Evidence Synthesis
Number 34

Primary Care Screening for Ocular Hypertension and Primary Open-Angle Glaucoma: Evidence Synthesis

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0024
Task Order No. 2
Technical Support of the U.S. Preventive Services Task Force

Prepared by:
Oregon Evidence-based Practice Center
Portland, Oregon

Craig Fleming, MD
Evelyn Whitlock, MD, MPH
Tracy Beil, MS
Barbara Smit, MD, PhD

March 2005

Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) and Evidence Syntheses through its Evidence-based Practice Program. With guidance from the U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, the Oregon Evidence-based Practice Center systematically reviews the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, and chemoprevention, in the primary care setting. The SERs and Evidence Syntheses—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER and Evidence Synthesis.

The SERs and Evidence Syntheses document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs and Evidence Syntheses on the AHRQ Web site (http://www.ahrq.gov/clinic/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs and Evidence Syntheses) and recommendations of the USPSTF in print and on the Web. These are available through the AHRQ Web site and through the National Guideline Clearinghouse (http://www.ngc.gov).

We welcome written comments on this Evidence Synthesis. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Suite 3000, Rockville, MD 20850, or e-mail uspstf@ahrq.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P. A., M.S.P.H.
Director
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

*The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, and chemoprevention--in the primary care setting. AHRQ convened the current USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

Acknowledgments

This Evidence Synthesis was funded by the Agency for Healthcare Research and Quality (AHRQ) for the U.S. Preventive Services Task Force (USPSTF), and the investigators acknowledge the contributions of Gurvaneet Randhawa, MD, MPH, Task Order and Medical Officer, AHRQ. Members of the USPSTF who served as leads for this project include: Alfred O. Berg, MD, MPH; and Russell Harris, MD, MPH. Additional members of the Oregon EPC project team include Daphne Plaut, MLS, research librarian. The authors would like to thank Steven L. Mansberger, MD, MPH, and the other reviewers for their contributions to this project.

Request for Reprints

Reprints are available from the AHRQ Web site at www.ahrq.gov (click on Preventive Services) and in print through the AHRQ Publications Clearinghouse (call1-800-358-9295).

Disclaimer

The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Structured Abstract

Purpose: Primary open-angle glaucoma (POAG) is a leading cause of blindness and vision-related disability. This review examines the effectiveness of screening and treatment of asymptomatic individuals with early POAG.

Methods: We identified studies of glaucoma screening and treatment from MEDLINE, the Cochrane Library, and glaucoma experts. Two reviewers abstracted relevant studies and graded articles according to U.S. Preventive Services Task Force criteria.

Data Synthesis: No randomized, controlled trials of population screening for POAG have been reported. We found no population-based studies demonstrating that screening is feasible, accurate, or reliable for detecting early glaucoma. Two randomized, controlled trials examined the efficacy of treatment to lower intraocular pressure (IOP) compared with no treatment for persons with early primary open-angle glaucoma. In a Swedish trial, treatment reduced progression at 5 years from 62% without treatment to 45% with treatment (ARR 17%, NNT 5.8, $p = 0.007$). In a U.S. trial of patients with early POAG and normal IOP, progression at 5 years was observed in 39% without treatment and 33% with treatment ($p = 0.21$). The benefit of delaying progression of visual field loss on vision-related function in patients with early POAG is unclear. The principal harm of treatment is loss of visual acuity due to an increased risk of cataract formation.

Conclusions: Treatment to lower intraocular pressure may delay progression of visual field deficits in some asymptomatic individuals with early POAG. Further studies of population screening are needed to demonstrate that early recognition and treatment of glaucoma in asymptomatic patients is effective in improving vision-specific functional outcomes and health-related quality of life

Contents

Figure

Table

Appendixes

Chapter 1. Introduction

Glaucoma is a progressive optic neuropathy that results in structural changes in the optic nerve head and visual field defects that may lead to severe visual impairment or blindness. Glaucoma may arise secondary to other causes such as trauma, steroid therapy, or inflammatory processes such as uveitis. Most cases of glaucoma, however, have no identifiable etiology and are termed *primary glaucoma.* Glaucoma is also classified as either *open-angle glaucoma,* in which the angle between the cornea and the pupil is normal, or *closed-angle glaucoma,* in which this angle is narrowed.

Primary open-angle glaucoma (POAG) is the most prevalent type in the U.S. population. Based on estimates for the year 2000, 2.5 million people in the U.S. have POAG, of whom 130,000 will be blind as a result of the disease.[1] Half of those with POAG may not be aware they have the disease.[2,3] The pathogenesis of optic nerve damage in POAG is not well understood, but is likely multifactorial.[4] The primary risk factor for development of POAG is an increase of intraocular pressure (IOP) above 21 mm Hg, which is considered to be the upper limit of normal for IOP. In population studies, increasing IOP is associated with an increased prevalence of POAG.[3,5,6] Increased IOP was once considered a defining feature of POAG. However, a significant proportion (25-50%) of individuals with primary glaucomatous optic disc changes and visual field deficits have normal IOP measurements, a condition known as normal-tension glaucoma (NTG). As a result, increased IOP is no longer considered to be part of the definition of POAG.[4]

Race is also an important risk factor for POAG. There is a four-fold increase in the prevalence of POAG in persons of African descent. In a population survey conducted in East Baltimore, the prevalence of POAG was 4.2% in blacks vs. 1.1% in whites.[7] Since the distribution of IOP is similar between blacks and whites,[5] other pathogenic factors must account for this difference.

The incidence and prevalence of POAG also increase with age. The prevalence of POAG in whites is less than 1.0% for those younger than 70, and 2-3% for those older than70. In blacks, the prevalence increases progressively from approximately 1% in those aged 40-49 to 11% in those older than 80.[7] Family history is also an important risk factor, indicating that glaucoma is partly attributable to genetic factors. For example, there is an approximately four-fold increase in risk of POAG in siblings of patients with glaucoma.[8] Additional risk factors may include decreased central cornea thickness; low diastolic perfusion pressures (diastolic blood pressure – intraocular pressure); diabetes; and severe myopia.[9]

There have been no long-term, prospective studies of untreated patients with POAG. As a result, the natural history of POAG is not well understood. Based on estimates derived from a case-series of patients with newly diagnosed POAG, the time of progression to blindness varies from 3 years in patients with IOP measurements > 30 mm Hg to 14 years in patients with IOP measurements in the range of 21-25 mm Hg.[10] A model based on cross-sectional data in a population with POAG predicts that the average 40-year-old person presenting with initial visual field deficits would not progress to blindness until the age of 80.[11] The average 60year-old person presenting with initial visual field deficits would not progress to blindness in either eye during his or her expected lifetime. Overall progression of visual field deficits develops in a linear fashion over time,[11] although progression is faster with higher levels of IOP.[10] Although

glaucoma is a frequent cause of blindness,[1] estimated rates of progression do not appear sufficient to lead to complete blindness during the lifetime of the majority of those affected.[11]

Since IOP is the only modifiable risk factor in POAG, the cornerstone of glaucoma therapy is IOP reduction. Treatment options include topical medications, systemic medications, laser surgery, and incisional surgery, alone or in combination. In recent years, several large randomized clinical trials have examined the benefits of various treatment strategies for both increased IOP without glaucoma (ocular hypertension), and glaucoma, with and without increased IOP.[12-14] To update prior USPSTF recommendations, we critically reviewed these recent studies for quality and strength of evidence to support treatment and screening for POAG.

Chapter 2. Methods

The Oregon Evidence-based Practice Center performed an evidence synthesis with particular focus on the critical examination of glaucoma treatment trials published since the 1996 USPSTF recommendation was issued. In addition, we looked for new information regarding harms of either treatment or screening.

As a prelude to this review, the Research Triangle Institute-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) conducted a preliminary literature review to determine if a sufficient amount of new evidence existed to warrant a more complete evidence synthesis. The RTI-UNC EPC conducted a MEDLINE search for new studies from 1994 through 2002. In addition, 11 expert reviewers were contacted for comments. We used the RTI-UNC EPC search strategy, keywords, and terms to conduct additional searches from January 2001 through January 2004 (Appendix A). Titles and abstracts from the RTI-UNC EPC review and our updated search were downloaded into an electronic bibliographic database. Titles and abstracts were reviewed for possible inclusion by two investigators [CF, EW] based on specific inclusion/exclusion criteria. (Appendix B) We obtained copies of all studies meeting the inclusion criteria. In addition, we obtained studies cited by the RTI-UNC EPC expert reviewers or identified through our expert contacts, from the 1996 USPSTF recommendation,[15] and from review of study bibliographies. We rated trials meeting inclusion criteria for quality based on accepted USPSTF criteria.[16] Study quality was rated as good if adequate randomization methods were used; treatment and control groups were comparable at baseline; loss to follow-up was accounted for and comparable groups were maintained throughout the study; outcomes were determined by objective criteria or by assessors masked to group randomization assignment; appropriate statistical methods were used; and analysis was based on intent-to-treat. To guide our review, we focused on a set of key questions addressing the benefits and harms of treatment and screening (Figure 1).

Chapter 3. Results

Our combined database searches located 246 abstracts and titles for review. Seven citations were identified from these searches along with 12 from the 2002 review and 7 from outside sources, with 4 duplicates eliminated. After reviewing the 22 full-text articles, 13 were included in the update, 8 were excluded (Appendix C), and one article described an ongoing study. Appendix D summarizes the MEDLINE search and retrieval results.

Key Question 1. Is there new evidence that screening for open-angle glaucoma reduces severe visual impairment?

We found no studies assessing the screening and treatment of open-angle glaucoma in a population setting.

Key Question 3. Is there new evidence that feasible screening tests are accurate and reliable in detecting increased intraocular pressure or open-angle glaucoma?

The diagnosis of POAG is based on the finding of characteristic degenerative changes in the optic disc, along with a progressive loss of visual field sensitivity and development of scotomas, or blind spots in the field of vision. In addition, the angle between the iris and the cornea, which together form the anterior chamber of the eye, must be "open" or normal. Secondary causes of glaucoma, such as steroid use or trauma, must also be excluded. The finding of increased IOP, once considered a part of the definition of POAG, is no longer required, since IOP may be persistently normal in 25-50% of those with glaucomatous optic nerve damage.[4] In such patients, a definitive diagnosis of glaucoma may require demonstration of progressive visual loss over time, since non-progressive glaucomatous damage may also be seen on a single exam when secondary causative factors, such as prior steroid use, are no longer present.[17]

Progressive changes in the optic nerve head are characteristic of POAG, and may include increased cupping of the optic nerve head, asymmetry in the amount of cupping between eyes, and optic disc hemorrhages. Either direct ophthalmoscopy of the dilated eye or slit lamp examination may be used to examine the optic nerve head. Direct ophthalmoscopy has a reported sensitivity of 59% and a specificity of 73% in detecting and classifying optic disc changes associated with glaucoma.[18] Even among experts, however, there is wide variability in both interobserver agreement and intraobserver reliability in detecting glaucomatous optic disc progression.[19] Consequently, using current methods, optic nerve assessment is neither a practical nor reliable tool for population screening.

Although increased intraocular pressure is a principal risk factor for glaucoma, the effectiveness of IOP measurement as a population-screening tool for either ocular hypertension or POAG is limited. In one population-based survey, increased IOP above 21 mmHg, the usual cutoff point for the diagnosis of ocular hypertension, was found to have a sensitivity of 47.1% and a specificity of 92.4% for diagnosing glaucoma. There was no value of IOP that provided a reasonable balance of sensitivity and specificity, and tonometry did not perform better in high-risk groups defined by age, race, gender, or family history.[7] Because IOP fluctuates over time and diurnally, 50% of those with increased IOP may have normal readings on a single measurement. The performance of tonometry, as a test for ocular hypertension or POAG, also varies based on the proportion of those having either condition in the test population (i.e., spectrum bias), as well as other biases that affect evaluations of its performance.[20] Also, while the risk of glaucoma rises with increasing IOP, most individuals with ocular hypertension will never develop glaucoma.[3,5,21]

Characteristic patterns of visual field loss also assist in making a definitive glaucoma diagnosis.[11] *Perimetry* is a technique for assessing visual field loss by mapping a patient's response to visual stimuli presented in various locations within the visual field. Perimetry may be performed by manual or automated methods. The sensitivity and specificity of perimetry varies based on the method used, the cutoff point for defining visual field defects, as well the test used as the gold standard.[22] At the present time, perimetry has a limited role in population-screening programs because of the expense of equipment, the amount of time necessary for testing (up to 10-20 minutes per eye), and the relative lack of portability of most instruments.

One instrument, the Henson Visual Field Analyzer, is already in use for population screening by the organization Prevent Blindness America. In a study of this instrument, no abnormal results were found in a test of 82 normal subjects.[23] In 83 cases of glaucoma and suspected glaucoma referred to specialty clinics, the test identified 38 of 39 who had moderate to severe visual field loss and 49 of 58 patients who had any abnormality on visual field testing using Humphrey perimetry as a gold standard. While this indicates that this instrument may have both high sensitivity and specificity in diagnosing glaucoma, assessment of its true sensitivity and specificity would require further evaluation in an unselected population setting.

A newly developed technique for assessing visual field loss, frequency-doubling technology (FDT) perimetry, holds promise as a screening instrument because of its portability, ease of administration, and short time required for testing. Using a rapid screening mode, the test may be performed in less than 90 seconds.[24] In a study of 137 patients referred to a glaucoma specialist, the test had a reported sensitivity of 95% and a specificity of 93% for detecting moderate to severe glaucoma.[25] As for the Henson Visual Field Analyzer, population studies of FDT perimetry are needed to determine its true performance as a screening tool. Studies examining the use of the Henson Visual Field Analyzer and FDT perimetry in larger populations are reportedly under way or nearing publication.

The benefit of any screening program may be limited by the low prevalence of glaucoma in the general population.[24,26] For example, if the prevalence of glaucoma is 1.5% in an unselected population of whites, and the screening test used is IOP measurement, with sensitivity of 47% and specificity of 92% for diagnosing glaucoma with an IOP measurement over 21 mmHg, then the predictive value of a positive test will be 8.2%.[7] For every case of glaucoma identified, however, 11 individuals with a false-positive test would be referred for further diagnostic evaluation and possible unnecessary treatment.

Rather than relying on a single screening test, combined use of two or more screening tests might be considered. For example, Prevent Blindness America combines visual field testing (Henson Visual Field Analyzer) with IOP measurement in its screening algorithm.[23] A combined testing strategy, however, may not improve the accuracy of testing, particularly if the sensitivity and specificity of each test are similar.[24] An individual with disease would have additional opportunities to be identified by a positive test, so sensitivity would be expected to increase. At the same time, each healthy individual would have an increased chance of a false-positive test, so specificity would decrease.

The yield of a population-screening program would be based on the number of new cases of glaucoma detected incidental to usual care. As part of the comprehensive adult medical eye evaluation,[27] the American Academy of Ophthalmology recommends visual fields by confrontation; intraocular pressure measurement; and examination of the fundus: vitreous, retina, vasculature, and optic nerve. The guideline also states that a dilated pupil examination is necessary for optimal evaluation of structures posterior to the iris, including the optic nerve.

We were not able to identify studies that directly assessed the sensitivity and specificity of the adult medical eye examination for the diagnosis of glaucoma. A study from Sweden compared persons with glaucoma identified through population screening with self-selected patients seen in clinical practice.[28] From 1992 to 1997, population screening was carried out in residents aged 57 to 79 in Malmö, Sweden. Self-selected patients with glaucoma were identified by a retrospective review of records for patients seen in the prior year at the Eye Department of the Malmö University Hospital. Among 4,117 patients with a visit in the prior year, 354 had a diagnosis of glaucoma. Screening was carried out in 32,818 persons in the population, and 402 persons with previously undiagnosed cases of glaucoma were identified. Among the screened population, 250 of 402 (62%) had previously been seen by an ophthalmologist, and 67 of 402 (17%) had been seen in the 2 years prior to screening. This study suggests that a more extensive eye examination, including automated visual field screening and a dilated pupil examination in all patients, may increase the likelihood that glaucoma is detected as part of usual ophthalmologic care.

Key Question 4. Is there new evidence that treating increased intraocular pressure reduces the incidence of primary open-angle glaucoma?

Increased intraocular pressure is the principal risk factor for development of POAG.[26] The Ocular Hypertension Treatment Study (OHTS)[21] was a randomized clinical trial comparing ocular hypotensive medications with no treatment in 1,636 individuals with increased intraocular pressure without evidence of visual field deficits or optic disc changes indicative of POAG. Participants were recruited from patients referred to 22 clinical centers. Based on USPSTF rating criteria,[16] the quality of the OHTS study was rated "good" (Table 1).

The primary endpoint was development of visual field deficits and/or optic disc changes, indicating progression to POAG. At 60 months follow-up, progression to POAG occurred in 4.4% of those treated with medications vs. 9.5% of untreated participants. The "number needed to treat" (NNT) to prevent one case of progression from ocular hypertension to POAG was 19.6.

Over the duration of the study, the hazard ratio for progression of ocular hypertension to POAG in all treated vs. untreated participants was 0.40 (95% CI, 0.27-0.59).

To study the benefit of treatment for ocular hypertension in blacks, recruitment for the OHTS study was stratified to include 408 (25%) blacks. At 72 months, the median duration of follow-up for black participants, progression to POAG occurred in 6.9% of those receiving medications vs. 12.7% of those not treated (NNT, 17.9). The hazard ratio for progression of ocular hypertension to POAG in treated vs. untreated black participants was 0.54 (95% CI, 0.28-1.03) compared with a hazard ratio of 0.34 (95% CI, 0.21-0.56) for other participants. This difference was not statistically significant.

Key Question 5. Is there new evidence that treating increased intraocular pressure reduces severe visual impairments?

We found no studies that assessed the treatment of ocular hypertension using delay of progression to severe visual impairment as an endpoint.

Key Question 6. Is there new evidence that treating open-angle glaucoma with drugs, laser, and/or surgery reduces severe visual impairment?

We identified two studies that examined treatment of newly diagnosed glaucoma with medication, argon laser treatment, or surgery compared with untreated control subjects.

The Early Manifest Glaucoma Trial (EMGT)[12] was a randomized clinical trial comparing treatment with no treatment in 255 individuals with early POAG. Participants, virtually all of whom were white, were identified through population screening of 44,243 individuals, aged 50 and older, in Malmö and Helsingborg, Sweden. Based on USPSTF rating criteria,[16] the quality of the EMGT study was rated "good" (Table 1).

Overall, 531 (1.2%) of those screened were found to have glaucoma. This was similar to the prevalence of glaucoma among whites in other population-screening studies.[2,3,6,29] The diagnosis of early glaucoma was based on: the presence of repeatable, but not severe, visual field defects; no previous diagnosis or treatment for POAG; and mean IOP of 30 mm Hg or less. Of the 531 individuals with glaucoma, 255 (48%) met the entry criteria for early glaucoma and agreed to participate in the study. Among these, 132 participants (53%) had normal-tension glaucoma based on repeated IOP measurements less than 21 mm Hg.

One hundred and twenty-nine participants were randomized to treatment with argon laser trabeculoplasty (ALT) and topical beta-blocker eye drops. The remaining 126 control participants received no treatment. The primary trial endpoint was progression of POAG based on new visual field loss, optic disc deterioration, or both. At 48 months, the minimum planned follow-up, 30% of treated subjects reached a progression endpoint vs. 49% of control subjects (NNT, 5.3; 95% CI, 4.35-14.29). In survival analyses, median time to progression was 66 months in the treatment group and 48 months in control patients. The risk of progression

decreased by 10% for each 1 mm Hg reduction in IOP. In multivariate analyses, no treatment effects were observed other than those related to IOP reduction.

In the Collaborative Normal-Tension Glaucoma Study (CNTGS),[30] 145 eyes of 145 individuals with manifestations of POAG, but without recorded IOP elevation (>24 mm Hg) on repeated testing, were randomized to receive treatment with medications or surgery to lower IOP by 30%, or to receive no treatment. Participants were recruited from patients referred to 24 ophthalmic practices, mainly at university-affiliated medical centers. Participants were followed for approximately 5 years. Based on USPSTF rating criteria,[16] the quality of the CNTGS study was rated "fair" (Table 1).

Randomization occurred at the time that high-risk visual field defects (threat to central fixation), progressive visual field defects, or new optic disc hemorrhages were found. The primary intent of this study was to examine the role of IOP in the pathogenesis of NTG by comparing outcomes of untreated patients with outcomes of treated patients in whom targeted IOP reductions were achieved. The endpoint for progression was defined as worsening of an existing visual field defect, the appearance of new visual field defects, or a new threat to central visual fixation. Baseline measurements for assessing progression were obtained at the time that target IOP reductions were achieved in the group assigned to medication or surgery. To adjust for potential biasing effects of time delays in the untreated control eyes, baseline measurements were obtained after a delay matched to the corresponding delays in the treated group. Five patients who withdrew from the trial protocol before IOP stabilization were excluded from analyses.

A total of 35 progression endpoints were observed. Seven of 61 eyes (12%) in the treated group reached progression endpoints compared with 28 of 79 (35%) in the untreated group. The mean survival time to progression in the treated eyes was 2,688 ± 123 days, compared with 1,695 ± 143 days in untreated eyes ($p < 0.0001$). These findings indicate that IOP is part of the pathogenic process in normal-tension glaucoma, and that lowering IOP may be beneficial in its treatment.

In a companion paper,[31] analysis of the same patients was performed based on intent-to-treat. In this analysis, progression endpoints were assessed from the time of randomization for all eyes. The five eyes excluded from the treatment group in the first study were included in the intent-to-treat analysis. Progression was defined on the basis of the same endpoint used in the first paper. A total of 53 progression endpoints were observed. Twenty-two of 66 eyes (33%) in the treated group reached a progression endpoint, compared with 31 of 79 eyes (39%) in the untreated group. The mean survival time to progression in the treated eyes was 1,796 ± 151 days, compared with 1,525 ± 152 days in untreated eyes ($p = 0.21$). Apparently, the additional 18 endpoints included in this analysis occurred prior to the time when baseline measurements were obtained for the first analysis.

In the CNTGS study, 23 of 66 treated eyes (35%) developed loss of visual acuity due to cataracts, compared with 11 of 79 eyes in the control group (14%) ($p = 0.0011$). The highest incidence of cataracts (16 of 33) occurred in the surgically treated eyes. The rate of cataract formation in untreated eyes was lower than surgically treated eyes ($p = 0.0001$), but was not significantly different from medically treated eyes ($p = 0.18$).

In a secondary analysis of the intent-to-treat data, observations were censored at the time cataracts were diagnosed. This resulted in an apparent improvement in survival time before glaucoma progression for treated eyes compared with control eyes ($p = 0.008$). This assumes, however, that eyes censored from observation after cataracts developed would not develop

progression endpoints in the future. Since cataract formation does not protect against glaucomatous progression, and because treatment increases the risk of cataract formation, this creates a strong bias favoring treatment.

The first CNTGS [30] paper indicates that IOP does play a pathogenic role in normal-tension glaucoma. However, the results of the second paper[31] do not indicate whether treating IOP would effectively reduce glaucoma progression in patients with NTG. In the EMGT study, secondary analyses show that increased IOP is a significant risk factor for progression (For IOP ≥ 21 mm Hg, HR 1.70, 95% CI, 1.18-2.43 vs. IOP < 21 mm Hg).[32] This indicates that treatment directed at lowering IOP is definitely beneficial for eyes with increased IOP, but of uncertain benefit in eyes with normal IOP.

Three other studies compared different treatment interventions, without untreated controls, in individuals with POAG. In the Collaborative Initial Glaucoma Treatment Study (CIGTS), 607 individuals with newly diagnosed glaucoma were recruited from self-selected patients at 14 clinical centers. Forty-four percent of participants were non-white. Participants were randomized to treatment with surgical trabeculectomy (n = 300), an incisional surgical technique to lower IOP, or to a stepwise medication regimen (n = 307).[13] Target values for IOP reduction were calculated using baseline IOP measurements combined with results of visual field testing, so that the target of IOP was lower if greater visual field loss was evident at baseline. ALT was also performed in the medication group, if needed, to achieve targeted IOP reductions. The primary outcome was a study-defined visual field (VF) score based on perimetry testing. Based on USPSTF rating criteria,[16] the quality of the CIGTS study was rated "fair" (Table 1).

After complete follow-up through 4 years, there was no difference in VF scores between treatment groups. Because the baseline VF score in the medically treated group was lower, though not significantly, the investigators conducted secondary analyses to adjust for this difference. These analyses showed a slight advantage for surgical treatment although the difference was marginally significant. In the CIGTS study, 38.1% of participants were black. In an analysis controlling for treatment effect of age and gender, non-white race was a significant predictor of progression (OR 1.50; 95% CI, 1.08-2.07), defined as a decrease in visual field score ≥ 3 units.

Visual acuity (VA) measures in surgically treated patients were 2.3 letters lower than for medically treated patients (p = 0.0001), which clinically accounts for a difference of ½ line on a VA chart. Surgically treated patients had a significantly higher rate of cataract extractions (52/300; 17.3%) than medically treated patients (19/307; 6.2%) (p = 0.0001). In secondary analyses adjusting for cataract extractions, VA outcomes in surgically treated patients remained significantly lower (p = 0.0001). Race was marginally significant as a predictor of decreased visual acuity over time.

In the CIGTS study, VF scores remained essentially unchanged from baseline for both treatment groups over the course of the study. In the EMGT study, both treated and untreated groups experience progression over time, although the rate of progression was significantly lower in the treated group.[12] This difference between studies may be explained in part by differences in baseline IOP measurements between studies. In the EMGT study, 52% of participants had baseline IOP < 21 mm Hg (treatment group mean IOP 20.6 ± 4.1; control group mean IOP 20.9 ± 4.1). In the CIGTS study, all participants had baseline IOP ≥ 20 mm Hg (medicine group mean IOP 27.6 ± 5.5 mm Hg; surgery group mean IOP 27.4 ± 5.7 mm Hg). In the EMGT study, IOP was a strong risk factor for progression, and the risk of progression decreased by 10% for each 1 mm Hg lowering of IOP.[12,32]

The hypothesis that treatment is more beneficial for those with high-tension glaucoma (IOP ≥ 21 mm Hg), compared with normal-tension glaucoma, is also supported by the CNTGS findings.[31] Based on intent-to-treat analysis, there was no significant difference in outcomes between treated eyes and untreated eyes with normal-tension glaucoma.

The CIGTS investigators conclude that both medical and surgical treatment result in similar VF outcomes. They caution, however, that 4 to 5 years of follow-up in a chronic disease is not adequate to draw treatment conclusions, and that the CIGTS findings do not support a change in current treatment approaches to POAG.[13]

The Glaucoma Laser Treatment (GLT)[33] study compared initial treatment with ALT to a stepwise regimen of topical and systemic ocular hypotensive medications. Patients were recruited at 8 tertiary care clinical centers. Thirty-two percent of participants had received glaucoma treatment prior to study entry. Forty-four percent of participants were black, and all participants had elevated IOP at baseline (IOP ≥ 22 mm Hg; mean IOP 27.3 mm Hg).[34] Based on USPSTF rating criteria,[16] the quality of the GLT study was rated "fair" (Table 1).

Among 271 participants with POAG, one eye was randomized to laser treatment, and its companion eye to treatment with medications. Medications were added for eyes in either group if targeted IOP reductions were not achieved, or if visual field or optic disc deterioration was seen. The primary endpoint of the GLT study, the number of medications required to control IOP for laser treated vs. medically treated eyes, was reported in 1990.[33]

After 24 months, targeted IOP reduction was achieved in 44% of eyes treated with ALT alone, and 33% of eyes treated with topical beta-blocker eye drops ($p < 0.001$). Targeted IOP reduction was achieved in 89% of eyes treated with ALT first, with or without subsequent addition of medications, and 66% of eyes treated with medication only ($p < 0.001$). After 24 months of follow-up, 56% of eyes treated with ALT required supplemental medication, although significantly more eyes in the medication group required simultaneous administration of two or more medications to control IOP ($p < 0.001$). There were no observed differences between treatment groups in either visual acuity or visual field changes over 24 months.

In a subsequent report after median follow-up of 3.5 years, 23% of eyes initially treated with ALT showed visual field deterioration on at least one occasion, compared with 31% of eyes treated with medication ($p = 0.02$). Approximately the same proportion of eyes (12% ALT; 14% medication) had persistent visual field deterioration on repeated exams.[23] In a later report,[35] 203 of the original participants were followed for a median duration of 7 years. Sixty-eight participants were not enrolled in the follow-up study because of death (18), serious illness (7), refusal (14), or because they could not be located or had moved out of the study area (29). Because there was no adjustment for missing participants, the analysis was not based on intent-to-treat. Based on USPSTF rating criteria,[16] the quality of the GLT follow-up study was rated "poor" (Table 1).

Compared with baseline measures at study inception, ALT-treated eyes showed improved visual field status (mean change per test location +0.5 to1.1 dB) through 7 years of follow-up, and deterioration at 8 (-0.3 dB) and 9 (-1.5 dB) years. Medically treated eyes showed improvement in the first 3 years (+0.1 to 0.6 dB), and no change or deterioration thereafter (0.0 to –2.3 dB). The overall difference in visual field status was significant but small (−0.1 dB for medical vs. ALT treatment, $p = 0.005$). There were no observed differences in visual acuity between eyes based on initial treatment ($p = 0.276$). The investigators conclude that ALT is at least as efficacious as medication for initial treatment of POAG.

The Advanced Glaucoma Intervention Study (AGIS)[36] compared outcomes for two sequences of surgical trabeculectomy (T) or ALT (A): ATT or TAT. Patients were recruited from patients referred to 11 clinical centers. All participants had advanced POAG based on a combination of IOP measurements, visual field deterioration, and optic disc changes. All participants were receiving maximal medical therapy for glaucoma at the time of enrollment. Fifty-six percent of participants were black.

In this study, 789 eyes of 591 participants were randomized to either ATT or TAT sequences. The primary outcomes were changes in visual function as measured by changes in visual field or visual acuity measures. In a report on two measures,[37] sustained decrease of visual field (SDVF) and sustained decrease of visual acuity (SDVA), the AGIS investigators analyzed outcomes for 745 of 789 enrolled eyes (94.4%) after median follow-up of 10.8 years. Forty-four eyes were excluded from the analysis because of loss-to-follow-up (1 eye), mistakenly receiving the same intervention that the fellow eye was randomized to (2 eyes in the same participant), or less than 3 follow-up visits at which visual outcomes were measured (41 eyes). Because there was no adjustment for missing participants, the analysis was not based on intent-to-treat. Based on USPSTF rating criteria,[16] the quality of the AGIS study was rated "poor" (Table 1).

At 10 years, an SDVF endpoint was reached in 30.3% of eyes. There were no significant differences in risk of progression between the two treatment sequences ($p = 0.11$). SDVA endpoints occurred in 34.2% of eyes treated with surgical trabeculectomy initially vs. 25.6% of eyes treated with ALT initially ($p = 0.007$). Cataracts developed in more that half of eyes in the study, and more cataracts developed in eyes initially treated with surgery (57.4%) than with ALT (48.9%).[38] The relative risk of cataract following surgical trabeculectomy, whether as the first or second intervention in a sequence, was 1.78 ($p = 0.004$).

Baseline VF scores were significantly lower for black participants than for white participants ($p < 0.001$), although baseline IOP scores and VA scores were similar. Comparing black with white participants, the relative risk of reaching an SDVF or SDVA endpoint over 9 years of follow-up was 1.51 (95% CI, 0.92-2.46) and 1.39 (95% CI, 0.90-2.12), respectively. Fewer SDVF endpoints were reached in white participants undergoing ATT than TAT ($p = 0.002$). Fewer SDVA endpoints were reached in black participants undergoing TAT than ATT ($p < 0.001$). Overall, white participants appeared to fare better with TAT and black participants with ATT.[39]

The Relation of Visual Field Loss to Functional Impairment

For this update, we adopted the key questions proposed by RTI-UNC in its topic review. In these questions, the critical questions regarding benefits of treatment specify "severe visual impairment" as the outcome. Interpretation of the benefits of treatment based on this outcome is difficult. Although POAG is one of the most common causes of blindness in the U.S.,[1] only a small proportion of affected individuals will eventually become blind.[11] In a National Academies of Science report on visual impairment and disability,[40] the panel concluded that there was no scientific basis for choosing any threshold of vision loss for disability determination.

A more salient concern may be the relation between visual field loss of any degree and its impact on vision-specific functioning, general health status, and quality of life (QOL). In a study of vision-specific QOL in patients with glaucoma,[41] there was a linear relationship between increased visual field loss and decreased vision-specific QOL, as measured by previously

validated National Eye Institute visual function questionnaires.[42,43] The study also found that visual field loss and visual acuity were independent predictors of vision-specific QOL.

A second study examining the impact of binocular visual field impairment, using the same questionnaires,[44] found significant correlations between binocular visual field loss and impairment of peripheral vision activities (r = 0.60), distance activities (r = 0.56), and vision-specific dependency (r = 0.56). When adjusted for visual acuity, the magnitudes of these correlations were weaker (r, −0.32 to –0.44) but remained significant. Both studies found, at most, a weak relationship between visual field loss and MOS-36 (Medical Outcomes Study 36-Item Short Form) general health status.[45]

A population-based survey from Rotterdam of the association of visual field loss and impairment of daily activities[46] found that persons with bilateral visual field loss or severe unilateral visual field loss were significantly more likely to be moderately or severely disabled; unable to enjoy reading or television; require a walking aid; have a history of hip or wrist fracture; or experience more than 4 falls within 2 years after initial evaluation. Visual acuity in persons with visual field loss was significantly lower compared with those without visual field loss; however, the associations above remained significant after adjusting for low visual acuity.

For ethical reasons, the treatment studies presented here used sensitive indicators of progression to minimize the impact of visual field loss in untreated or less intensively treated participants. The Early Manifest Glaucoma Trial investigators described the relationship between their visual field progression endpoint and conventional method of measuring visual field loss.[47] For example, the mean deviation (MD) at baseline for affected eyes was –5.0 dB in the treatment group and –4.4 dB in the control group (p = NS).[12] In eyes reaching progression, the mean change in MD from baseline was −1.93 (95% CI, –2.31 to −1.54). By comparison, the MD for a functionally blind eye would be around –25 dB or worse.[12] In regression analyses, the changes in MD from baseline were found to be independent of baseline IOP, baseline MD, or time to progression.

Presently, there is no clear way to quantitatively relate specific degrees of visual field loss to impairment of vision-specific QOL, and studies examining these associations have not established a relationship between changes in vision-specific QOL and specific treatment approaches.[48] The EMGT investigators assessed vision-specific QOL using the National Eye Institute Visual Function Questionnaire, [43] but these data have not been reported at this time.

There is also no standard definition for visual field progression. A study comparing measures of progression from 3 different studies (EMGT, CIGTS, and AGIS) demonstrated significant variations in classification of progression depending on which method was used.[49] When applied to longitudinal observations on 67 eyes of 56 participants in a natural history study of glaucoma, a total of 22 of 67 eyes (32.8%) were classified as having visual field progression based on any of the three methods. For individual methods, AGIS classified 7 of 67 persons (10.4%) as having visual field progression, compared with 14 of 67 persons (21%) with EMGT criteria and 13 of 67 (19.4%) with CIGTS criteria. The EMGT and CIGTS methods, used in studies of newly diagnosed glaucoma, appear to be more sensitive than the AGIS method, used in a study of advanced glaucoma. In the 22 persons classified as having visual field progression overall, the methods agreed on classification of progression in only 5 of 22 persons (23%).

Key Question 7. Is there new evidence that screening results in adverse effects? Is screening acceptable to patients?

We found no new studies addressing the harms or acceptability of screening for ocular hypertension or POAG. Known short-term adverse effects of screening include eye irritation and dysgeusia associated with topical anesthetics; corneal abrasions and infections with instruments that touch the eye; and apprehensiveness about the exam.

Key Question 8. Is there new evidence that treatment of increased intraocular pressure and/or open-angle glaucoma results in adverse effects?

Most of the included trials provide information on the possible harms associated with treatment based on comparisons between groups. Ocular symptoms, such as dryness, tearing, and itching, were frequently reported. In the OHTS study, for example, ocular symptoms occurred in 57% of treated patients and 47% of control subjects ($p < 0.001$).[21] Other symptoms, such as darkening of the eyelids or eyelash growth, were reported in 23% of treated patients vs. 18% of control subjects ($p < 0.001$).

The CIGTS trial reported intraoperative and postoperative complication for surgical trabeculectomy in 525 participants. Intraoperative complications included bleeding in the anterior chamber (7.1%) and conjunctival buttonhole defects (1.0%). Complications within 30 days postoperatively included shallow or flat anterior chamber (14.2%); failed or encapsulated filtering bleb (11.9%); ptosis (11.9%); serous choroidal detachment (11.3%); and anterior chamber bleeding, or hyphema (10.5%).[13] The long-term implication of these complications was not reported.

Serious systemic adverse effects of treatment were also reported. In the EMGT study, more participants died in the in the group treated with topical medications and ALT (15 of 22) than in the untreated control group (7 of 22, $p = 0.08$).[12] Most of these deaths occurred among males in the first 2 years of the study. The patterns of cause-specific mortality, primarily cardiovascular events and malignancy, were similar to those expected in a population of the same age and gender.

In the OHTS study, there were no observed differences between the treated and untreated participants in total hospitalizations, worsening of preexisting conditions, or mortality.[21] Serious psychiatric adverse effects were reported in 5.5% (44 of 800) of the treated group vs. 3.4% (27 of 802) of the control group ($p = 0.05$). Serious genitourinary adverse effects occurred in 1.5% (12of 800) of the treated group vs. 0.5% (4of 802) of the control group ($p = 0.04$). There was no evident biological connection between these complications and the medications used. There was also no significant difference in the likelihood of these complications after adjustment for multiple comparisons.

There is a known association between surgical treatment for open-angle glaucoma and an increased risk of cataract formation.[12] In the CIGTS study, with no adjustment for variable follow-up, more cataracts requiring extraction occurred in the surgically treated group (17.3%)

than in the medically treated group (6.2%).[13] In survival analyses, adjusted rates of cataract extraction were 11.6% in the surgery group vs. 2.7% in the medical group. Over time, the cataract extraction rate in the surgery group remained significantly higher than in the medication group ($p = 0.0001$).

Two other studies compared the risks of cataract formation in medically treated vs. untreated eyes. In the EMGT study,[12] cataract development was more likely in group treated with ALT plus betaxolol than in untreated control subjects ($p = 0.002$), and the risk of cataracts related to treatment increased over time ($p = 0.02$). Cataract extraction was performed in 6 (4.8%) treatment group participants and 2 (1.8%) control participants, which was a nonsignificant difference. In the OHTS study of individuals with ocular hypertension without glaucoma, there were slightly more cataract extractions in medically treated participants (52 of 806, 6.4%) than in untreated control subjects (35 of 813, 4.3%). This difference was not significant ($p = 0.06$).[21]

Excluded Studies

Studies excluded from this evidence synthesis are shown in Appendix C. Reasons these studies were not considered include a study design other than randomized controlled trial was used; there were large attrition rates; or the analysis was not based on intent-to-treat.

Ongoing Trials

The European Glaucoma Prevention Study is a randomized, double-blinded, controlled trial comparing a topical medication (dorzolamide) to placebo in preventing or delaying progression to POAG.[50] Between January 1997 and May 1999, 1,077 participants were enrolled and randomized. Follow-up will continue for 5 years or until a specified number of participants have developed visual field or optic disc changes characteristic of POAG.

Chapter 4. Discussion

In this review, we examined one randomized clinical trial of treatment of ocular hypertension[21] and four randomized trials of treatment for POAG (including one follow-up study).[12-14,31,33,35,37,39] Table 1 provides a summary of the evidence from each trial. The OHTS study,[21] the EMGT study,[12] the CNTGS study,[31] and the GLT study[35] were rated to be of "good" or "fair" quality based on accepted USPSTF criteria.[16] The quality of the AGIS trial[37] was rated "poor." No adjustments were made for 44 of 789 eyes that were excluded from the analysis because of incomplete data. Thus, analyses of the trial results were not reported based on intent-to-treat. The GLT follow-up study[35] was also rated to be of "poor" quality for the same reason, although the primary trial[14,33] was rated "fair."

The OHTS and EMGT studies provide good evidence that treatment for ocular hypertension and early POAG is beneficial.[12,21] Because only a small percentage of people with ocular hypertension ever progress to POAG, screening and treatment for ocular hypertension is probably not warranted, particularly given the poor sensitivity and specificity of IOP measurements in detecting increased IOP.[7] If ocular hypertension is incidentally found as part of a routine eye examination, treatment may be warranted if IOP is substantially increased.[51] Also, we do not know whether the results of the EMGT trial, which was conducted among whites in Scandinavia, will generalize to the U.S. population, particularly with the increased incidence of POAG among African Americans.

The CNTGS provides fair evidence that lower IOP does delay progression of normal-tension glaucoma.[31] In this study, progression events were not counted until IOP reduction targets were reached. For the control group, counting of progression events was delayed based on time intervals matching time to achieve targeted IOP reduction in the treated group. When study data were analyzed based on intent-to-treat,[31] participants were considered to be randomized when a progression occurred or when risk factors were present initially, such as a threat to fixation. This resulted in inclusion of more progression endpoints in both groups than were excluded in the first analysis.[30] In the intent-to-treat analysis,[31] similar numbers of progression events and similar rates of progression were seen in treated vs. untreated participants. A secondary analysis, which shows that treatment appeared effective if participants were censored at the time of cataract formation, is suspect because it implicitly assumes that those with cataracts would not experience further visual field progression after censoring. Because treatment, particularly surgical trabeculectomy, is a significant risk factor for cataract formation, this creates a strong bias favoring treatment.

Three trials and one follow-up study compared different interventions for treatment of POAG. The CIGTS study compared surgical trabeculectomy with a stepped-medication regime (plus ALT if necessary) to achieve target IOP reductions in participants with newly diagnosed glaucoma and IOP $\geq$ 20 mm Hg.[13] After 4 years of follow-up, no difference in outcomes was seen between groups based on a study-defined visual field score. Also, there was no significant change from baseline visual field scores in either treatment group. This finding is difficult to interpret because progression was observed in all other studies of treatment of POAG.[12,14,35,37] The CIGTS investigators conclude that both medical and surgical treatment result in similar visual field outcomes. In the CIGTS study, 38.1% of participants were black. In an analysis

controlling for treatment effect of age and gender, non-white race remained a significant predictor of progression (OR 1.50; 95% CI, 1.08-2.07).

The GLT study compared initial treatment with ALT to a stepwise regimen of topical and systemic ocular hypotensive medications.[14,33] In the first 3.5 years median follow-up, approximately the same number of eyes showed persistent visual field deterioration (12% ALT; 14% medication, NS). In a follow-up study,[35] 203 of the original participants were followed for a median duration of 7 years. Compared with baseline measures at study inception, ALT-treated eyes showed significantly less visual field loss than medication-treated eyes ($p = 0.005$), although the difference was small (−0.1 dB for medical vs. ALT treatment). The investigators conclude that ALT is at least as efficacious as medication for initial treatment of POAG.

The AGIS study compared outcomes for two sequences of surgical trabeculectomy (T) or ALT (A): ATT or TAT.[36] At 10 years, there was no significant difference in risk of visual field progression between the two treatment sequences ($p = 0.11$).[37] Surgical trabeculectomy as the initial procedure resulted in greater loss of visual acuity than initial treatment with ALT ($p = 0.007$). This finding was associated with an increased risk of cataracts following surgical trabeculectomy, whether as the first or second intervention in a sequence ($p = 0.004$). In comparing outcomes for white vs. black participants,[39] white participants appeared to fare much better with the TAT sequence, and black participants fared slightly better with the ATT sequence.

The benefit of treatment for POAG appears to be primarily related to the level of IOP elevation. Although the CNTGS study provided evidence that IOP does play some pathogenic role in the disease,[30] treatment to lower IOP does not lead to improved outcomes.[31] In the EMGT trial, in which approximately half of participants had normal-tension glaucoma,[12] most of the benefit for treatment appeared to be in participants with elevated IOP.[32] In the CIGTS study,[13] all participants had increased IOP. Although no untreated control group was available, no progression in visual field loss was observed with either medication or surgery. As noted above, this finding is difficult to interpret since progression was observed to some extent in all other trials.

Taken together, these trials provide fair to good evidence that treatment is effective in slowing the progression of visual field loss for persons with POAG. The greatest benefit of treatment appears to be in those with increased POAG. Treatment appears to benefit blacks as well as whites, although POAG may be a more aggressive disease in blacks. Since the distribution of IOP is similar in blacks and whites,[5] other pathogenic factors must account for this difference.

The benefits of treatment must also be weighed against its potential harms. The chief harm of treatment is an excess risk of cataract formation, which is particularly associated with surgical treatment.[12] Ophthalmologists we have spoken with indicate that cataract formation is not considered to be a serious complication, since lens extraction is a simple procedure with low morbidity. In all trials, however, surgical treatment was associated with decreased visual acuity that persisted over time. Visual acuity is an independent risk factor for decreased vision-related quality of life,[41] and contributes significantly to impaired performance of everyday tasks of living.[52] In the several trials comparing surgical, laser, and medical treatment,[13,14,35,37] there was little difference between outcomes. This finding suggests that the least invasive approach that will lower IOP would be best, in order to minimize harms.

There is good evidence that visual field loss is related in a linear fashion to vision-specific QOL.[41,44] As discussed above, there is fair to good evidence that treatment of POAG is effective

in slowing the progression of visual field loss for persons with POAG. The lack of a criteria standard for classifying progression of glaucoma makes it difficult to relate the intermediate outcome of visual field loss to the functional outcomes of visual impairment. Even among studies, there is poor agreement between different methods of defining progression.[49] Reportedly, there are studies that are ongoing or nearing publication that may establish a clearer link between specific amounts of visual field loss and vision-related QOL.

Presently there are no good tests that would support a population-screening program for glaucoma. There are ongoing trials in larger populations of both the Henson Visual Field Analyzer and FDT perimetry for glaucoma screening. Based on the Malmö screening study,[28] it is conceivable that a significant proportion of persons with undiagnosed glaucoma are already being seen by ophthalmologists and optometrists for other reasons. If so, then including both automated visual field testing and dilated eye examination as part of the comprehensive adult eye examination[27] could result in a significant increase in the number of undiagnosed cases of glaucoma that are detected early in their course.

The yield of population screening for glaucoma is related to the number of individuals found who have a treatable form of glaucoma. The EMGT investigators compared screened patients (32,918 attended from a population of 42,947 invited) to self-selected patients seen in the eye clinic of the regional hospital in the prior year.[28] They found 354 patients with a previous glaucoma diagnosis in the clinic, of whom 92% met the EMGT criteria. In the population screening, 401 of 402 (99%) met the EMGT criteria. Among self-selected patients, only 14% had NTG. Among screened patients, 53% had NTG. Since treatment of NTG is apparently not effective in reducing the rate of progression, based on the intent-to-treat analysis of the CNTGS data,[31] fewer than half of patients identified from screening would benefit from screening.

With the exception of the EMGT study, in which participants were obtained from population screening, all other trials were conducted with participants who were self-selected through referral to an ophthalmologist. Self-selected patients probably represent a different spectrum of disease than presents in the general population. In one study comparing self-selected individuals with glaucoma to individuals identified through population screening, the self-selected group had significantly higher mean IOP measurements, two-thirds fewer cases of NTG, and significantly greater visual field deficits at the time of diagnosis.[28] It is not clear how such differences would affect generalization of these trial results to a population setting.

In order to promote better understanding of treatment for increased intraocular pressure and primary open-angle glaucoma, further research is needed. We suggest that such research should include development of standardized and objective measures for glaucoma progression and visual field loss; validation of such measures in relation to vision-specific and general health status measures across the entire spectrum of disease; double-blind, placebo-controlled trials for early disease interventions; and population-based trials of screening instruments in multiple geographic locales to determine whether accurate, reliable, and practical approaches to screening exist.

References

1. Quigley HA, Vitale S. Models of open-angle glaucoma prevalence and incidence in the United States. *Investigative Ophthalmology & Visual Science* 1997; 38(1):83-91.

2. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *JAMA* 1991; 266(3):369-374.

3. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1996; 103(10):1661-1669.

4. Quigley HA. Open-angle glaucoma. *New England Journal of Medicine* 1993; 328(15):1097-1106.

5. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Archives of Ophthalmology* 1991; 109(8):1090-1095.

6. Leske MC, Connell AM, Wu SY, Nemesure B, Li X, Schachat A et al. Incidence of open-angle glaucoma: the Barbados Eye Studies. The Barbados Eye Studies Group. *Archives of Ophthalmology* 2001; 119(1):89-95.

7. Tielsch JM, Katz J, Singh K, Quigley HA, Gottsch JD, Javitt J et al. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. *American Journal of Epidemiology* 1991; 134(10):1102-1110.

8. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Family history and risk of primary open angle glaucoma. The Baltimore Eye Survey. *Archives of Ophthalmology* 1994; 112(1):69-73.

9. American Academy of Ophthalmology. *Preferred Practice Pattern. Primary Open-Angle Glaucoma*. Limited revision ed. 2003.

10. Jay JL, Murdoch JR. The rate of visual field loss in untreated primary open angle glaucoma. *British Journal of Ophthalmology* 1993; 77(3):176-178.

11. Quigley HA, Tielsch JM, Katz J, Sommer A. Rate of progression in open-angle glaucoma estimated from cross-sectional prevalence of visual field damage. *American Journal of Ophthalmology* 1996; 122(3):355-363.

12. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Archives of Ophthalmology* 2002; 120(10):1268-1279.

13. Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001; 108(11):1943-1953.

14. The Glaucoma Laser Trial (GLT): 6. Treatment group differences in visual field changes. Glaucoma Laser Trial Research Group. *American Journal of Ophthalmology* 1995; 120(1):10-22.

15. U.S. Preventive Services Task Force. Screening for Glaucoma. In: DiGuiseppi C, Atkins D, Woolf SH, Kamerow DB, editors. *Guide to Clinical Preventive Services*. Washington, DC: Office of Disease Prevention and Health Promotion, 1996: 383-391.

16. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM et al. Current methods of the US Preventive Services Task Force: a review of the process. *American Journal of Preventive Medicine* 2001; 20(3:Suppl):21-35.

17. Kamal D, Hitchings R. Normal tension glaucoma--a practical approach. *British Journal of Ophthalmology* 1998; 82(7):835-840.

18. Quigley HA, Katz J, Derick RJ, Gilbert D, Sommer A. An evaluation of optic disc and nerve fiber layer examinations in monitoring progression of early glaucoma damage. *Ophthalmology* 1992; 99(1):19-28.

19. Coleman AL, Sommer A, Enger C, Knopf HL, Stamper RL, Minckler DS. Interobserver and intraobserver variability in the detection of glaucomatous progression of the optic disc. *Journal of Glaucoma* 1996; 5(6):384-389.

20. Harper R, Henson D, Reeves BC. Appraising evaluations of screening/diagnostic tests: the importance of the study populations. *British Journal of Ophthalmology* 2000; 84(10):1198-1202.

21. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Archives of Ophthalmology* 2002; 120(6):701-713.

22. Ellish NJ, Higginbotham EJ. Evaluating a visual field screening test for glaucoma: how the choice of the gold standard affects the validity of the test. *Ophthalmic Epidemiol* 2001; 8(5):297-307.

23. Sponsel WE, Ritch R, Stamper R, Higginbotham EJ, Anderson DR, Wilson MR et al. Prevent Blindness America visual field screening study. The Prevent Blindness America Glaucoma Advisory Committee. *American Journal of Ophthalmology* 1995; 120(6):699-708.

24. Wilson MR. Screening paradigms in glaucoma. *Journal of Glaucoma* 2001; 10(5:Suppl 1):S25-S27.

25. Patel SC, Friedman DS, Varadkar P, Robin AL. Algorithm for interpreting the results of frequency doubling perimetry. *American Journal of Ophthalmology* 2000; 129(3):323-327.

26. Coleman AL. Glaucoma. *Lancet* 1999; 354(9192):1803-1810.

27. American Academy of Ophthalmology. *Comprehensive adult medical eye evaluation*. 2000.

28. Grodum K, Heijl A, Bengtsson B. A comparison of glaucoma patients identified through mass screening and in routine clinical practice. *Acta Ophthalmologica Scandinavica* 2002; 80(6):627-631.

29. Klein BE, Klein R, Sponsel WE, Franke T, Cantor LB, Martone J et al. Prevalence of glaucoma. The Beaver Dam Eye Study. *Ophthalmology* 1992; 99(10):1499-1504.

30. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *American Journal of Ophthalmology* 1998; 126(4):487-497.

31. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *American Journal of Ophthalmology* 1998; 126(4):498-505.

32. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E et al. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. *Archives of Ophthalmology* 2003; 121(1):48-56.

33. The Glaucoma Laser Trial (GLT). 2. Results of argon laser trabeculoplasty versus topical medicines. The Glaucoma Laser Trial Research Group. *Ophthalmology* 1990; 97(11):1403-1413.

34. The Glaucoma Laser Trial (GLT): 5. Subgroup differences at enrollment. Glaucoma Laser Trial Research Group. *Ophthalmic Surg* 1993; 24(4):232-240.

35. The Glaucoma Laser Trial (GLT) and glaucoma laser trial follow-up study: 7. Results. Glaucoma Laser Trial Research Group. *American Journal of Ophthalmology* 1995; 120(6):718-731.

36. AGIS (Advanced Glaucoma Intervention Study) Investigators. The Advanced Glaucoma Intervention Study (AGIS): 1. Study design and methods and baseline characteristics of study patients. *Controlled Clinical Trials* 1994; 15(4):299-325.

37. AGIS (Advanced Glaucoma Intervention Study) Investigators. The Advanced Glaucoma Intervention Study (AGIS): 12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. *American Journal of Ophthalmology* 2002; 134(4):499-512.

38. AGIS (Advanced Glaucoma Intervention Study) Investigators. The Advanced Glaucoma Intervention Study: 8. Risk of cataract formation after trabeculectomy. *Archives of Ophthalmology* 2001; 119(12):1771-1779.

39. AGIS (Advanced Glaucoma Intervention Study) Investigators. The Advanced Glaucoma Intervention Study (AGIS): 9. Comparison of glaucoma outcomes in black and white patients within treatment groups. *American Journal of Ophthalmology* 2001; 132(3):311-320.

40. National Research Council. Committee on Disability Determination for Individuals with Visual Impairments. *Visual Impairments: Determining Eligibility for Social Security Benefits.* Lennie P, Van Hemel SB, editors. National Academies Press, 2002.

41. Gutierrez P, Wilson MR, Johnson C, Gordon M, Cioffi GA, Ritch R et al. Influence of glaucomatous visual field loss on health-related quality of life. *Archives of Ophthalmology* 1997; 115(6):777-784.

42. Cassard SD, Patrick DL, Damiano AM, Legro MW, Tielsch JM, Diener-West M et al. Reproducibility and responsiveness of the VF-14. An index of

functional impairment in patients with cataracts. *Archives of Ophthalmology* 1995; 113(12):1508-1513.

43. Mangione CM, Lee PP, Pitts J, Gutierrez P, Berry S, Hays RD. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). NEI-VFQ Field Test Investigators. *Archives of Ophthalmology* 1998; 116(11):1496-1504.

44. Parrish RK, Gedde SJ, Scott IU, Feuer WJ, Schiffman JC, Mangione CM et al. Visual function and quality of life among patients with glaucoma. *Archives of Ophthalmology* 1997; 115(11):1447-1455.

45. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical Care* 1994; 32(1):40-66.

46. Ramrattan RS, Wolfs RC, Panda-Jonas S, Jonas JB, Bakker D, Pols HA et al. Prevalence and causes of visual field loss in the elderly and associations with impairment in daily functioning: the Rotterdam Study.[erratum appears in *Archives of Ophthalmology* 2002 Apr;120(4):525]. *Archives of Ophthalmology* 2001; 119(12):1788-1794.

47. Heijl A, Leske MC, Bengtsson B, Bengtsson B, Hussein M, Early Manifest Glaucoma Trial Group. Measuring visual field progression in the Early Manifest Glaucoma Trial. *Acta Ophthalmologica Scandinavica* 2003; 81(3):286-293.

48. Lee BL, Wilson MR. Health-related quality of life in patients with cataract and glaucoma. *Journal of Glaucoma* 2000; 9(1):87-94.

49. Katz JS, Congdon NM, Friedman DS. Methodological variations in estimating apparent progressive visual field loss in clinical trials of glaucoma treatment. *Archives of Ophthalmology* September 1999; 117(9):1137-1142.

50. European Glaucoma Prevention Study Group. The European glaucoma prevention study design and baseline description of the participants. *Ophthalmology* 2002; 109(9):1612-1621.

51. Jampel HD. We should treat fewer patients with elevated intraocular pressure now that we know the results of the Ocular Hypertension Treatment Study. *Archives of Ophthalmology* 2004; 122(3):378-379.

52. West SK, Rubin GS, Broman AT, Munoz B, Bandeen-Roche K, Turano K. How does visual impairment affect performance on tasks of everyday life? The SEE Project. Salisbury Eye Evaluation. *Archives of Ophthalmology* 2002; 120(6):774-780.

53. Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Archives of Ophthalmology* 1999; 117(5):573-583.

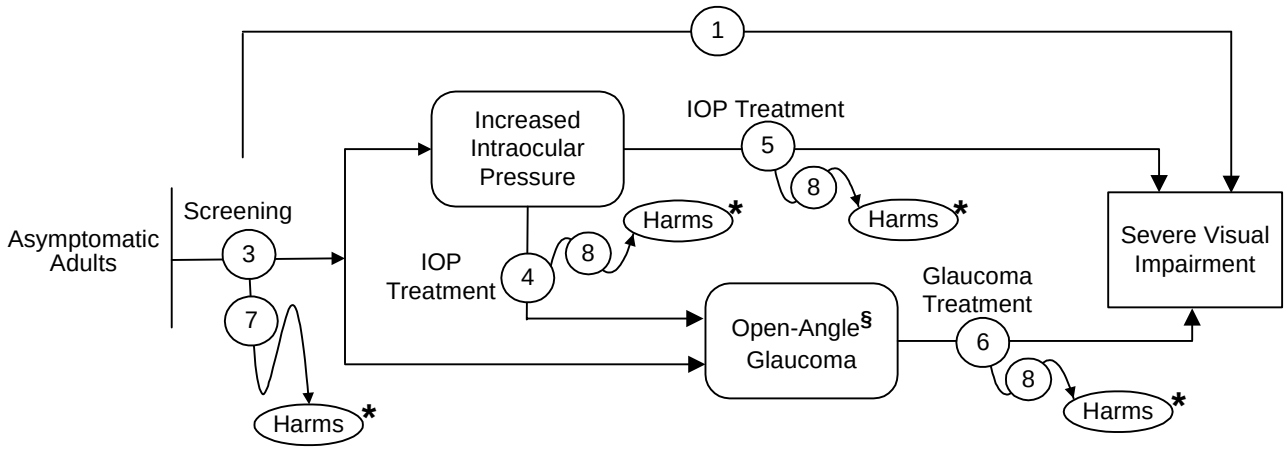
54. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology* 1999; 106(11):2144-2153.

55. Musch DC, Lichter PR, Guire KE, Standardi CL. The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. *Ophthalmology* 1999; 106(4):653-662.

56. Janz NK, Wren PA, Lichter PR, Musch DC, Gillespie BW, Guire KE et al. The Collaborative Initial Glaucoma Treatment Study: interim quality of life findings after initial medical or surgical treatment of glaucoma. *Ophthalmology* 2001; 108(11):1954-1965.

.

Figure 1. Primary Care Screening for Increased Intraocular Pressure and Open-AngleGlaucoma Analytic Framework and Key Questions



Critical Key Questions

KQ 1: Is there new evidence that screening for open-angle glaucoma[§] reduces severe visual impairment?

KQ 3: Is there new evidence that feasible screening tests are accurate and reliable in detecting increased intraocular pressure or open-angle glaucoma[§]?

KQ 4: Is there new evidence that treating increased intraocular pressure reduces the incidence of primary open-angle glaucoma[§]?

KQ 5: Is there new evidence that treating increased intraocular pressure reduces severe visual impairments?

KQ 6: Is there new evidence that treating open-angle glaucoma[§] with drugs, laser, and/or surgery reduces severe visual impairment?

KQ 7: Is there new evidence that screening results in adverse effects? Is screening acceptable to patients*?

KQ 8: Is there new evidence that treatment of increased intraocular pressure and/or open-angle glaucoma results in adverse effects*?

§ The term, open-angle glaucoma, refers to both primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG)

* Key questions added by CHR/Oregon EPC to 2003 update

Table 1. Evidence Table

Study	Population	Interventions	Main Outcomes/Results	Adverse Effects	Quality
OHTS Kass et al, 2002[21] Gordon and Kass, 1999	**N** = 1,636 **Age:** 40-80 yr (mean 55.4); male 34%; white 70% **Inclusion criteria:** increased IOP (24-32 mm Hg) without POAG **Setting**: U.S., 22 specialty centers	**Treatment:** stepped regimen of topical ocular hypotension medications **Control:** observation **Follow-up**: 72 mo for African Americans; 78 mo for others	**Primary endpoint:** development of POAG: VF loss or optic disc changes **Results:** 60 months (treatment vs. control) Cumulative probability of POAG development (4.4% vs. 9.5%) (NNT 19.6) Hazard ratio of POAG development 0.40 (95% CI, 0.27-0.59, p < 0.0001). In African Americans, POAG development (6.9% vs. 12.7%) (NNT 17.6) Hazard ratio for POAG development 0.54 (95% CI, 0.28-1.03)	(treatment vs. control) **Ocular symptoms:** dryness, tearing, itching (57% vs. 47%) (NNH 10, p < 0.001) **Symptoms affecting skin, hair, and nails:** (23% vs. 18%) (NNH 20, p < 0.001) **Serious psychiatric events:** (1.5% vs. 0.5%) (NNH 100, p = 0.05) **Serious genitourinary symptoms:** (5.5% vs. 3.4%) (NNH 48, p = 0.04)	**GOOD**
EMGT Heijl et al, 2002[12] Leske et al, 1999	**N**=255 **Age:** 50-80 yr (mean 68.1); male 34%; almost 100% white **Inclusion criteria**: newly detected glaucoma based on VF defects, no prior treatment **Setting:** Sweden, population-based screening and specialty referrals	**Treatment:** ALT plus topical betaxolol eye drops **Control:** no initial treatment **Follow-up:** (treatment vs. control) 66 vs. 69 mo Range 51-102 mo	**Primary endpoint:** progression of glaucoma: VF loss and/or optic disc changes **Results:** 48 mo (treatment vs. control) progression (30% vs. 49%, p = 0.004) (NNT 5.3, 95% CI, 4.3-14.3) Partial follow-up to 102 mo, median time to progression (66 vs. 48 mo)	(treatment vs. control) **Ocular symptoms:** NS **Mortality**: death (12% vs. 5.7%, p = 0.08); cause-specific mortality judged to be typical for the age and gender composition of each group **Cataracts:** cataract formation was more likely in treated vs. control patients (p = 0.002); risk of cataracts related to treatment increased over time (p = 0.02); cataract surgery (6 vs. 2, NS)	**GOOD**

AGIS, Advanced Glaucoma Intervention Study; ALT, argon laser trabeculoplasty; CI, confidence interval; CIGTS, Collaborative Initial Glaucoma Treatment Study; CNTGS, Collaborative Normal-Tension Glaucoma Study; EMGT, Early Manifest Glaucoma Trial; GLT, Glaucoma Laser Treatment; GLTFS, Glaucoma Laser Treatment follow-up study; IOP, intraocular pressure; NNH, number needed to harm; NNT, number needed to treat; NS, not significant; OHTS, Ocular Hypertension Treatment Study; POAG, primary open-angle glaucoma; QOL, quality of life; VA, visual acuity; VF, visual field

Table 1. Evidence Table

Study	Population	Interventions	Main Outcomes/Results	Adverse Effects	Quality
CNTGS CNTG Study Group, 1998[30,31]	**N** = 145 participants **Age**: mean age 66 yr (treated group 66.3, control group 65.5); male 34%; white 83% **Inclusion criteria:** glaucoma based on VF or optic disc changes, and no recorded IOP > 24 mm Hg **Setting:** U.S., 24 specialty centers	One eye of each participant randomized to **Treatment:** medical or surgical management to achieve IOP reduction of 30% from baseline **Control:** no treatment Randomization occurred when high-risk VF defects or new optic disc hemorrhages were found.	**Primary endpoint**: progression of VF loss, change in optic head, hemorrhage in optic disc. **Results:** Endpoints were observed in 33% of the treatment group and 39% in the control group (p = 0.21). Mean survival time was not significantly different: 4.9 yr (treatment) vs. 4.2 yrs (control).	(treatment vs. control) **Cataracts:** (35% vs. 14%) (p = 0.0011). Within the treated group, 48% of surgically treated, 25% treated with medications and laser trabeculoplasty only	**FAIR** Outcomes assessors not blinded to treatment group assignment, duration of follow-up not recorded, treatment group had higher IOP at baseline.
CIGTS Lichter et al, 2001[13] Musch et al, 1999 Janz et al, 2001	**N** = 607 **Age:** 25-75 yr (surgery group mean 58.1, medicine group mean 56.9); male 55%; white 56% **Inclusion criteria:** newly diagnosed glaucoma **Setting:** U.S., 14 specialty centers	**Treatment 1:** surgical trabeculectomy **Treatment 2:** stepped regimen of topical ocular hypotension medications **Follow-up:** Interim results based on complete follow-up to 48 mo	**Primary endpoint**: VF progression based on a measure derived from VF testing **Secondary endpoints:** VA, change in IOP, occurrence of cataracts, QOL **Results:** At 60 mo VF scores remained virtually unchanged from baseline in both groups. VA was significantly worse for surgery group until 48 mo, when average VA became equal across groups. QOL based on multiple eye-related and general health measures. Surgery group had more problems with VA (p = 0.024). QOL between treatment groups NS. Worry about blindness decreased from 50% at baseline to 25% over time.	(surgery vs. medication) **Cataracts:** (17.3% vs. 6.2%) (NNH 90, p = 0.0001). **Surgical complications:** (30 days post-operative): bleeding in the anterior chamber (7.1%); conjunctival buttonhole defects (1.0%); shallow or flat anterior chamber (14.2%); failed filtering bleb (11.9%); ptosis (11.9%); serous choroidal detachment (11.3%); anterior chamber bleeding or hyphema (10.5%).	**FAIR** Outcomes assessors not blinded to treatment group assignment

Table 1. Evidence Table

Study	Population	Interventions	Main Outcomes/Results	Adverse Effects	Quality
GLT GLT Research Group: GLT 2, 1990	**N** = 542 eyes, 271 patients **Age:** ≥ 35 yr (mean 60 yr); male 44%; white 45% **Inclusion criteria:** newly diagnosed glaucoma with IOP > 22 mm Hg **Setting:** U.S., 8 specialty centers	One eye of each patient received stepped regimen of topical medication, and the fellow eye was treated with ALT with medications added if needed. **Follow-up:** 24 mo	**Primary endpoint:** number of medications required to control IOP **Secondary endpoints:** VF loss, VA **Results:** At 24 months more eyes in the medication group required two or more medications to control IOP ($p < 0.001$). No significant differences between groups regarding VA or VF.	Ocular and systemic symptoms were reported for all patients. No comparative data since each patient received both treatments.	**FAIR** Outcomes assessors not blinded to treatment group assignment; method for VF measurement changed after start of trial
GLT Research Group: GLT 6, 1995[14]	Follow-up study	**Follow-up:** 3.5 yr	**Results:** 12% of ALT-treated eyes vs. 14% of medication-treated eyes had persistent VF loss		
GLTFS GLT Research Group: GLT 7, 1995[35]	Follow-up study **N** = 203 of 271 patients from GLT	**Follow-up:** 6-9 yr	**Results:** ALT-treated eyes showed improved VF status (mean change per test location +0.5 to 1.1 dB) through 7 years of follow-up, and deterioration at 8 (-0.3 dB) and 9 (-1.5 dB) years. Medically treated eyes showed improvement in the first 3 years (+0.1 to 0.6 dB), and no change or deterioration thereafter (0.0 to –2.3 dB). The overall difference in VF status was significant but small (−0.01 db for medical vs. ALT treatment, $p = 0.005$). There were no observed differences in VA between eyes based on initial treatment ($p = 0.276$).		**POOR** Analysis not based on intent-to-treat: no adjustment for missing data for 68 patients from original study lost to follow-up; outcomes assessors not masked to treatment assignment group
AGIS AGIS 1, 1994[36] AGIS 12, 2002[37]	**N** = 789 eyes of 591 participants **Age:** 35-80 yr (median 67 yr); male 46%; white 42%	2 sequences of surgical trabeculectomy (T) or ALT (A). **Treatment 1: TAT** **Treatment 2: ATT** Next treatment in sequence used if	**Primary outcomes:** Sustained decrease of visual field (SVDF) and sustained decrease of visual acuity (SDVA). **Results:** At 10 years, the SDVF endpoint was reached in 30% of eyes. There was no significant difference in risk of progression between the two treatment sequences ($p =$	Cataracts developed in more that half of eyes in the study, and more cataracts developed in eyes initially treated with surgery (57.4%) than with ALT (48.9%). The relative risk of cataract following surgical	**POOR** Analysis not based on intent-to-treat: 44 eyes excluded from analysis due to incomplete

Table 1. Evidence Table

Study	Population	Interventions	Main Outcomes/Results	Adverse Effects	Quality
	Inclusion criteria: advanced POAG based on IOP measurements, VF changes, optic disc changes **Setting:** U.S., 11 specialty centers	progression occurs **Follow-up:** median 10.8 yr	0.11). SDVA endpoints occurred in 34.2% of eyes treated with TAT vs. 25.6% of ATT eyes (p = 0.007). Baseline VF scores were significantly lower for black participants than for white participants (p < 0.001);baseline IOP scores and VA scores were similar. Relative risk of reaching an SDVF or SDVA endpoint over 9 years of follow-up was similar for blacks and whites, and no significant advantage was seen for either treatment regimen.	trabeculectomy, whether as the first or second intervention in a sequence, was 1.78 (p = 0.004).	measurements; outcomes assessors not masked to treatment assignment group

Appendixes

Search Strategy: MEDLINE® 1994 through January, 2004

RTI-UNC EPC Search 1

1 exp glaucoma
2 exp glaucoma, open-angle
3 exp intraocular pressure
4 exp ocular hypertension
5 exp laser surgery
6 exp therapeutics
7 exp treatment outcome
8 exp visual fields
9 exp visual acuity
10 randomized controlled trial.pt. or exp randomized controlled trials/ or exp random allocation/ or exp double blind method/ or single blind method
11 exp meta-analysis/ or meta-analysis.pt.
12 10 or 11
13 1 or 2 or 3 or 4
14 limit 13 to (human and english language and yr=2001-2004)
15 5 or 6 or 7
16 12 and 14 and 15

RTI-UNC EPC Search 2

1 exp Therapeutics/ or treatment.mp.
2 exp Intraocular Pressure
3 exp Glaucoma, Open-Angle
4 randomized controlled trial.pt. or exp randomized controlled trials/ or exp random allocation/ or exp double blind method/ or single blind method
5 exp Pharmaceutical Preparations
6 exp Ocular Hypertension
7 2 or 6
8 limit 7 to (human and english language and yr=2001-2004)
9 1 or 5
10 8 and 9 and 3
11 10 and 4

Appendix B. Inclusion/Exclusion Criteria

Inclusion/Exclusion Criteria

Key Question 1	• Randomized clinical trials (good or fair quality) • Unselected population, relevant to primary care • Mass screening • Health outcome
Key Question 3,7	• Unselected population, relevant to primary care • Gold standard as control • Feasible new screening test
Key Questions 4,5,6,8	• Randomized clinical trials (good or fair quality) • Health outcome • If no randomized controlled trials, extend to observational studies and case-control studies • Follow up > 2 yr

Excluded Studies

Study Identification	Reason for Exclusion
Bergea B, Lennart B, Svedbergh B. Primary argon laser trabeculoplasty vs pilocarpine: III. Long-term effects on visual fields. *Acta Ophthalmologica Scandinavica* 1995; 73(3):207-215. Bergea B, Bodin L, Svedbergh B. Primary argon laser trabeculoplasty vs pilocarpine. IV. Long-term effects on optic nerve head. *Acta Ophthalmologica Scandinavica* 1995; 73(3):216-221.	**Study Quality**: Analysis not based on intention-to-treat: 6/82 subjects excluded from analysis because of withdrawal or inadequate follow-up.
Heijl A, Bengtsson B. Long-term effects of timolol therapy in ocular hypertension: a double-masked, randomised trial. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 2000;238:877-883.	**Study Quality**: Analysis not based on intent-to-treat; large attrition rate.
Kaiser HJ, Flammer J, Stumpfig D, Hendrickson P. Long-term visual field follow-up of glaucoma patients treated with beta-blockers. *Survey of Ophthalmology.*1994; 38 Suppl:S156-S159.	**Study Quality**: Analysis not based on intent-to-treat; large attrition rate (34%).
Koseki N, Araie M, Yamagami J, Shirato S, Yamamoto S. Effects of oral brovincamine on visual field damage in patients with normal-tension glaucoma with low-normal intraocular pressure. *Journal of Glaucoma* 1999; 8:117-123.	**Study Quality**: Analysis was not based on intent-to-treat. Four subjects who withdrew because of medication side effects were excluded from analysis. Japanese study. Intervention medication not available in US.
Migdal C, Walter G, Hitchings R. Long-term functional outcome after early surgery compared with laser and medicine in open-angle glaucoma. *Ophthalmology* 1994; 101:1651-1657.	**Study Quality**: Analysis not based on intent-to-treat. Patients were excluded from analysis of outcomes if initially assigned treatment (medication, laser, ALT) failed to lower IOP to < 22 mm Hg.
Stewart WC, Sine CS, LoPresto C. Surgical vs medical management of chronic open-angle glaucoma. *American Journal of Ophthalmology* 1996; 122:767-774.	**Study Type**: Not RCT: matched-pairs study design.
Watson PG, Barnett MF, Parker V, Haybittle J. A 7 year prospective comparative study of three topical beta blockers in the management of primary open angle glaucoma. *British Journal of Ophthalmology* 2001; 85:962-968.	**Study Quality**: 53% attrition rate by 12 mo

ALT, argon laser trabeculoplasty; IOP, intraocular pressure; RCT, randomized controlled trial.

MEDLINE® Search and Retrieval Results