Evidence-based medicine

The Finnish evidence-based guideline for open-angle glaucoma

A. Tuulonen,1 P. J. Airaksinen,1 E. Erola,2 E. Forsman,3 K. Friberg,4 M. Kaila,5,6 A. Klemetti,7 M. Mäkelä,8 P. Oskala,9 P. Puska,9 L. Suoranta,10 H. Teir,11 H. Uusitalo,12 E. Vainio-Jylhä,13 and M-L. Vuori13

1Department of Ophthalmology, University of Oulu, Finland
2Viherlaakso Health Care Centre, Espoo, Finland
3Medical Centre Ekenäs Öga, Ekenäs, Finland
4Silmääsemat Group, Espoo, Finland
5Finnish Medical Society Duodecim, Finland
6University of Tampere, Finland
7Muurame, Finland
8Finnish Office for Health Care Technology Assessment, Helsinki, Finland
9Helsinki University Hospital, Finland
10Medical Centre Mehilainen, Helsinki, Finland
11Medical Centre Mehilainen Forum, Helsinki, Finland
12University of Kuopio, Finland
13Turku University Hospital, Finland

ABSTRACT.
In most patients, chronic open-angle glaucoma is a slowly progressive disease. Eyes with very high intraocular pressure (IOP > 30mmHg) represent an exception to this and should be treated and followed extremely intensively. As lowering IOP is, so far, the only means of treating glaucoma, the majority of research reports deal with the IOP-lowering effect of the treatment. The primary goal of treatment, however, is to prevent glaucomatous damage to the structures and function of the eye. The effectiveness of treatment is monitored with optic disc and retinal nerve fibre layer imaging and with visual field examinations. If the glaucomatous changes are progressing, more effective treatment should be given. In the course of follow-up, it should be noted that the changes in the optic nerve structure and function appear and progress at different time-points with delays of up to several years. The assessment of abnormalities is dependent on the examination method and requires a great deal of experience on the part of the examiner. The important risk factors in glaucoma are elevated IOP (even if IOP is within normal range in half of patients), age, positive family history, exfoliation, race and myopia.

Keywords: open-angle glaucoma – evidence-based – guideline

Introduction
In 1995 the Finnish Medical Society Duodecim initiated a project for producing national evidence-based current care guidelines for important public health issues in Finland. The Finnish Glaucoma Guideline Team, appointed by the Finnish Ophthalmologic Society and the Finnish Glaucoma Society, held its first meeting in February 2000. In addition to clinical and academic experts from both public and private sectors, guideline teams always include a general practitioner (GP). The first step for all guideline teams is to obtain methodological training in evidence-based evaluation of the literature. Duodecim organizes this training.

In the literature search, we first used the Cochrane Library. The search was then expanded for specific questions to Medline searches and reference lists of articles. The time frame for the original search includes the years 1975–2000.
For the years 2001–02, only the most important results of randomized, controlled trials were included in the guideline. Other more recent publications will be evaluated in the first update of the Glaucoma Guideline planned for 2004. When available, data for white subjects were used for the purposes of national recommendations.

After critical appraisal of the literature, the evidence was evaluated for validity and applicability, based on criteria originally outlined by the Evidence-Based Medicine Working Group (Guyatt & Rennie 1993). Depending on the quality and size of original studies, the strength of each statement is graded from A to D. Level A represents ‘strong research-based evidence’, that is multiple, relevant, high-quality studies with homogenous results (e.g. two or more randomized, controlled trials), or a systematic review with clearly positive results. Level B represents ‘moderate evidence’ (e.g. one randomized, controlled trial, or multiple adequate studies). Level C represents ‘limited research-based evidence’ (e.g. open, controlled, prospective studies). Level D represents ‘no evidence’ (e.g. retrospective studies, or the consensus reached by the group in the absence of good quality evidence). Recommendations for action are then formulated based on the studies of highest quality.

In order to achieve wider involvement of Finnish ophthalmologists and to facilitate the implementation of the guideline, the supporting societies organized a 2-day symposium at the mid-point of the project (March 2001). During the symposium, summaries of literature reviews and suggestions for recommendations produced by the Glaucoma Guideline Team were introduced and discussed with 164 Finnish ophthalmologists, representing 45% of those at working age. The final guideline was later circulated widely to stakeholders in the subject, achieving a response rate of 29% (20 of 70 organizations and physicians).

The present English summary is based on an electronic version (in Finnish: http://www.duodecim.fi/kh), which for wide and easy availability (Bero et al. 1998) is the main media for Finnish guidelines, including the Glaucoma Guideline (Mäkelä & Kunnamo 2001). To explore the statements and recommendations more closely, the electronic version (130 pages) contains short summaries of the 275 referred articles.

Goals and limits of the guideline

The purpose of this guideline is to uniform treatment patterns of glaucoma patients by providing evidence-based knowledge on central issues (Table 1). This guideline is designed for use in both public and private health care. In particular, the authors hope that it will help in drawing an individual treatment plan together with the patient. The recommended practice patterns of this working group (Tables 3–10 and Figs. 1–2) are based on the literature review presented in the text format.

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 comprises also ocular hypertension, i.e. elevated intraocular pressure (IOP) without optic disc and visual field abnormalities. The guideline does not deal with closed-angle glaucoma, other secondary glaucomas or congenital and juvenile glaucoma.

The disease and its epidemiology

Glaucoma is a progressive neuropathy of the optic nerve with typical structural and functional abnormalities in the optic disc, retinal nerve fibre layer and visual field. In the majority of patients, the glaucomatous abnormalities progress slowly over the years. In a minority of patients, the disease may, however, lead to serious optic nerve damage within just a few months. It is important to identify these high risk patients. In this guideline, high risk patients are therefore dealt with as a separate group.

Among individuals over the age of 50 years, the prevalence of glaucoma is approximately 1.5% (Bononi et al. 1998; Dielemans et al. 1994; Klein et al. 1992; Leske et al. 1999; Mitchell et al. 1996; Sommer et al. 1991). Prevalence increases with age (Dielemans et al. 1994; Hirvelä et al. 1995; Häkkinen 1984; Klein et al. 1992; Mitchell et al. 1996; Tuck & Crick 1998; Wensor et al. 1998) (A). It has been estimated that there were 67 million glaucoma patients worldwide in the year 2000, approximately 10% of whom were blind. In developed countries, less than half of glaucoma subjects are aware of their status (Quigley 1996; Tuck & Crick 1997a).

After age-related macular degeneration, chronic open-angle glaucoma is the second most prevalent cause of registered visual handicap of the elderly in Finland (Ojamo 2000). In 2000, over 60000 patients were entitled to special refunds of medicines for glaucoma (National Agency for Medicines & Social Insurance Institution 1995–2000). If the number of patients increases at the present rate (3% per year) there will be over 80000 glaucoma patients in Finland by 2010. Even a larger group of patients is suspected of having glaucoma. These patients will also require follow-up because a proportion of them may develop glaucomatous abnormalities later.

Risk factors

In half of patients with glaucoma, IOP falls within the statistically determined ‘normal’ range (10–21 mmHg). The risk of developing glaucomatous damage rises when IOP increases (particularly with IOP levels over 30 mmHg) (Ekström

---

**Table 1.** The purpose of this treatment guideline is to provide an answer to the following questions.

1. Which factors increase the risk of glaucoma?
2. Which examinations are needed for the diagnosis of glaucoma?
3. Is screening for glaucoma worthwhile?
4. What is the effect of lowering IOP in patients with glaucoma and ocular hypertension? Can progression be prevented?
5. Which treatment forms are most effective in lowering IOP?
6. What is the treatment goal and which treatment plan should be followed?
7. Glaucoma follow-up: which examinations should be performed and how often?
8. How do we treat and follow patients with an aggressive form of the disease?
9. Which quality criteria may be used in glaucoma care?
Based studies are presented in Table 2.

**Table 2. Which factors increase the risk of glaucoma?**

<table>
<thead>
<tr>
<th>Risk factors*</th>
<th>Risk</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Doubles every 10 years</td>
<td>(A)</td>
</tr>
<tr>
<td>IOP 22–29 mmHg</td>
<td>10–13-fold</td>
<td>(A)</td>
</tr>
<tr>
<td>&gt;30–35 mmHg</td>
<td>40-fold</td>
<td>(A)</td>
</tr>
<tr>
<td>Myopia</td>
<td>2–4-fold</td>
<td>(A)</td>
</tr>
<tr>
<td>Exfoliation</td>
<td>5–10**-fold</td>
<td>(A)</td>
</tr>
<tr>
<td>Family history</td>
<td>3–9-fold</td>
<td>(B)</td>
</tr>
<tr>
<td>Decreased perfusion</td>
<td>3-fold</td>
<td>pressure together with age</td>
</tr>
</tbody>
</table>

* In addition black race has been stated as a risk factor (Sommer et al. 1991) (A). On the other hand, the significance of diabetes as a risk factor is uncertain (Dielemans et al. 1996; Ellis et al. 2000; Klein et al. 1994; Mitchell et al. 1997; Tielsch et al. 1995a) (C).

** Risk among individuals over the age of 65–70 years.


**Intraocular pressure**

In chronic open-angle glaucoma ophthalmologists measure IOP by using a Goldmann applanation tonometer attached to a slit-lamp. The non-contact tonometer used by Finnish opticians may give different readings to the applanation tonometer (Rouhiainen & Teräsvirta 1990; Shields 1980). The Schötz tonometer used by GPs is best suited for the diagnosis of acute closed-angle glaucoma.

A single value of IOP does not give a true picture of the diurnal variation of IOP. Intraocular pressure varies at different times of the day and the highest values are usually measured in the morning (David et al. 1992). The least progression of the disease has been found in glaucoma patients whose diurnal pressure variation was modest (Asrani et al. 2000; Bergé et al. 1995) (B).

Small central corneal thickness value may result in low IOP readings and large value in high IOP readings (Brandt et al. 2001; Doughty & Zaman 2001). A meta-analysis reported that a 10% difference in corneal thickness results in approximately 3.4 mmHg difference in IOP (Doughty & Zaman 2001). One fourth of patients in the Ocular Hypertension Treatment Study (OHTS) had thicker corneas than the general population (Brandt et al. 2001).

**Gonioscopy**

Gonioscopy for anterior chamber angle examination is necessary for the classification of open-angle and closed-angle glucomas. There are several chamber angle classifications, but in Finland the Schaffer classification is used.

**Diagnosis of structural and functional abnormalities**

There is a lot of variation in the parameters measuring ocular structure and function. The variation depends on the examination method, the examiner and the examiner as well as the severity of the disease. Therefore, the accuracy of diagnostics increases when results of different examination methods are combined (Bengtsson & Heijl 1999a; Caprioli 1992; Caprioli et al. 1996; Harper & Reeves 2000; Heijl et al. 1987; Jonas & Gründler 1997; Jonas et al. 2000; O’Connor et al. 1993; Paczka et al. 2001; Quigley et al. 1994; Sommer et al. 1984; Tielsch et al. 1988, 1991; Varma et al. 1992) (B). If the diagnosis of glaucoma is defined by visual field examination methods, the clinical significance of a single abnormal visual field is small (Glaucoma Laser Trial Research Group 1995a; Kass & Mae 2000).

**Glucoma diagnostics**

The diagnosis of glaucoma is based on the examination of the optic nerve head, nerve fibre layer, visual fields, IOP level and gonioscopy. There is, however, no consistent and generally approved definition of the diagnostic criteria in the scientific literature (Bathija et al. 1998). In Table 3 we present a recommendation for the basis of diagnosis.

**Table 3. Examinations needed for the diagnosis of glaucoma.**

<table>
<thead>
<tr>
<th>Very good level*</th>
<th>IOP**</th>
<th>Gonioscopy</th>
<th>Visual field***</th>
<th>Optic disc images</th>
<th>RNFL images</th>
<th>(1, 2, 3, 4, 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good level</td>
<td>IOP**</td>
<td>Gonioscopy</td>
<td>Visual field***</td>
<td>Optic disc or RNFL images</td>
<td>(4, 6, 7, 8, 9, 10)</td>
<td></td>
</tr>
<tr>
<td>Insufficient level</td>
<td>IOP**</td>
<td>Gonioscopy</td>
<td>Visual field***</td>
<td>Optic disc images</td>
<td>(10, 11, 12, 13, 14)</td>
<td></td>
</tr>
</tbody>
</table>

* In addition blue-on-yellow perimetry (Johnson et al. 1995), the central 10 degree visual field (Tuulonen et al. 1993) and quantitative optic nerve head analysis (e.g. Heidelberg Retina Tomograph) may provide useful additional information (Burk et al. 1992)

** Diurnal IOP when needed (David et al. 1992). Regular calibration of the tonometer.

*** Preferably 2 automated visual field examinations with a threshold program for determination of the base line (Schulzer 1994; Glaucoma Laser Trial Research Group 1995; Kass & Mae 2000; Bergea˚ et al. 1995) (B).


Structural abnormalities in the optic disc and retinal nerve fibre layer pre-cede visual field abnormalities. Most cases of glaucoma – including the pre-perimetric glaucoma – may be diag-nosed when the optic disc and the nerve fibre layer are examined in ad-dition to visual field examination (Caprioli et al. 1996; Ekström 1996; Girkin et al. 2000; Heijl & Bengtsson 1989; Jonas & Grundler 1997; Kass et al. 2002; Katz et al. 1997; Odberg & Riise 1985; Paczka et al. 2001; Pederson & Anderson 1980; Quigley et al. 1992, 1994; Tuulonen & Airaksinen 1991; Zeyen & Caprioli 1993) (B). The pre-perimetric glaucoma is defined by normal visual field in spite of structural abnormalities in the optic disc and the nerve fibre layer. The guideline for glaucoma diagnostics is presented in Table 4.

Optic disc

In glaucoma diagnostics and follow-up, description of the optic disc; estimation of the cup–disc ratio or a drawing are not as accurate as optic disc photography or imaging. However, optimum usage of images requires profound experience (Coleman et al. 1996; Heijl & Bengtsson 1989; Odberg & Riise 1985; Tielsch et al. 1988) (B). The appearance of a healthy optic disc varies greatly due to differing optic disc sizes (Britton et al. 1987; Burk et al. 1992; Heijl & Mölder 1993; Jonas et al. 1988a, 1988b, 1990, 1991, 1995, 1999; Tuulonen & Airaksinen 1992; Varma et al. 1994) (B). Among healthy individuals, the cup–disc ratio may vary from 0 to 0.9 (Jonas et al. 1988b), limiting its ability to separate the healthy from the sick. A large cup in a large disc raises suspicions of glaucoma even if the IOP is not elevated (Burk et al. 1992; Jonas et al. 1999). A small optic nerve head is more insidious because early disc abnormalities may go unnoticed (Heijl & Mölder 1993; Jonas et al. 1990).


Peripapillary atrophy

Peripapillary atrophy is more prevalent in glaucoma subjects than in the healthy population but its significance for the aetiology and progression of disease abnormalities is unclear and its presence cannot be used to distinguish between healthy and glaucomatous subjects (Airaksinen et al. 1987; Jonas

---

Table 4. The guide line for diagnosis of glaucoma (the ‘2 out of 3 rule’). When ordering examinations the ophthalmologist should take into account patient’s age, degree of glaucomatous damage and other possible ocular diseases.

<table>
<thead>
<tr>
<th>Abnormal finding</th>
<th>Normal finding</th>
<th>Diagnosis</th>
<th>Comments</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNFL Optic disc Visual field</td>
<td>Normal</td>
<td>Glaucoma</td>
<td>Diagnosis is clear</td>
<td>(1, 2)</td>
</tr>
<tr>
<td>RNFL Optic disc Visual field</td>
<td>Normal</td>
<td>Glaucoma</td>
<td>Probably a small optic disc</td>
<td>Initiate (or consider initiating) treatment</td>
</tr>
<tr>
<td>RNFL Optic disc Visual field</td>
<td>Normal</td>
<td>Preperimetric glaucoma</td>
<td>Blue-on-yellow perimetry or 8–10 degree visual field may be abnormal</td>
<td>(5, 6, 7, 8)</td>
</tr>
<tr>
<td>RNFL Optic disc Visual field</td>
<td>Normal</td>
<td>Diagnosis other than glaucoma? (e.g. neurological disease)</td>
<td>Very rare in glaucoma if RNFL image is of high quality*</td>
<td>(see also Fig.1.) (*)</td>
</tr>
<tr>
<td>RNFL Optic disc Visual field</td>
<td>Normal</td>
<td>Preperimetric glaucoma?</td>
<td>Follow and look for progression (Blue-on-yellow perimetry or 8–10 degree visual field may be abnormal)</td>
<td>(6, 9, 10, 11, 12)</td>
</tr>
<tr>
<td>RNFL Optic disc Visual field</td>
<td>Normal</td>
<td>Suspected glaucoma</td>
<td>Large optic disc or optic disc anomaly?</td>
<td>Follow without treatment (unless IOP &gt; 30 mmHg)</td>
</tr>
<tr>
<td>RNFL Optic disc Visual field</td>
<td>Normal</td>
<td>Suspected glaucoma</td>
<td>Repeat visual field examination. Other cause for visual field abnormalities?</td>
<td>(15, 16, 17)</td>
</tr>
</tbody>
</table>

* In the literature there are no reports on this type of glaucoma cases.


**Retinal nerve fibre layer**

Examination of the nerve fibre layer facilitates and supports the glaucoma diagnostics based on the optic disc and visual field evaluation, in particular with unusually small or large optic discs (Jonas et al. 1988a, 1989). It is possible to observe glaucomatous abnormalities in the nerve fibre layer before abnormalities can be detected in the optic disc and/or the visual field (Katz et al. 1997; Quigley et al. 1994; Tuulonen et al. 1990, 1993) (C), see also (Caprioli et al. 1996; Girkin et al. 2000; Heijl & Bengtsson 1989; Katz et al. 1997; Odelberg & Riese 1985; Quigley et al. 1992; Tuulonen & Airaksinen 1991; Zeyen & Caprioli 1993).

High technology instruments (the Heidelberg retina tomograph, retinal nerve fibre analyser and optical coherence tomography), developed for nerve fibre layer and optic disc imaging and measurements, are not yet ready for routine glaucoma diagnostics. Due to their sensitivity and specificity, some instruments may be used for the follow-up of glaucoma (Ophthalmic Procedures Assessment (OPA) (American Academy of Ophthalmology 1999).

**Visual field examination**

The largest number of scientific reports has been made with the Humphrey and Octopus automated perimeters. Despite the fact that there are several different definitions for visual field abnormalities in the literature, there are no generally approved and used criteria for glaucomatous visual field defects (AGIS Investigators 1994; 1998, 2000; Collaborative Normal Tension Glaucoma Study Group 1998a, 1998b, 2001; Gordon et al. 1999; Keltner et al. 2000; Leske et al. 1999; Schulzer et al. 1994) (A).

For diagnosis and evaluation of progression, the visual field examination should be reliable and repeatable. Visual field examination is dependent on patient response, which varies both during and between tests (Bengtsson et al. 1998; Bengtsson & Heijl 1998, 1999a, 1999b; Bengtsson 2000; Birt et al. 1997; Blumenthal et al. 2000; Heijl & Drance 1983; Heijl et al. 1987; Hudson et al. 1994; Langerhorst 1988; Lewis et al. 1986; Wild et al. 1999). The visual field examination strategy affects the measurement results. Therefore, it is advisable to use the same instrument and the same examination protocol while following patients (Anderson et al. 1989; Bengtsson et al. 1998; Bengtsson & Heijl 1998, 1999a, 1999b; Bengtsson 2000; Wild et al. 1999), see also (Glaucoma Laser Trial Research Group 1995a; Kass et al. 2002; Keltner et al. 2000; Schulzer et al. 1994) (A). Our recommendation for visual field examination strategy is presented in Table 5.

In this review, the arguments related to verification of visual field abnormalities and their progression are based on studies which used the traditional threshold strategy. Traditional threshold strategies have been also been used in the recent longterm, randomized studies (Early Manifest Glaucoma Trial, Ocular Hypertension Treatment Study, Collaborative Initial Glaucoma Treatment Study) (Gordon et al. 1999; Leske et al. 1999; Musch et al. 1999). We do not know how the shortened test time will affect longterm fluctuation and nor do we know the number of visual fields needed for verification of visual field progression with fast and sensitive new methods of testing (e.g. SITA).

In particular, in early glaucoma the visual field abnormalities are detected earlier with static automated perimeter than with kinetic visual field examination (Airaksinen & Heijl 1983). The kinetic visual field examination is, however, useful for examination of the peripheral visual field (e.g. for examination of a glaucoma patient who is applying for a driving licence [II/4 isopter]), in advanced glaucoma or in cases where automated perimeter is unreliable. Blue-on-yellow perimetry may detect visual field abnormalities earlier and identify them as larger in size than traditional white-on-white perimetry (Girkin et al. 2000; Johnson et al. 1993a, 1993b, 1995; Sample & Weinreb 1992; Teesalu et al. 1998; Ugurlu et al. 2000) (C).

**Glaucoma screening**

The purpose of screening for a symptom-free population is to find disease in its early phases, in order for treatment to be as effective as possible and/or in order to detect individuals with a greater susceptibility to the disease (Pelkonen 2000). Although this guideline deals with evaluation of screening methods, their financial aspects are also important. Recommendations for glaucoma screening are presented in Table 6.

**Intraocular pressure**

Measurement of IOP is insufficient for glaucoma screening. Its usefulness is limited by low sensitivity and specificity (Bengtsson 1981; Klein et al. 1992).

---

**Table 5.** Visual field test strategies. Visual field test strategies recommended for the diagnosis and the follow-up are presented in **bold.** The strategies are presented in the order in which they were created.

<table>
<thead>
<tr>
<th>EXAMINATION STRATEGY</th>
<th>HUMPHREY</th>
<th>OCTOPUS</th>
<th>Reduction of test time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional thresholding test</td>
<td>Full threshold (1, 2)</td>
<td>Normal (3)</td>
<td>**</td>
</tr>
<tr>
<td>Accelerated traditional test</td>
<td>Fastpac (4, 5, 6, 7)</td>
<td>Dynamic (8)</td>
<td>**</td>
</tr>
<tr>
<td>Fast thresholding strategy</td>
<td>SITA standard (1, 2, 9, 10, 11, 12)</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Super fast strategy</td>
<td>SITA Fast*** (1)</td>
<td>TOP** (13, 14, 15)</td>
<td>**</td>
</tr>
</tbody>
</table>

Sommer et al. 1991) (A). In a screening study of an adult population, more than half of individuals with glaucoma had IOP within the normal range (Sommer et al. 1991).

Examination of ocular fundus
In one population-based study, no distinct parameters could be found to describe the structures of the optic nerve head which would sufficiently distinguish glaucoma patients from healthy individuals (Tieltsch et al. 1991) (B). Ophthalmoscopic examination of the fundus has proven too demanding in mass screening studies. There may be considerable variation in the evaluation of glaucomatous abnormalities even among experienced ophthalmologists (Coleman et al. 1996; Lichter 1976) (C), see also (Caprioli et al. 1996; Ugurlu et al. 2000; Varma et al. 1992).

Retinal nerve fibre layer
There is insufficient experience in the use of nerve fibre layer images in large scale mass screening studies, but screening in selected populations has given good results (Komulainen et al. 1992; Niessen et al. 1997; Tuulonen et al. 1990; Wang et al. 1994) (C).

Visual field examination
Visual field threshold examination used for diagnostics has not been shown to be a useful method of screening (Quigley 1998; Shields 1995). Even if several instruments have been used with reasonably good results (Johnson & Samuels 1976) (C), see also (Caprioli et al. 1996; Ugurlu et al. 2000; Varma et al. 1992).

Treatment efficacy
The purpose of treatment is to prevent glaucoma induced visual disability. There are relatively few studies published on treatment efficacy in prevention of glaucomatous damage. The majority of studies concentrate on the IOP-lowering effect of the treatment as lowering IOP is, so far, the only treatment modality for glaucoma.

Treatment efficacy in ocular hypertension
The reduction of IOP delays or prevents glaucomatous damage in patients with ocular hypertension (Kass et al. 2002) (B). In the Ocular Hypertension Treatment Study (OHTS), half of the 1636 patients received topical medication while the control subjects were untreated (Gordon et al. 1999; Kass et al. 2002). Initial IOP levels were 24–32 mmHg. The goal was to reduce IOP by at least 20% and below 24 mmHg. IOP readings below 18 mmHg were not required (Kass et al. 2002). All commercially available topical ocular hypertensive medications were used. In 40% of patients, at least two medications had to be used to achieve the target pressure.

During the 5-year follow-up, 4% of the treated eyes and 10% of the control eyes developed glaucomatous visual field and optic disc abnormalities. Visual field progression was detected in 2% of treated patients and in 4% of control subjects (Kass et al. 2002). Increases in age, cup-disc ratio, IOP and corrected pattern standard deviation (CPSD) and decreases in corneal thickness predicted the development of glaucomatous changes (Gordon et al. 2002).

In previous studies, topically administered timolol alone has not been shown to prevent development of glaucomatous abnormalities in patients with elevated IOP (22–30 mmHg) without optic disc and visual field abnormalities (Epstein et al. 1989; Heijl & Bengtsson 2000; Kass et al. 1989; Ontoso et al. 1997; Rossetti et al. 1993; Schulzer et al. 1991) (B). In these reports, drawing conclusions is difficult due to indistinctly defined diagnoses, small patient samples and a large number of dropouts.

Treatment efficacy in open-angle glaucoma
The Early Manifest Glaucoma Trial (EMGT) is the first adequately powered, randomized trial with an untreated control arm to evaluate the effects of IOP reduction in open-angle glaucoma (Heijl et al. 2002; Leske et al. 1999). Intent-to-treat analysis showed beneficial effects of treatment (B). Progression was less frequent in the treated group (45%) than in control group (62%) and occurred significantly later in treated patients.

The EMGT patients, mainly identified by a population screening, were randomized to laser trabeculoplasty and topical betaxolol (n = 129) or no initial treatment (n = 126) with close follow-up (visual fields every 3 months and disc photography every 6 months). The median IOP was 20 mmHg. Patients with IOP >30 mmHg or advanced field loss were excluded. After follow-up of 6 years, treatment reduced IOP by 25% (5 mmHg). While progression rates varied across patient categories, treatment effects were present in older and younger patients, in high and normal tension glaucoma, and in eyes with less and more field loss. Increases of clinical nuclear lens opacity gradings were associated with treatment.

In the Collaborative Normal Tension Glaucoma Study, control subjects with manifest glaucoma were followed for 5 years without treatment. The intent-to-treat analysis showed no difference in progression rates between treated and untreated patients. The protective efficacy of the treatment could be demonstrated only after later modifica-

Table 6. Is screening for glaucoma worthwhile?

<table>
<thead>
<tr>
<th>Table 6. Is screening for glaucoma worthwhile?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A national mass screening in the public sector</td>
</tr>
<tr>
<td>A recommendation for Finnish people at their own initiative</td>
</tr>
<tr>
<td>An ocular examination performed by an ophthalmologist</td>
</tr>
<tr>
<td>Age 40–45–&gt;60 years Every 3 years</td>
</tr>
<tr>
<td>Over the age of 60 Every 3 years</td>
</tr>
<tr>
<td>More often if deemed necessary by an ophthalmologist, in particular in individuals with several risk factors such as myopia and/or family history of glaucoma (see Table 2).</td>
</tr>
</tbody>
</table>
tion of the progression criteria and correction of the visual fields for cataract (Collaborative Normal Tension Glaucoma Study Group 1998a, 1998b, 2001).

In the Advanced Glaucoma Intervention Study (AGIS), IOP was lowered with laser and surgical treatment in patients in whom the efficacy of medical treatment was insufficient. The correlation between IOP and progression of abnormalities was not statistically significant (AGIS Investigators 1994; 1998, 2000). The efficacy of the treatment could be demonstrated only with a post hoc analysis. When the patient material was divided into subgroups defined retrospectively, the group with IOP < 14 mmHg seemed to have the least amount of progression. However, the subgroups were not randomized and were not comparable at the beginning of the study, which may cause selection bias.

Methods of lowering intraocular pressure

Methods of selection of glaucoma treatment and treatment goals are presented in Fig. 1 and Table 7.

Medical treatment

Lowering the intraocular pressure is currently the only form of treatment for glaucoma. Some medications have been promoted as having a beneficial effect on ocular blood flow as well as on the survival of ganglion cells (so-called neuroprotection) but there are no adequate controlled clinical trials to support these theoretical effects.

The IOP-lowering effect of medications should be determined individually. The IOP-lowering efficacy is not presented either in mmHg or in percentages in the official book of medications in Finland (Pharmacca Fennica, Helsinki). There are two meta-analyses on scientific reports from 1967 to 1995 on the IOP-lowering effect of timolol in ocular hypertension (Ohtsuki et al. 1997; Rossetti et al. 1993). According to six placebo-controlled studies, beta-blocker treatment lowers IOP on average by 4.9 mmHg (95% CI 2.5–7.3 mmHg) (Rossetti et al. 1993).

A meta-analysis would also be the most reliable means for comparing the IOP-lowering effect of various medications in patients with manifest glaucoma. However, no such analysis is available. The results available from published studies vary according to the trial setting, thus complicating significantly the comparability of the results. Usually a medication has been compared to another preparation, which again varies from one study to the next. There are hundreds of published papers on some medications, but information is very scanty on some of the more recent compounds. In such cases, pharmacological companies and health care authorities have data on-file. Drug registration information in the National Agency for Medicines in Finland is secret and will not be made accessible to outsiders. As a meta-analysis is not available, the degree of evidence of the IOP-lowering effect of various glaucoma medications is not determined in this guideline.

In general, treatment compliance with glaucoma medication is poor (Granström 1982; Patel & Speth 1995; Rotchkford & Murphy 1998; Zimmerman & Zalta 1983) (B). According to some studies, up to half of patients do not comply with their treatment plan and one fifth of patients in whom treatment has been initiated do not attend check-up visits. The most common systemic side-effects of glaucoma drugs are presented in Table 8.

Laser trabeculoplasty

When laser trabeculoplasty is given as primary therapy, approximately half of patients do not require medication for 1–2 years after treatment (Bergé et al. 1995; Glaucoma Laser Trial Research Group 1995a; Southampton 1996; Tuulonen et al. 1989) (A). The IOP-lowering effect of laser trabeculoplasty diminishes by approximately 8% per year (Chung et al. 1998; Eendebak et al. 1990) and follow-up of up to 7 years has indicated that only 20% of patients manage without medical treatment (Glaucoma Laser Trial Research Group 1995b). However, fewer medications are needed if glaucoma treatment is initiated with laser trabeculoplasty (Glaucoma Laser Trial Research Group 1995b).

Cyclophotocoagulation

According to short-term follow-up studies, transscleral Krypton laser cyclophotocoagulation is often an effective and well-tolerated means of lowering IOP in refractory glaucoma but the need for repeated treatments is frequent (Bloom et al. 1997; Gupta & Weinreb 1997; Immonen et al. 1994; Kosoko et al. 1996; Spencer & Vernon 1999; Threlkeld & Johnson 1999; Yap-Veloso et al. 1998) (D). Prior to cyclophotocoagulation, patients should be given additional IOP-lowering medication in order to avoid post laser pressure spikes (Immonen et al. 1994; Kosoko et al. 1996; Yap-Veloso et al. 1998) (B).

Surgical treatment

Surgical treatment reduces IOP more than medical or laser treatment (AGIS Investigators 1998; Lichter et al. 2001; Migdal et al. 1994) (A). Moreover, the diurnal variation of IOP is better controlled with surgical treatment (Migdal et al. 1994) (B). In spite of lower levels of IOP, surgical treatment did not reduce the incidence of progression of visual field defects during a 5-year follow-up period, when preoperative IOP was less than 30 mmHg in the Collaborative Initial Glaucoma Treatment Study (CIGTS) (Lichter et al. 2001) (B). On the other hand, early surgical treatment has been reported to slow the progression of visual field damage more than laser or medical treatment if initial IOP is high (> 30 mmHg) (Dastur 1994; Jay & Murray 1988; Migdal et al. 1994) (A). Surgically treated patients need cataract surgery more often than medically treated patients (Lichter et al. 2001) and they complain more about local eye problems (Janz et al. 2001).

The visual field defects may progress despite the decrease in IOP after trabeculectomy (AGIS Investigators 2000; Chen et al. 1997; Migdal et al. 1994; Molteno et al. 1999; Nouri-Mahdavi et al. 1995; Roth et al. 1991; Watson et al. 1990) (B). It has not been possible to determine any clear cut-off IOP value, which would prevent all progression in surgically treated patients (AGIS Investigators 2000; Watson et al. 1990).

There is no general agreement on the criteria for successful glaucoma surgery in the literature. The success rate of trabeculectomy varies considerably from one study to another depending on the criteria used, for example 26–98% during 5 years (AGIS Investigators 2000; Bauer et al. 1995; Chen et al. 1997; Jerndal & Lundström 1980; Migdal et al. 1994; Molteno et al.
Should glaucoma be treated or followed without treatment?

<table>
<thead>
<tr>
<th>Patient’s age and life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of glaucoma (both eyes)</td>
</tr>
<tr>
<td>Rate of progression: how rapidly the changes have progressed</td>
</tr>
<tr>
<td>Intraocular pressure: at which level the damage has appeared</td>
</tr>
<tr>
<td>Risk factors</td>
</tr>
<tr>
<td>Patient’s other (ocular) diseases, medication and allergies and possible pregnancy*</td>
</tr>
</tbody>
</table>

**Decision to initiate the treatment**

- Beta blockers
- Prostaglandins
- Alfa-agonist
- CAI** (topical)
- Pilocarpine
- Laser trabeculoplasty
- Ophthalmologist chooses the treatment
  - If no response -> change medication, use a combination when needed
  - Consider carefully is you wish to add the 3rd bottle into the medication
  - Note possible need for IOP and cataract operation

No or insufficient response or the above mentioned therapy forms are not suitable or the changes progress in spite of the lowered IOP level

- Filtration surgery
- Combined cataract and filtration surgery or cataract surgery
- Shunt surgery
- Cyclophotocoagulation
- The ocular surgeon chooses the method of operation

![Diagram](image)

Fig. 1. How to select glaucoma treatment (use also Tables 3 and 4).

*Most drugs cannot be used during pregnancy. Beta-blockers and pilocarpine may be used. Always consult the obstetrician about the use of glaucoma medication during pregnancy.

**Oral product designed mainly for temporary use.

1999; Nouri-Mahdavi et al. 1995; Roth et al. 1991; Watson & Grierson 1981; Watson et al. 1990). Long follow-up times (10–15 years) have been reported only in retrospective studies, in which the data are incomplete for the majority of patients (70–96%) (Jerndal & Lundström 1980; Molteno et al. 1999; Watson et al. 1990).

Two Cochrane reviews have been published on the use of antimetabolites in glaucoma surgery (Wilkins et al. 2002; Wormald et al. 2000). 5-fluorouracil is beneficial if the risk for failure of trabeculectomy is high (Wormald et al. 2000) (C). The poor quality of the studies may, however, have led to introduction of systemic bias and overestimation of the effect. The review provides no good evidence to justify the routine use of 5-fluorouracil injections in trabeculectomy.

During short-term follow-up, mitomycin C reduces mean IOP after trabeculectomy more than placebo both in high risk eyes and those undergoing surgery for the first time (Wilkins et al. 2002) (A). No significant effect on failure was noted in the group undergoing trabeculectomy combined with cataract extraction. The general quality of studies was low. In none of the studies was visual field preservation used as an outcome measure. None of the trials were large enough or of sufficient duration to address the longterm risk of bleb infection and endophthalmitis. Mitomycin C increases the risk of cataract.

Glaucoma shunts are no more effective than trabeculectomy if the patient does not have risk factors for increased conjunctival fibrosis (Välimäki 1998; Wilson et al. 2000) (C). The IOP-lowering effect of deep sclerectomy does not differ significantly from that of trabeculectomy after short-term follow-up, but it has been shown to have less
postoperative complications (El Sayyad et al. 2000; Mermoud et al. 1999) (B). There are no controlled studies published so far. Phacoemulsification and intraocular lens (IOL) implantation decreases IOP by 3–4 mmHg in glaucoma patients, who have a low or moderately increased IOP preoperatively. The risk of postoperative pressure peaks has to be considered (Gimbel et al. 1995; Kim et al. 1999; Perasalo 1997; Pohjalainen 1997; Pohjalainen et al. 2001; Storr-Paulsen et al. 1998; Yalcın et al. 1997) (B).

Combined trabeculectomy-phacoemulsification reduces IOP 6–8 mmHg (Gimbel et al. 1995; Mamalis et al. 1996; Wedrich et al. 1995).

Glaucoma follow-up

Glaucoma is usually a slowly progressive disease where the rates of change to the nerve fibre layer, optic disc and visual field abnormalities vary greatly between patients. It can take several years to detect progression of abnormalities (Collaborative Normal Tension Glaucoma Study Group 1998a, 1998b, 2001; Heijl et al. 2002; Odberg & Riise 1985; Pohjanpelto 1985; Rasker et al. 2000) (A). In patients under treatment, the time between the appearance of the first visual field changes to blindness is estimated to vary from 30 to 40 years (Bergera et al. 1995; Jay & Murdoch 1993; Quigley et al. 1996; Rasker et al. 2000) (C).


The frequency of progression is increased by patient’s age (Caprioli et al. 1996; Katz et al. 1997; Lichter et al. 2001; Migdal et al. 1994; Musch et al. 1999) (B).

Table 7. The goals of the glaucoma treatment and the target IOP. The treatment goal is to prevent glaucoma induced visual disability.

The goal of lowering the 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 patient (1, 2, 3, 4, 5, 6, 7). Target IOP has to be updated during check-ups by monitoring the progression of structural and visual field abnormalities (see Fig. 2).

IOP reduction

If the treatment is started the IOP should be lowered by at least 25% from the initial level (2, 8, 9)

<table>
<thead>
<tr>
<th>Initial IOP (mmHg)</th>
<th>Minimum target IOP (~25%) (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;12</td>
<td>&lt;10</td>
</tr>
<tr>
<td>12–14</td>
<td>9–11</td>
</tr>
<tr>
<td>14–16</td>
<td>11–12</td>
</tr>
<tr>
<td>16–18</td>
<td>12–14</td>
</tr>
<tr>
<td>18–20</td>
<td>14–15</td>
</tr>
<tr>
<td>20–24</td>
<td>15–17</td>
</tr>
<tr>
<td>24–26</td>
<td>17–18</td>
</tr>
<tr>
<td>26–29</td>
<td>18–20</td>
</tr>
</tbody>
</table>

The target IOP level may be even lower if there is

Far advanced glaucoma
Aggressive glaucoma
Several risk factors
Long life expectancy

Table 8. Most common systemic side-effects of glaucoma drugs.

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug</th>
<th>Systemic side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-agonists</td>
<td>apraclonidine,</td>
<td>Dry mouth, taste aversion, reduced heart rate, reduced</td>
</tr>
<tr>
<td></td>
<td>brimonidine</td>
<td>blood pressure, fatigue</td>
</tr>
<tr>
<td>Beta-blockers Non-selective</td>
<td>timolol</td>
<td>Bradycardia, arterial hypotonia, asthma, dizziness, sleep</td>
</tr>
<tr>
<td></td>
<td>carteolol</td>
<td>disturbances, depression, nausea. Non-selective beta-blockers are contraindicated in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>patients with asthma, sinus bradycardia, arterial hypotonia, untreated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic side-effects are more rare but are the same as with non-selective beta-blockers</td>
</tr>
<tr>
<td>Carbonic-anhydrase inhibitors</td>
<td>acetazolamide</td>
<td>Fatigue, dizziness, gastrointestinal disturbances, metabolic acidosis, depression,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>paresthesias, allergic reactions, low potassium values, renal stones</td>
</tr>
<tr>
<td></td>
<td>dorzolamide</td>
<td>Taste aversion, dry mouth. Other systemic side-effects of sulphonamides and carbonic</td>
</tr>
<tr>
<td></td>
<td>brinzolamide</td>
<td>anhydrase inhibitors are also possible</td>
</tr>
<tr>
<td>Prostaglandin analogs</td>
<td>latanoprost</td>
<td>No known common systemic side-effects</td>
</tr>
<tr>
<td></td>
<td>travoprost</td>
<td></td>
</tr>
<tr>
<td></td>
<td>unoprostone</td>
<td></td>
</tr>
<tr>
<td>Parasympathomimetics</td>
<td>pilocarpine</td>
<td>Head ache at the beginning of treatment</td>
</tr>
<tr>
<td></td>
<td>carbacol</td>
<td>Other systemic side-effects are rare</td>
</tr>
</tbody>
</table>

In one third of patients, progression of optic disc changes precedes the abnormalities detected by automated perimetry (Girkin et al. 2000; Heijl & Bengtsson 1989; Katz et al. 1997; Odberg & Riise 1985; Tuulonen & Airaksinen 1991) (B). It may be necessary 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 using the same examination programme with the same instrument (Glaucoma Laser Trial Research Group 1995a; Kass et al. 2002; Keltner et al. 2000; Schulzer et al. 1994) (A). When visual field examination was repeated only once or twice, the progression of visual field abnormalities could not be confirmed in half of patients (Glaucoma Laser Trial Research Group 1995a; Schulzer et al. 1994). When the visual fields in patients with ocular hypertension were examined an average of three times per year for 5 years, the appearance of a visual field abnormality was noted in 0.5% of the visual fields (Keltner et al. 2000).

Doubling the frequency of visual field examinations shortens the time to detection of a statistically significant linear mean defect (MD) index change by approximately one third (Smith et al. 1996). It has been estimated that detection of visual field progression takes 5 years when the visual fields are examined only once a year and progression is monitored with visual field indices.

The literature does not provide any generally used or accepted definition of the criteria of visual field progression (Birch et al. 1995; Katz et al. 1999; Smith et al. 1996) (C). When the visual field criteria of three randomized studies (AGIS, EMGT and CIGTS) were applied to a patient material, the conformity on progression was only 25% (Katz et al. 1999). A recommendation for a glaucoma follow-up pattern is presented in Fig. 2. Guidelines on how to treat and follow high risk glaucoma patients are presented in Table 9.

**Quality of care**

The impact of glaucoma on quality of life

Glaucomatous visual field damage lowers the quality of life of a glaucoma patient. The degree of deterioration correlates with the severity of the visual field damage. However, unless the field defect is very severe, the quality of life is more affected by the subjective threat of loss of vision than by glaucomatous abnormalities themselves (Bour et al. 1993; Gutierrez et al. 1997; Janz et al. 2001; Mills 1998; Odberg et al. 2001; Parrish et al. 1997; Perfetti et al. 1998; Sherwood et al. 1998; Wändell et al. 1997; Wilson et al. 1998; ) (B). Further problems are caused by the practical inconvenience of constant and regular therapy and control visits. The patient is likely to comply more successfully when they are given personalized information and guidance (Busche & Gramer 1997).

**Quality control of glaucoma care**

The official statistics provided by Finnish health care organisations are not suited for the quality assessment and quality control of the diagnosis and treatment of glaucoma. A computer-aided monitoring program of the quality of glaucoma care has been developed at the Eye Research Institute, University of Kuopio (Glaucoma Laser Trial Research Group 1995a).

**References**

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

Typical characteristics of high-risk glaucoma patients
1. Rapidly progressing glaucomatous changes independent of the IOP level
2. The patient has definitive optic disc, RNFL and visual field abnormalities with an IOP over 30–35 mmHg (Ekström 1996; Sommer et al. 1991)
3. Strong family history
4. Several risk factors (in addition to the above)
   - Myopia, exfoliation
   - Problems with blood circulation

Guideline on how to treat and follow high-risk glaucoma patients
1. Aggressive lowering of the intraocular pressure (1, 2)
   - In patients with high pressure level* at least <20 mmHg (3)
   - At lower pressure levels at least 30% IOP lowering (4, 5)
   - One drug (or laser treatment alone) is usually not sufficient (6)
   - Very easily surgical treatment (7, 8, 9)
2. Frequent follow-up
   - Daily/weekly (monthly) until the pressure is low enough and/or progression has stopped

* Do not forget to check gonioscopy to rule out closed angle glaucoma.

References

Bengtsson B & Heijl A (1999a): Inter-subject variability and normal limits of the SITA Standard, SITA Fast, and the Humphrey


Rasker MTE, van den Enden A, Bakker D &, Ringvold A, Blika S, Elsa˚sT
Sample PA & Weinreb RN (1992): Progressive
Rouhiainen H & Tera¨svirta M (1990): Inci-
Roth SM, Spaeth GL, Starita RJ, Birbillis EM &
Schulzer M & the Normal Tension Glaucoma
Sherwood MB, Garcia-Siekavizza A, Meltzer
Smith SD, Katz J & Quigley HA (1996): Ana-
Sponsor WE, Ritch R, Stamper R, Higginbo-
Spencer R (1998): Glaucoma screening. [Editor-
torial.] J Glaucoma 7: 149–150.
Stein-Paulsen, Pedersen JH & Laugesen C (1998): A prospective study of combined phacoemulsification-trabeulectomy versus conventional phacoemulsification in catar-
act patients with coexisting open-angle glau-
Tezel G, Kass MA, Kolker AE & Wax MB (1996): Comparative optic disc analysis in normal pressure glaucoma, primary open-
Tuulonen A, Airaksinen PJ (1991): Initial glaucomatous optic disc and retinal nerve fibre layer abnormalities and their progres-
Tuulonen A, Jonas JB, Välimäki S, Alanko HI & Airaksinen J (1996): Interobserver variation in the measurements of peripapillary atro-
Tuulonen A, Koponen J, Alanko HI & Airaksinen PJ (1989): Laser trabeculectomy versus medication treatment as primary ther-
Tuulonen A, Lehtola J & Airaksinen PJ (1993): Nerve fibre layer defects with normal visual fields. Do normal optic disc and normal visual field indicate absence of glaucom-
atous damage? Ophthalmology 100: 587–598.
Ugurlu S, Hoffman D, Garway-Heath DF & Caprioli J (2000): Relationship between structural abnormalities and short wave-
Watson PG & Grierson I (1981): The place of trabeculotomy in the treatment of glau-


Received on August 19th, 2002. Accepted on October 17th, 2002.

Correspondence:
P. Juhani Airaksinen
Department of Ophthalmology
University of Oulu
Box 5000
FIN-90014
Finland
Tel: +358 8 315 33 49
Fax: +358 8 315 3351
Email: juhani.airaksinen@oulu.fi