower IOP 1 mmHg more than timolol alone and 2.8 (2.5–3) mmHg more than brimonidine alone *[E58]* (C). Latanoprost (IOP reduction 7.5 mmHg) and a brimonidine-timolol combination (IOP reduction 7 mmHg) may lower IOP similarly *[E59]* (C).

Compliance

The treatment compliance with glaucoma medication is poor *[E60]* (C). According to different studies, 5–80% of patients do not follow their treatment plan. It is unclear whether patient education improves compliance *[E61]* (D).

Side effects

Glaucoma treatment may have local and systemic side effects, some of which may be severe [*E62]* (C). Although timolol seems to cause systemic side effects that can be serious, it seems to be locally tolerated better than prostaglandin analogs *[E63]* (B). Depending on the drug, a considerable number of patients may need to change or stop medications due to side effects. In cases of intolerance, the harmful drug should be discontinued. The side effects of glaucoma drugs are listed in Appendix 1. Compression of the nasolacrimal duct may reduce some side effects *[E72]* (C).

Laser trabeculoplasty

Laser trabeculoplasty and medications seem to induce a similar reduction in IOP *[E73]* (B). When given as primary therapy, approximately half of the patients do not need medication 1–2 years after laser treatment. The intraocular pressure-lowering effect of laser trabeculoplasty may diminish ca 8% per year. With a follow up of up to 7 years, only 20% of patients may manage without medical treatment. However, fewer medications are needed if glaucoma treatment is initiated with laser trabeculoplasty *[E73]* (B). Argon-, diode- and selective laser trabeculoplasty seem to cause a similar IOP-lowering effect *[E74]* (B).

Cyclophotocoagulation

According to short-term follow up studies on refractory glaucoma, transscleral laser cyclophotocoagulation may lower IOP, but the need for repeated treatments is frequent *[E75]* (D). Patients should be pre-treated with additional IOP-lowering medication in order to avoid post- operative pressure spikes *[E76]* (D).

Surgical treatment

Although surgical treatment seems to reduce intraocular pressure more than medical or laser treatment *[E77]* (B), *[E78]* (B), the rate of progression seems somewhat slower after surgery only in far advanced glaucoma *[E77]* (B). Initially, surgically treated patients complain more about local eye problems and need more cataract surgery than medically treated patients. However, after five years the need for cataract surgery does not seem to differ between the two groups. The visual field defects may also progress despite the decreased IOP after surgery. It has not been possible to determine any clear cut-off IOP that would prevent progression in surgically treated patients *[E79]* (B).

Trabeculectomy

The success rate of trabeculectomy varies considerably from one study to another depending on the criteria used, e.g. between 26% and 98% over 5 years. Long follow up times (10–15 years) have been

reported only in retrospective studies, where, however, the data is incomplete for the majority of patients (70–96%) *[E79].*

Antimetabolites

Mitomycin C may improve the lowering of IOP one year after trabeculectomy in eyes with a high risk for fibrosis and in eyes without previous surgery *[E80]* (C). No significant effect on failure was noted in the group undergoing trabeculectomy combined with cataract extraction. Mitomycin may accelerate cataract formation. The success rate of nonpenetrating surgery may be better when using Mitomycin C without an increased rate of complications *[E81]* (C).

Postoperative injections with 5-fluoruracil may improve the success of trabeculectomy in the first year in eyes with a high risk of scarring and without previous surgery *[E82]* (C). Additionally, beta radiation with trabeculectomy may prevent scarring *[E83]* (C).

Glaucoma shunts

Although IOP decreases equally in previously operated eyes undergoing surgery for Baerveldt shunt and trabeculectomy, the success rate after the shunt operation seems better *[E84]* (B). The outcome after shunts and trabeculectomy do not seem be different in eyes without increased risk of fibrosis, however. In the first 1–3 years of follow up, the efficacy of various shunts seems similar *[E85]* (B). During a one-year follow up, shunts without valves induce lower IOP than those with valves. However, risk of complications and additional surgery seems higher.

Non-penetrating surgery

Limited evidence indicates that short-term control of IOP may be better with trabeculectomy than viscocanalostomy, while no difference was found for deep sclerectomy. Although the studies were too small to provide definitive evidence regarding the relative safety of the surgical procedures, there may be relatively fewer complications with non-filtering surgery compared with trabeculectomy *[E86]* (C), *[E87]* (D). The evidence for collagen implants in the success rate of non-penetrating surgery is unclear *[E88]* (D).

Cataract surgery

Phacoemulsification with intraocular lens implantation decreases the IOP by 3–4 mmHg both in glaucoma patients with low to moderately increased preoperative IOP and in non-glaucomatous subjects.[e.g.32-37] The risk of postoperative pressure peaks must be considered.

The guideline for selecting glaucoma treatment is presented in Table 6.

Table 6. Which treatment plan should be followed (also use Tables 3 and 4)?

Before initiating treatment, consider the following factors:

- Patient's age and life expectancy
- Severity of glaucoma (both eyes)
- Rate of progression: How rapidly the changes have progressed
- At which IOP level abnormalities have appeared and/or progressed
- Risk factors
- Patient's other (eye) diseases, medications, allergies and the possibility of pregnancy[1]

Decision to initiate treatment

Lasertrabeculo-plasty ⟷ Prostaglandins ß-blockers

Alpha-agonists
Carboanhydrase inhibitors (topical)[2]
Pilocarpine

Ophthalmologist chooses initial therapy

- No response to medication: change drug, consider combination
- Only one drug per group, e.g. one prostaglandin at a time, etc.
- Consider carefully whether to add a 3rd bottle to treatment
- Consider the need for glaucoma and cataract surgery

Insufficient response, treatment unsuitable, and/or progression despite lowered IOP

Filtrating surgery ⟷ Cataract (or combined) surgery

Shunt surgery ⟷ Cyclophocoagulation

Surgeon chooses the type of surgery

[1] Most drugs cannot be used during pregnancy. Beta blockers and pilocarpine may be considered. Always consult the obstetrician about the use of glaucoma medication during pregnancy.
[2] Oral product usually for temporary use only.

Glaucoma follow up

There is no solid evidence for the most clinically effective and cost-effective monitoring schemes (e.g. tests and technologies to be used for detecting progression, plus their frequency and the timing of control visits) to prevent visual disability in patients with manifest glaucoma and ocular hypertension *[E14]* (D). Some modeling and retrospective studies suggest that more effective treatment plans could actually allow less frequent monitoring visits in ocular hypertension and glaucoma *[E89]* (D).

An optimum test would be sensitive and specific, capable of confirming progression with a small number of re-tests, and would vary minimally between different time points. No structural or functional method in glaucoma follow up fulfills all required criteria. In addition, the concordance of different methodologies seems poor.[e.g.38-39]

Rate of progression

Glaucoma is usually a slowly progressive disease. However, the rate of change of the nerve fiber layer, optic disc and visual field abnormalities seems to vary greatly from patient to patient, and it may take several years to detect the progression of abnormalities *[E90]* (B). It has been estimated that in patients under treatment, the time from the appearance of the first visual field changes to blindness may take 30 to 40 years *[E91]* (D).

The abnormalities progress in a considerable number of treated patients with glaucoma *[E92]* (B). Age, disc hemorrhages (for normal-tension glaucoma), baseline visual field loss, baseline intraocular pressure and exfoliation syndrome seem to be associated with glaucomatous visual field progression *[E93]* (B), as well as the length of follow up *[E33]* (B). The significance of measuring the diurnal variation of IOP on progression is unclear *[E16]* (D).

Clinical correlation of structure and function

During follow up, the clinically detectable changes in the optic nerve head, retinal nerve fiber layer and visual field may typically appear and progress at different time points (with a delay of 1–6 years).[e.g. 7-10] The visual field may be normal despite structural damage to the optic nerve head and retinal nerve fiber layer.[e.g. 11-15]. The variation in the beginning and the length of the follow up window in clinical studies and everyday clinics may define which abnormalities are detected “first”.

Imaging instruments and progression

The results of imaging instruments differ from each other both in diagnostics and follow up *[E21]* (C), *[E26]* (D). When analyzing disease progression, either trend-type or event-type analysis may be used. The confirmation of deterioration requires clear evidence which change from baseline exceeds the variability attributable to both the patient (e.g. cataract) and the instrument, and thus represents a clinically significant progression.

Although when compared with other imaging devices, spectral domain optical coherence tomography seems to provide better test-retest variability of the circumpapillary retinal nerve fiber layer and disc morphometric parameters, all systems need improvement in their test-retest variability measurement capabilities *[E21]* (C). On the other hand, regarding the life-long follow up of glaucoma, the rapidly evolving technologies and reports create a challenge when the most recent results may not be comparable with earlier examinations. Therefore, a traditional fundus picture is still important and necessary *[E29]* (C).[e.g. 40]

Although knowing the test-retest variability may be indispensable in determining the optimal frequency of performing imaging tests, in everyday clinical work it seems currently impossible to take into account the large number of parameters and their largely variable reproducibility *[E21]* (C).

It is crucial to constantly and consciously consider sufficiency of care: both under-testing, under-diagnosing and under-treatment – like over-testing, over-diagnosis and over-treatment (which may increase the number of false positives) may decrease quality of life *[E89]* (D).[4]

Frequency and evaluation of visual fields

One may need to repeat the visual field examination 2–6 times in order to confirm a visual field progression, even when the visual field has been examined with the same examination program using the same instrument *[E28]* (C). When a visual field examination was repeated once or twice, the progression of the visual field abnormalities could not be confirmed in half of the patients. When the visual fields were examined on average 3 times per year for 5 years in patients with ocular hypertension, the appearance of a visual field abnormality could be found only in 0.5% of the visual fields *[E28]* (C).

By doubling the visual field testing frequency, the time to detection of a statistically significant linear Mean Defect index change was estimated to be shortened by approximately one third. It has been estimated that by examining the visual fields once a year – when progression is monitored with the visual field indices – the detection of visual field progression could take 5 years. However, all these estimates are reported with conventional threshold strategies, and the impact of faster strategies on the testing frequency is unclear.

Several qualitative and quantitative methods have been developed to assess field progression, but the superiority of any of them in maintaining the quality of glaucoma patients’ lives has not been verified [E32] (D). The incidence of field progression varies considerably (2–62%) and depends mainly on the selected methodology. Some readily available data on printouts may aid clinical evaluation, e.g. Visual Field Index

(VFI), Mean deviation (MD) and Glaucoma Change Probability (GCP) [E32] (D). VFI has been developed to predict the future rate of change.

The VFI during three initial years of follow may predict the VFI after 8 years of follow-up (correlation coefficient of 0.78). In qualitative methods, the interpretation of results is dependent on the capacity of the observer, which may cause high interobserver variability. In the results of visual field examinations, 82% of the heterogeneity can be accounted for by the variety of methods used in the studies *[E33]* (B).

A recommendation for a glaucoma follow up pattern is presented in Table 7. A model to aid planning of follow-up is presented in Table 8, and a recommendation to treat and follow up high-risk glaucoma patients is presented in Table 9.

Table 7.
Follow up of stable glaucoma patients: Which examinations should be prescribed and how often?

- Glaucoma is considered to be stable when follow up reveals no progression, or the rate of progression is very low considering life expectancy.
- When prescribing follow up tests, the patient's age, stage of glaucoma, and other eye and systemic diseases need to be taken into account.
- The patient is given a written treatment plan that includes the goals for treatment.
- In addition, the side effects of both treatment and monitoring are analysed, including their impact on compliance.

Measurements of intraocular pressure (IOP)

- Frequency of measurement is determined individually; in glaucoma typically twice a year, in ocular hypertension every 1–2 years.
- Monitored with the same device (e.g. applanation or rebound tonometer).
- The untreated IOP level, and the IOP level under which disease has progressed, as well as target pressures (Tables 5 and 8) should to be recorded.

Clinical examination

- Gonioscopy at the time of diagnosis and repeatedly during follow up.
- Fundus examination.

Imaging and visual field examinations[1]

Level	1st follow up year	2nd year	3rd year	4th year, etc.
Very good	ONH[2] + RNFL[2] + VF	X[3]	ONH[2] + RNFL[2] + VF	X[3]
Good	ONH[2] *or* RNFL[2] + VF	X[3]	ONH[2] *or* RNFL[2] + VF	X[3]
Satisfactory	VF	VF	VF	VF
Insufficient		IOP monitoring only		

[1] Always the same methodology.
[2] If automated imaging technology is used, conventional imaging is also necessary.
[3] On suspicion of progression, consider the need for extra tests in collaboration with the patient.

ONH = Optic nerve head
RNFL = Retinal nerve fiber layer
VF = Visual field

Table 8.
Frame work to create a two-year treatment and monitoring plan in stable glaucoma.

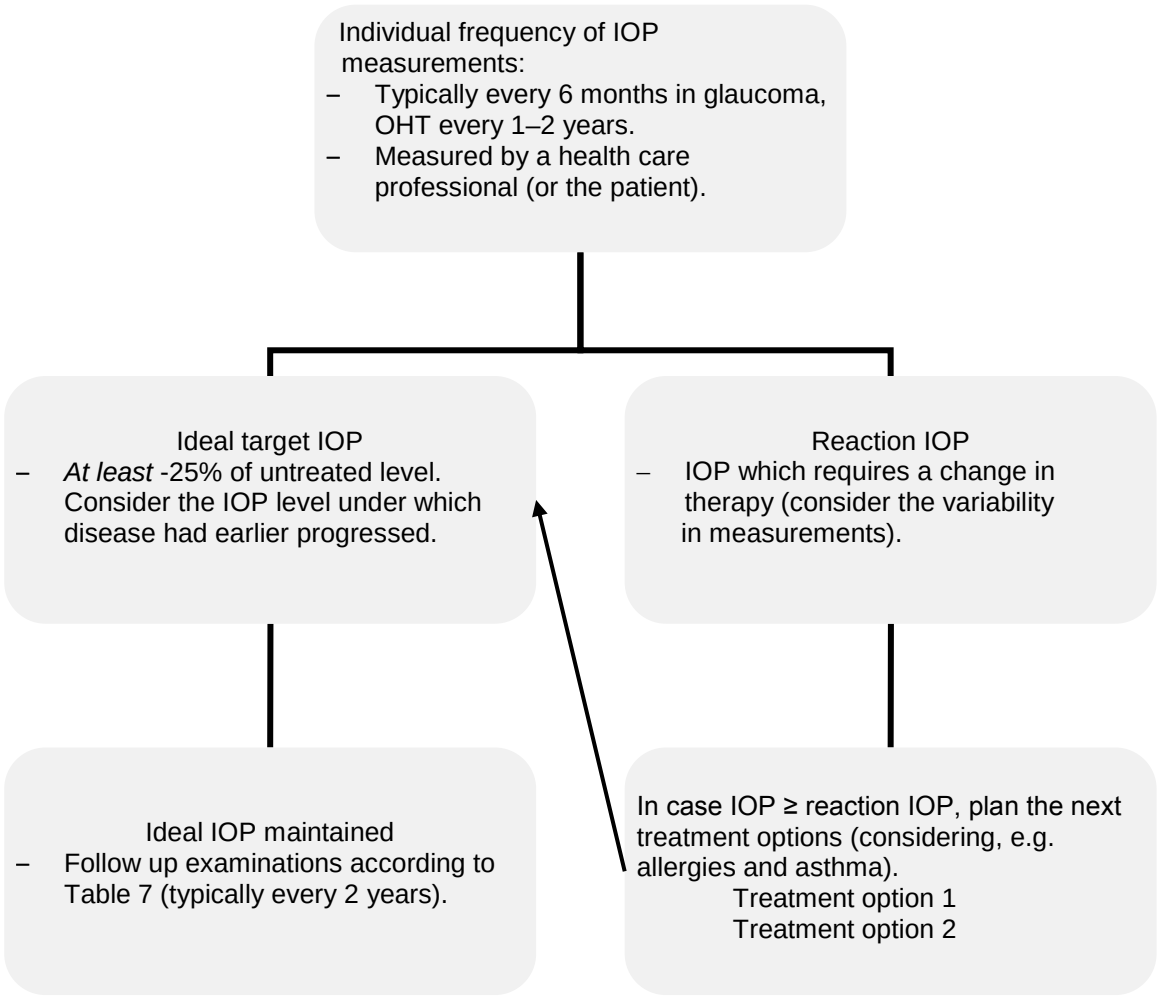

Table 9. Guideline on how to treat and follow up high-risk glaucoma patients.

Typical characteristics of high-risk glaucoma patients

1. Rapidly progressing glaucomatous changes independent of the IOP level.
2. The IOP is 30–35 mmHg and the patient has definitive optic disc, RNFL and visual field abnormalities.
3. Strong family history:
   Several relatives have glaucoma,
   Glaucoma appears at young age,
   Glaucoma-induced visual disability,
   Several risk factors (in addition to the above) (Table 2),
   e.g. exfoliation.

Guideline on how to treat and follow up high-risk glaucoma patients

1. Aggressive lowering of the intraocular pressure:
   In patients with a high pressure level[1] at least <20 mmHg.
   At lower pressure levels, *at least* 30% IOP-lowering.
   One drug (or laser treatment alone) is usually not enough.
   Very easily surgical treatment.
2. Frequent follow up
   Depending on IOP (monthly/weekly/daily) until the pressure is low enough and/or progression has stopped.

[1] Remember to check gonioscopy to rule out closed-angle glaucoma.

Quality of life

Glaucoma seems to worsen the patient's quality of life. The degree of deterioration seems to correlate with the severity of the visual field damage *[E94]* (B). However, unless the field defect is very severe, the quality of life seems to be affected more by the subjective threat of the loss of vision than the glaucomatous abnormalities themselves. Further problems may be caused by the practical inconvenience of the constant and regular therapy and control visits *[E94]* (B). Reliable utility data required for cost-effectiveness evaluations are thus far scarce. Glaucoma does not seem to influence mortality *[E95]* (B).

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Appendix 1. Side effects of glaucoma drugs (with links to evidence summaries).

Alpha-agonists (apraclonidine, brimonidine)

- Reduced heart rate and blood pressure, fatigue, cooperative actions with drugs affecting central nervous system, driving
- Dry mouth and nose, taste disturbances
- Follicular conjunctivitis
- Allergic reactions

Beta-blockers (betaxalol, timolol)

- Bradycardia and arterial hypotonia, asthma*[E63]* (B), dizziness, sleep disturbances, depression, nausea
- Non-selective beta-blockers are contraindicated in patients with asthma, sinus bradycardia, arterial hypotonia, untreated congestive heart failure or II and III degree heart block
- Dryness and stinging of mucous membranes, meibomian gland dysfunction *[E64]* (C)
- Allergic reactions

Carbonic-anhydrase inhibitors, s*ystemic* (acetazolamide)

- Fatigue, dizziness, gastrointestinal disturbances, metabolic acidosis, depression, paresthesy, allergic reactions (cross allergy with sulphonamides), anaphylaxis, low potassium values, renal stones, gout

Carbonic-anhydrase inhibitors, *topical* (dorzolamide, brinzolamide)

- Taste disturbances, dry mouth.
- Other systemic systemic side effects of sulfonamides and carbonic anhydrase inhibitors are also possible.

Prostaglandin analogs (latanoprost, bimatoprost, travoprost)

- Conjunctival hyperamia *[E65] (*B), iris pigmentation *[E66] (*B), long eyelashes and hyperpigmentation of periorbital skin *[E67]* (B)
- Also iritis *,* macular oedema and corneal changes *[E68] (*C)*,* periorbitopathy *[E69] (*C), meibomian gland dysfunction *[E64] (*C)
- The possible thinning effect of prostaglandin analogues on central corneal thickness is unclear *[E70]* (D).
- Systemic side-effects are rare, gastrointestinal side-effects may be possible *[E71] (*D).

Parasympathomimetics (pilocarpine)

- Head ache in the beginning of the treatment. Other systemic side effects are rare.
- Accomodation disturbances in young patients, blurring of vision.

Preservatives

- Benzalconium chloride may cause allergic and toxic reactions.