

Evidence Summaries for

How to interpret evidence into every-day practice –
Finnish Current Care Guideline for open-angle glaucoma

Running title: Finnish Current Care Guideline for Glaucoma

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[E1]

Level of evidence = B

Among individuals over the age of 50 years the prevalence of glaucoma is ca 2%, increasing to >3% in the age group over 75 years.

Systematic review 1

Structured Medline (January 1950 – January 2013) search and a hand search of references and citations of retrieved articles yielding 57 articles from 41 studies were included in the systematic review. The summary prevalence of glaucoma in the highest-quality studies was 2.6% (95% CI, 2.1%-3.1%).

References

Hollands H, Johnson D, Hollands S, Simel DL, Jinapriya D, Sharma S. Do findings on routine examination identify patients at risk for primary open-angle glaucoma? The rational clinical examination systematic review. *JAMA* 2013;309:2035-42; PMID: 23677315

Systematic review 2

The systematic review identified 4 383 reports from the search for studies on epidemiology, risk and disease progression, of which 285 were selected for full assessment for this review. 92 reports describing 27 studies met the inclusion criteria for the review. The date of last searches was December 2005.

The overall quality of each study was summarised as (A) no major flaws or (B) possible important flaws. Studies were included when they rated 'A' in all fields. Exceptions were made to include 'B' studies when no better evidence was available. In most studies (81%), participants were sampled adequately and selected from a relevant population. Suboptimal approaches to diagnose OAG (e.g. high IOP, absence of a visual test, unstandardised criteria) were used in five studies (19%). IOP status was obtained from a secure record (examination or examination records) in most studies.

In the UK, the estimated prevalence of OAG was 2.1% [95% confidence interval (CI) 1.7 to 2.5], ranging from 0.3% in people aged 40 to 3.3% in people aged 70 years.

The incidence ranged from 30 to 181 per 100 000 person-years for ages 50 years and 70 years, respectively.

References

Burr JM, Mowatt G, Hernández R. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11:iii-iv, ix-x, 1-190 PubMed

Comment

The reported prevalences are dependent on the definitions of glaucoma as well diagnostic tests and their selected threshold for abnormality which is no agreed upon. E.g. if the diagnosis is based on structure much higher prevalences have been reported in Finland [Hirvelä et al. 1995]. The major challenges to evaluate a diagnostic test in glaucoma is the lack of a perfect reference standard. The risk of bias of diagnostic study designs is an additional concern [see also E14, E26 and E27].

Other references

Sommer A, Tielsch JM, Katz J . Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol* 1991;109:1090-5; PMID: 1867550

Bonomi L, Marchini G, Marraffa M . Prevalence of glaucoma and intraocular pressure distribution in a defined population. The Egna-Neumarkt Study. *Ophthalmology* 1998;105:209-15; PMID: 9479277

Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1996;103:1661-9; PMID: 8874440

Wolfs RC, Borger PH, Ramrattan RS . Changing views on open-angle glaucoma: definitions and prevalences -- The Rotterdam Study. *Invest Ophthalmol Vis Sci* 2000;41:3309-21; PMID: 11006219

Armaly MF, Krueger DE, Maunder L . Biostatistical analysis of the collaborative glaucoma study. I. Summary report of the risk factors for glaucomatous visual-field defects. *Arch Ophthalmol* 1980;98:2163-71; PMID: 7447768

Georgopoulos G, Andreanos D, Liokis N . Risk factors in ocular hypertension. *Eur J Ophthalmol* 1997;7:357-63; PMID: 9457459

Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol* 1999;117:573-83; PMID: 10326953

Kass MA, Heuer DK, Higginbotham E . The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:701-13; PMID: 12049574

Hirvelä H, Tuulonen A, Laatikainen L. Intraocular pressure and prevalence of glaucoma in elderly people in Finland: a population-based study. *Int Ophthalmol* 1995;18:299-307; PMID: 7607812

[E2]

Level of evidence = B

More than half of patients with glaucoma seem to be undiagnosed.

Systematic review 1

The systematic review identified 4 383 reports from the search for studies on epidemiology, risk and disease progression, of which 285 were selected for full assessment for this review. 92 reports describing 27 studies met the inclusion criteria for the review. The date of last searches was December 2005.

The overall quality of each study was summarised as (A) no major flaws or (B) possible important flaws. Studies were included when they rated 'A' in all fields. Exceptions were made to include 'B' studies when no better evidence was available. In most studies (81%), participants were sampled adequately and selected from a relevant population. Suboptimal approaches to diagnose OAG (e.g. high IOP, absence of a visual test, unstandardised criteria) were used in five studies (19%). IOP status was obtained from a secure record (examination or examination records) in most studies.

The pooled prevalence rate from 19 studies was estimated to be 2.1% [95% confidence interval (CI) 1.7 to 2.5]. For previously undetected OAG, the pooled prevalence rate was 1.4% (95% CI 1.0 to 1.9), that is 67%.

References

Burr JM, Mowatt G, Hernández R. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11:iii-iv, ix-x, 1-190; PMID: 17927922

Systematic review 2

The objective of the analysis was to determine the strength of association between age, gender, ethnicity, family history of disease and refractive error and the risk of developing glaucoma. The medical advisory secretariat conducted a computerized search of literature in English-language articles, published from January 2000 to March 2006. In addition, a search was conducted for published guidelines, health technology assessments, and policy decisions. Bibliographies of references of relevant papers were searched for additional references.

Studies including participants ≥ 20 years old, population-based prospective cohort studies, population-based cross-sectional studies when prospective cohort studies were unavailable or insufficient and studies determining and reporting the strength of association or risk-specific prevalence or incidence rates were included in the review. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to summarize the overall quality of the body of evidence.

A total of 498 citations for the period January 2000 through February 2006 were retrieved and an additional 313 were identified when the search was expanded to include articles published between 1990

and 1999. An additional 6 articles were obtained from bibliographies of relevant articles. Of these, 36 articles were retrieved for further evaluation. Upon review, 1 meta-analysis and 15 population-based epidemiological studies were accepted for this review

POAG is undiagnosed in up to 50% of the population. **The quality of the evidence is moderate.**

References

Medical Advisory Secretariat. Routine eye examinations for persons 20-64 years of age: an evidence-based analysis. *Ont Health Technol Assess Ser* 2006;6:1-81; PMID: 23074485

Other references

Sommer A, Tielsch JM, Katz J . Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol* 1991;109:1090-5; PMID: 1867550

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Dielemans I, Vingerling JR, Wolfs RC . The prevalence of primary open-angle glaucoma in a population-based study in the Netherlands. The Rotterdam study. *Ophthalmology* 1994;101:1851-5; PMID: 7800368

Weih LM, Mukesh N, McCarty CA, Taylor HR. Prevalence and predictors of open-angle glaucoma. Results from the visual impairment project. *Ophthalmology* 2001;108:1966-72; PMID: 11713063

Mukesh BN, McCarty CA, Rait JL, Taylor HR. Five-year incidence of open-angle glaucoma. The Visual Impairment Project, Melbourne. *Ophthalmology* 2002;109:1047-51; PMID: 12045042

Wong EY, Keeffe JE, Rait JL . Detection of undiagnosed glaucoma by eye health professionals. *Ophthalmology* 2004;111:1508-14; PMID: 15288980

[E3]

Level of evidence = C

There may be 6 million visually disabled patients due to glaucoma globally, half of whom are blind. The estimated numbers in Europe correspond 560 000 visually handicapped patients and 220 000 are blind.

Population-base studies were searched in Medline and the WHO regional databases without language restrictions. To be included, the studies needed to be representative of the country and of the area sampled, with adequate sample size (1200-46 000), sufficient response rate ($\geq 80\%$), reporting data for persons, and with definitions of visual impairment in agreement with the WHO criteria. The prevalence of visual impairment and blindness were determined in 6 WHO regions globally. In the European Region four economic clusters were defined: 25 High Income countries, 11 Upper Middle Income countries, 14 Lower Middle Income countries, and 3 Low Income countries.

In 53 surveys (72% between 2005 and 2008) from 39 countries, the 2010 estimated number of visually impaired people in the world was 285 million of whom 14% were blind. 65% of people visually impaired and 82% of all blind are ≥ 50 years old. Globally the principal causes of visual impairment are uncorrected refractive error (43%), cataract (33%), and glaucoma (2%, i.e. 6 million people). Age-related macular degeneration (AMD), diabetic retinopathy, trachoma and corneal opacities account 1% each. A large proportion of 18% are undetermined. The causes of blindness are cataract (51%), glaucoma (8%, i.e. 3 million people), and AMD (5%) with 21% undetermined causes.

The total population of the European Region in 2010 was 889 million inhabitants of whom 3.2% were visually impaired (28 million inhabitants) and 0.3% blind (2.7 million inhabitants). Using the global percentages for glaucoma, Europe has about 560 000 subjects with glaucoma induced visual disability (2% of 28 million inhabitants with visual impairment) and 220 000 are blind due to glaucoma (8% of 2.7 million with blindness).

The prevalence of missing data can give errors that are difficult to estimate. The combined effect of uncertainties is possibly $\pm 20\%$.

References

World Health Organization. *Global Data on Visual Impairments 2010*,
<http://www.who.int/blindness/GLOBALDATAFINALforweb.pdf>

[E4]

Level of evidence = A

Although in cross-sectional population studies the intraocular pressure (IOP) is normal in half of the patients with glaucoma, the risk for development of glaucomatous abnormalities increases with elevated IOP, especially with IOP >30 mmHg.

Systematic review 1

The systematic review aimed to identify the magnitude of risk of OAG attributable to age, ethnicity, family history, myopia and diabetes. Population-based cohort and cross-sectional studies, investigating the risk of developing OAG were included, as well as meta-analyses and systematic reviews of observational population-based studies. Studies reporting populations in UK, Europe, North America, Canada or Australia were included. Hospital or clinic-based setting were excluded. The review was restricted to English language publications. The methodological quality of the included studies was assessed.

4 383 reports were identified from the search for studies on epidemiology, risk and disease progression, of which 285 were selected for full assessment for this review. 92 reports describing 27 studies met the inclusion criteria for the review.

The overall quality of each study was summarised as (A) no major flaws or (B) possible important flaws. Studies were included when they rated 'A' in all fields. Exceptions were made to include 'B' studies when no better evidence was available. In most studies (81%), participants were sampled adequately and selected from a relevant population. Suboptimal approaches to diagnose OAG (e.g. high IOP, absence of a visual test, unstandardised criteria) were used in five studies (19%). IOP status was obtained from a secure record (examination or examination records) in most studies.

Crude and adjusted relative risks (or odds ratios depending on study design) of OAG for the risk factors under investigation were abstracted. Where two or more studies contributed data, a random effects meta-analysis was undertaken. If both an unadjusted and adjusted ratio were reported in a study, an age- and gender-adjusted odds ratio was used in the meta-analysis. A relative risk was generated when an adjusted odds ratio was not reported and raw data were available.

High IOP was defined as ≥ 1 measurements with readings ≥ 26 mmHg. Other IOP cut-offs were also investigated. Seven studies described the prevalence of OAG by a range of IOP levels. Across the studies, the proportion of people with OAG who had an IOP above 21 mmHg was consistently higher than those who had an IOP of ≤ 21 mmHg. The proportion of people with high IOP varied widely across studies. However, all but one included cases with previously detected OAG already under glaucoma therapy, and therefore underestimate the true prevalence of OAG in people with high IOP. The risk of having glaucoma for those with IOP measurements ≥ 26 mmHg was estimated to be 13 times higher than that for those with lower IOP [relative risk (RR) 12.58, 95% CI 5.07 to 31.24].

References

Burr JM, Mowatt G, Hernández R. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11;iii-iv, ix-x, 1-190; PMID: 17927922

Systematic review 2

Structured Medline (January 1950 – January 2013) search and a hand search of references and citations of retrieved articles yielding 57 articles from 41 studies were included in a systematic review .

At the commonly used cutoff for high IOP (≥ 22 mmHg), the LR for developing glaucoma was 13 (95% CI, 8.2-17), while lower IOP made glaucoma less likely (LR, 0.65; 95% CI, 0.55-0.76).

References

Hollands H, Johnson D, Hollands S, Simel DL, Jinapriya D, Sharma S. Do findings on routine examination identify patients at risk for primary open-angle glaucoma? The rational clinical examination systematic review. *JAMA* 2013;309:2035-42; PMID: 23677315

Systematic review 3

The objective of the analysis of this systematic review was to determine the strength of association between age, gender, ethnicity, family history of disease and refractive error and the risk of developing glaucoma. The medical advisory secretariat conducted a computerized search of literature in English-language articles, published from January 2000 to March 2006. In addition, a search was conducted for published guidelines, health technology assessments, and policy decisions. Bibliographies of references of relevant papers were searched for additional references.

Studies including participants ≥ 20 years old, population-based prospective cohort studies, population-based cross-sectional studies when prospective cohort studies were unavailable or insufficient and studies determining and reporting the strength of association or risk-specific prevalence or incidence rates were included in the review. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to summarize the overall quality of the body of evidence.

A total of 498 citations for the period January 2000 through February 2006 were retrieved and an additional 313 were identified when the search was expanded to include articles published between 1990 and 1999. An additional 6 articles were obtained from bibliographies of relevant articles. Of these, 36 articles were retrieved for further evaluation. Upon review, 1 meta-analysis and 15 population-based epidemiological studies were accepted for this review.

Six cross-sectional studies and 1 prospective cohort study contributed data on the association between age and POAG. From the data it can be concluded that the prevalence and 4-year incidence of POAG increases with increasing age. The odds of having POAG are statistically significantly greater for people 50 years of age and older relative to those 40 to 49 years of age. There is an estimated 7% per year incremental odds of having POAG in persons 40 years of age and older, and 10% per year in persons 49 years of age and older.



References

Medical Advisory Secretariat. Routine eye examinations for persons 20-64 years of age: an evidence-based analysis. *Ont Health Technol Assess Ser* 2006;6:1-81; PMID: 23074485

[E5]

Level of evidence = A

With lower intraocular pressure levels (<30 mmHg) the conversion of ocular hypertension into glaucoma is, in addition to IOP level, best predicted by the age of the patient.

References

Sommer A, Tielsch JM, Katz J . Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol* 1991;109:1090-5; PMID: 1867550

Bonomi L, Marchini G, Marraffa M . Prevalence of glaucoma and intraocular pressure distribution in a defined population. The Egna-Neumarkt Study. *Ophthalmology* 1998;105:209-15; PMID: 9479277

Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1996;103:1661-9; PMID: 8874440

Wolfs RC, Borger PH, Ramrattan RS . Changing views on open-angle glaucoma: definitions and prevalences -- The Rotterdam Study. *Invest Ophthalmol Vis Sci* 2000;41:3309-21; PMID: 11006219

Armaly MF, Krueger DE, Maunder L . Biostatistical analysis of the collaborative glaucoma study. I. Summary report of the risk factors for glaucomatous visual-field defects. *Arch Ophthalmol* 1980;98:2163-71; PMID: 7447768

Georgopoulos G, Andreanos D, Liokis N . Risk factors in ocular hypertension. *Eur J Ophthalmol* 1997;7:357-63; PMID: 9457459

Gordon MO, Kass MA. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol* 1999;117:573-83; PMID: 10326953

Kass MA, Heuer DK, Higginbotham E . The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:701-13; PMID: 12049574

[E6]

Level of evidence= A

Age is a risk factor for glaucoma.

Systematic review 1

The systematic review aimed to identify the magnitude of risk of OAG attributable to age, ethnicity, family history, myopia and diabetes. Population-based cohort and cross-sectional studies, investigating the risk of developing OAG were included, as well as meta-analyses and systematic reviews of observational population-based studies. Studies reporting populations in UK, Europe, North America, Canada or Australia were included. Hospital or clinic-based setting were excluded. The review was restricted to English language publications. The methodological quality of the included studies was assessed.

4383 reports were identified from the search for studies on epidemiology, risk and disease progression, of which 285 were selected for full assessment for this review. 92 reports describing 27 studies met the inclusion criteria for the review.

The overall quality of each study was summarised as (A) no major flaws or (B) possible important flaws. Studies were included when they rated 'A' in all fields. Exceptions were made to include 'B' studies when no better evidence was available. In most studies (81%), participants were sampled adequately and selected from a relevant population. Suboptimal approaches to diagnose OAG (e.g. high IOP, absence of a visual test, unstandardised criteria) were used in five studies (19%). IOP, diabetes and myopia status were obtained from a secure record (examination or examination records) in most studies. However, only one (20%) obtained family history status from a secure source, by examination of first degree relatives of detected cases

Crude and adjusted relative risks (or odds ratios depending on study design) of OAG for the risk factors under investigation were abstracted. Where two or more studies contributed data, a random effects meta-analysis was undertaken. If both an unadjusted and adjusted ratio were reported in a study, an age- and gender-adjusted odds ratio was used in the meta-analysis. A relative risk was generated when an adjusted odds ratio was not reported and raw data were available.

All studies consistently showed that the prevalence of OAG increases with older age.

References

Burr JM, Mowatt G, Hernández R. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11;iii-iv, ix-x, 1-190; PMID: 17927922

Systematic review 2

Structured Medline (January 1950 – January 2013) search and a hand search of references and citations of retrieved articles yielding 57 articles from 41 studies were included in the systematic review.

The summary prevalence of glaucoma in the highest-quality studies was 2.6% (95% CI, 2.1%-3.1%). Among risk factors evaluated: increasing age increased the risk (especially age >80 years; OR, 2.9; 95% CI, 1.9-4.3).

References

Hollands H, Johnson D, Hollands S, Simel DL, Jinapriya D, Sharma S. Do findings on routine examination identify patients at risk for primary open-angle glaucoma? The rational clinical examination systematic review. *JAMA* 2013;309:2035-42; PMID: 23677315

Systematic review 3

The objective of the analysis of this systematic review was to determine the strength of association between age, gender, ethnicity, family history of disease and refractive error and the risk of developing glaucoma. The medical advisory secretariat conducted a computerized search of literature in English-language articles, published from January 2000 to March 2006. In addition, a search was conducted for published guidelines, health technology assessments, and policy decisions. Bibliographies of references of relevant papers were searched for additional references.

Studies including participants ≥ 20 years old, population-based prospective cohort studies, population-based cross-sectional studies when prospective cohort studies were unavailable or insufficient and studies determining and reporting the strength of association or risk-specific prevalence or incidence rates were included in the review. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to summarize the overall quality of the body of evidence.

A total of 498 citations for the period January 2000 through February 2006 were retrieved and an additional 313 were identified when the search was expanded to include articles published between 1990 and 1999. An additional 6 articles were obtained from bibliographies of relevant articles. Of these, 36 articles were retrieved for further evaluation. Upon review, 1 meta-analysis and 15 population-based epidemiological studies were accepted for this review

Six cross-sectional studies and 1 prospective cohort study contributed data on the association between age and POAG. From the data it can be concluded that the prevalence and 4-year incidence of POAG increases with increasing age. The odds of having POAG are statistically significantly greater for people 50 years of age and older relative to those 40 to 49 years of age. There is an estimated 7% per year incremental odds of having POAG in persons 40 years of age and older, and 10% per year in persons 49 years of age and older.

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References

Medical Advisory Secretariat. Routine eye examinations for persons 20-64 years of age: an evidence-based analysis. *Ont Health Technol Assess Ser* 2006;6:1-81; PMID: 23074485

[E7]

Level of evidence = B

Exfoliation together with increased IOP seems to increase the risk of glaucoma.

References

- Lindberg J.** Clinical investigations on depigmentation of the pupillary border and translucency of the iris. *Acta Ophthalmol* 1989;67:1-96; PMID: 2541596
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[E8]

Level of evidence = B

Optic disc hemorrhage seems to increase the risk for glaucoma.

Systematic review

Structured Medline (January 1950 – January 2013) search and a hand search of references and citations of retrieved articles yielding 57 articles from 41 studies were included in the systematic review. The summary prevalence of glaucoma in the highest-quality studies was 2.6% (95% CI, 2.1%-3.1%). Among risk factors evaluated, disc hemorrhage (LR, 12; 95% CI, 2.9-48) was highly suggestive of glaucoma, but the absence of a hemorrhage was nondiagnostic (LR, 0.94; 95% CI, 0.83-0.98).

References

Hollands H, Johnson D, Hollands S, Simel DL, Jinapriya D, Sharma S. Do findings on routine examination identify patients at risk for primary open-angle glaucoma? The rational clinical examination systematic review. *JAMA* 2013;309:2035-42; PMID: 23677315

[E9]

Level of evidence = B

Diabetes seems to increase the risk for glaucoma.

Systematic review

The systematic review aimed to identify the magnitude of risk of OAG attributable to age, ethnicity, family history, myopia and diabetes. Population-based cohort and cross-sectional studies, investigating the risk of developing OAG were included, as well as meta-analyses and systematic reviews of observational population-based studies. Studies reporting populations in UK, Europe, North America, Canada or Australia were included. Hospital or clinic-based setting were excluded. The review was restricted to English language publications. The methodological quality of the included studies was assessed.

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The overall quality of each study was summarised as (A) no major flaws or (B) possible important flaws. Studies were included when they rated 'A' in all fields. Exceptions were made to include 'B' studies when no better evidence was available. In most studies (81%), participants were sampled adequately and selected from a relevant population. Suboptimal approaches to diagnose OAG (e.g. high IOP, absence of a visual test, unstandardised criteria) were used in five studies (19%). Diabetes was defined as people on treatment for diabetes (type 1 or 2) or those testing positive on urinalysis, glycosylated haemoglobin (HbA1c) or a glucose tolerance test. Diabetes status was obtained from a secure record (examination or examination records) in most studies.

Crude and adjusted relative risks (or odds ratios depending on study design) of OAG for the risk factors under investigation were abstracted. Where two or more studies contributed data, a random effects meta-analysis was undertaken. If both an unadjusted and adjusted ratio were reported in a study, an age- and gender-adjusted odds ratio was used in the meta-analysis. A relative risk was generated when an adjusted odds ratio was not reported and raw data were available.

The prevalence of OAG by diabetes status was reported in four studies that established diabetes by clinical tests. Three of those provided adjusted estimates for odds ratios. The prevalence of OAG among participants with diabetes varied from 1.2% to 5.5%, with a pooled estimate of 3.3% (95% CI 1.8 to 4.8%). This investigation demonstrated almost twice the risk of OAG onset among people with diabetes when compared with people without diabetes (RR 1.93, 95% CI 1.38 to 2.69).

References

Burr JM, Mowatt G, Hernández R. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11;iii-iv, ix-x, 1-190; PMID: 17927922

Other references

Klein BE, Klein R, Jensen SC. Open-angle glaucoma and older-onset diabetes. The Beaver Dam eye study. *Ophthalmology* 1994;101:1173-7; PMID: 8035979

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Dielemans I, de Jong PT, Stolk R. Primary open-angle glaucoma, intraocular pressure and diabetes mellitus in the general elderly population. The Rotterdam study. *Ophthalmology* 1996;103:1271-5; PMID: 8764798

Ellis JD, Evans JM, Ruta DA . Glaucoma incidence in an unselected cohort of diabetic patients: is diabetes mellitus a risk factor for glaucoma? *Br J Ophthalmol* 2000;84:1218-24; PMID: 11049943

[E10]

Level of evidence = C

Myopia may increase the risk of glaucoma.

Systematic review 1

The systematic review aimed to identify the magnitude of risk of OAG attributable to age, ethnicity, family history, myopia and diabetes. Population-based cohort and cross-sectional studies, investigating the risk of developing OAG were included, as well as meta-analyses and systematic reviews of observational population-based studies. Studies reporting populations in UK, Europe, North America, Canada or Australia were included. Hospital or clinic-based setting were excluded. The review was restricted to English language publications. The methodological quality of the included studies was assessed.

4383 reports were identified from the search for studies on epidemiology, risk and disease progression, of which 285 were selected for full assessment for this review. 92 reports describing 27 studies met the inclusion criteria for the review.

The overall quality of each study was summarised as (A) no major flaws or (B) possible important flaws. Studies were included when they rated 'A' in all fields. Exceptions were made to include 'B' studies when no better evidence was available. In most studies (81%), participants were sampled adequately and selected from a relevant population. Suboptimal approaches to diagnose OAG (e.g. high IOP, absence of a visual test, unstandardised criteria) were used in five studies (19%). Myopia status was obtained from a secure record (examination or examination records) in most studies. Participants with myopia were defined as having ≥ 1 measurements with refractive errors greater than 0.5 D, ascertained by either measurement of present spectacles or a refraction examination.

Crude and adjusted relative risks (or odds ratios depending on study design) of OAG for the risk factors under investigation were abstracted. Where two or more studies contributed data, a random effects meta-analysis was undertaken. If both an unadjusted and adjusted ratio were reported in a study, an age- and gender-adjusted odds ratio was used in the meta-analysis. A relative risk was generated when an adjusted odds ratio was not reported and raw data were available.

The proportion of people with OAG appeared to be higher in participants with myopia than in those without myopia. The prevalence of OAG among people with myopia ranged from 1.4 to 4.3%, with a pooled estimate of 2.7% (95% CI 1.5 to 3.9). The pooled relative risk of OAG among participants with myopia (any definition) compared with non-myopes was estimated to be **1.88 (95% CI 1.53 to 2.31)**. **This result should be treated with caution** as there was no standardisation on the definition of myopia across the studies and therefore the risk for low (<-6 D) and moderate (>-6 D) could not be determined.

References

Burr JM, Mowatt G, Hernández R. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11;iii-iv, ix-x, 1-190; PMID: 17927922

Systematic review 2

Structured Medline (January 1950 – January 2013) search and a hand search of references and citations of retrieved articles yielding 57 articles from 41 studies were included in the systematic review. The summary prevalence of glaucoma in the highest-quality studies was 2.6% (95% CI, 2.1%-3.1%). Among risk factors evaluated high myopia increased the risk of glaucoma (≥ 6 diopters; odds ratio [OR], 5.7; 95% CI, 3.1-11).

References

Hollands H, Johnson D, Hollands S, Simel DL, Jinapriya D, Sharma S. Do findings on routine examination identify patients at risk for primary open-angle glaucoma? The rational clinical examination systematic review. *JAMA* 2013;309:2035-42; PMID: 23677315

Systematic review 3

The objective of the analysis of this systematic review was to determine the strength of association between age, gender, ethnicity, family history of disease and refractive error and the risk of developing glaucoma. The medical advisory secretariat conducted a computerized search of literature in English-language articles, published from January 2000 to March 2006. In addition, a search was conducted for published guidelines, health technology assessments, and policy decisions. Bibliographies of references of relevant papers were searched for additional references.

Studies including participants ≥ 20 years old, population-based prospective cohort studies, population-based cross-sectional studies when prospective cohort studies were unavailable or insufficient and studies determining and reporting the strength of association or risk-specific prevalence or incidence rates were included in the review. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to summarize the overall quality of the body of evidence.

A total of 498 citations for the period January 2000 through February 2006 were retrieved and an additional 313 were identified when the search was expanded to include articles published between 1990 and 1999. An additional 6 articles were obtained from bibliographies of relevant articles. Of these, 36 articles were retrieved for further evaluation. Upon review, 1 meta-analysis and 15 population-based epidemiological studies were accepted for this review

Four cross-sectional studies assessed the association of myopia and POAG. These data suggest an association between myopia defined as a spherical equivalent of $-1.00D$ or worse and prevalent POAG. However, there is inconsistency in results regarding the statistical significance of the association between myopia when defined as a spherical equivalent of $-0.5D$. **The quality of the evidence is very low.**

References

Medical Advisory Secretariat. Routine eye examinations for persons 20-64 years of age: an evidence-based analysis. *Ont Health Technol Assess Ser* 2006;6:1-81; PMID: 23074485

[E11]

Level of evidence = C

Positive family history may increase the risk for glaucoma.

Systematic review 1

The systematic review aimed to identify the magnitude of risk of OAG attributable to age, ethnicity, family history, myopia and diabetes. Population-based cohort and cross-sectional studies, investigating the risk of developing OAG were included, as well as meta-analyses and systematic reviews of observational population-based studies. Studies reporting populations in UK, Europe, North America, Canada or Australia were included. Hospital or clinic-based setting were excluded. The review was restricted to English language publications. The methodological quality of the included studies was assessed.

4383 reports were identified from the search for studies on epidemiology, risk and disease progression, of which 285 were selected for full assessment for this review. 92 reports describing 27 studies met the inclusion criteria for the review.

The overall quality of each study was summarised as (A) no major flaws or (B) possible important flaws. Studies were included when they rated 'A' in all fields. Exceptions were made to include 'B' studies when no better evidence was available. In most studies (81%), participants were sampled adequately and selected from a relevant population. Suboptimal approaches to diagnose OAG (e.g. high IOP, absence of a visual test, unstandardised criteria) were used in five studies (19%). Family history of OAG was defined as participants having any first-degree relative affected by OAG confirmed by clinical examination. Only one (20%) obtained family history status from a secure source, by examination of first degree relatives of detected cases.

Crude and adjusted relative risks (or odds ratios depending on study design) of OAG for the risk factors under investigation were abstracted. Where two or more studies contributed data, a random effects meta-analysis was undertaken. If both an unadjusted and adjusted ratio were reported in a study, an age- and gender-adjusted odds ratio was used in the meta-analysis. A relative risk was generated when an adjusted odds ratio was not reported and raw data were available.

The relationship between family history of glaucoma and OAG was investigated in five studies. Only four presented data sufficiently similar to allow for quantitative synthesis. However, the Rotterdam Study was removed from the analysis because their uptake rate was low (<75%). The prevalence of OAG among participants with a positive family history varied from 4.2 to 8.6%, with a pooled estimate of 6.7% (95% CI 5.0 to 8.4). The meta-analysis showed that a family history of glaucoma is associated with a **three-fold excess** age-adjusted risk of OAG (RR 3.14, 95% CI 2.32 to 4.25). These **results should be interpreted with caution, as these studies are methodologically weak** because family history of glaucoma was based solely on participant self-report of family history. This method is suboptimal as it relies on the imperfect knowledge among participants (a form of recall bias). This association remained statistically significant when data from the Rotterdam Study¹³⁵ were also considered (RR 3.23, 95% CI 2.40 to 4.37). This study

investigated the relationship of OAG with family history by means of a nested case–control study and was initially excluded from this analysis because of the high degree of uncertainty surrounding the results owing to its small sample size. However, it was the only study that ascertained a positive family history by examining first-degree relatives of patients with glaucoma and control subjects from the population-based Rotterdam Study.

References

Burr JM, Mowatt G, Hernández R. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11;iii-iv, ix-x, 1-190; PMID: 17927922

Systematic review 2

Structured Medline (January 1950 – January 2013) search and a hand search of references and citations of retrieved articles yielding 57 articles from 41 studies were included in the systematic review. The summary prevalence of glaucoma in the highest-quality studies was 2.6% (95% CI, 2.1%-3.1%). Among risk factors evaluated family history increased the risk of glaucoma (OR, 3.3; 95% CI, 2.0-5.6)

References

Hollands H, Johnson D, Hollands S, Simel DL, Jinapriya D, Sharma S. Do findings on routine examination identify patients at risk for primary open-angle glaucoma? The rational clinical examination systematic review. *JAMA* 2013;309:2035-42; PMID: 23677315

Systematic review 3

The objective of the analysis of this systematic review was to determine the strength of association between age, gender, ethnicity, family history of disease and refractive error and the risk of developing glaucoma. The medical advisory secretariat conducted a computerized search of literature in English-language articles, published from January 2000 to March 2006. In addition, a search was conducted for published guidelines, health technology assessments, and policy decisions. Bibliographies of references of relevant papers were searched for additional references.

Studies including participants ≥ 20 years old, population-based prospective cohort studies, population-based cross-sectional studies when prospective cohort studies were unavailable or insufficient and studies determining and reporting the strength of association or risk-specific prevalence or incidence rates were included in the review. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to summarize the overall quality of the body of evidence.

A total of 498 citations for the period January 2000 through February 2006 were retrieved and an additional 313 were identified when the search was expanded to include articles published between 1990 and 1999. An additional 6 articles were obtained from bibliographies of relevant articles. Of these, 36 articles were retrieved for further evaluation. Upon review, 1 meta-analysis and 15 population-based epidemiological studies were accepted for this review.



Three cross-sectional studies investigated the association between family history of glaucoma and prevalent POAG. These data suggest a 2.5 to 3.0 fold increase in the odds having POAG in persons with a family history (any first-degree relative) of POAG. **The quality of the evidence is moderate.**

References

Medical Advisory Secretariat. Routine eye examinations for persons 20-64 years of age: an evidence-based analysis. *Ont Health Technol Assess Ser* 2006;6:1-81; PMID: 23074485

[E12]

Level of evidence = C

Reduced perfusion pressure may be associated with the risk for glaucoma.

Thessaloniki Eye Study-study

Association of primary open-angle glaucoma and pseudoexfoliative glaucoma with ocular perfusion pressure status (ocular perfusion pressure with or without antihypertensive treatment) was studied in Thessaloniki Eye Study. Of the total of 2 554 randomly selected, ≥ 60 -year old subjects participating in the study, only clinic-visit participants ($n = 2\,261$), who had uniformly collected data, were included in the analyses. In the logistic regression model, the covariates included age, sex, diastolic ocular perfusion pressure, antihypertensive treatment, intraocular pressure (IOP), IOP-lowering treatment, pseudoexfoliation, and vascular factors identified as risk factors for glaucoma in a previous analysis. Among clinic-visits, 1 212 subjects (54%) were using antihypertensive treatment. An association of borderline significance was found between low diastolic ocular perfusion pressure and POAG (OR = 0.84 per 10 mm Hg, 95% CI = 0.70-1.01, $P = .059$). The effect of antihypertensive treatment on POAG was not statistically significant (OR = 1.20, 95% CI = 0.75-1.91, $P = .45$). In subgroup analyses, diastolic ocular perfusion pressure was significantly associated with POAG in subjects using antihypertensive treatment (OR = 0.78 per 10 mm Hg, 95% CI = 0.62-0.97, $P = .028$). No association was found between diastolic ocular perfusion pressure and PEXG, regardless of the use of antihypertensive treatment.

References

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Other references

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Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. *Am J Ophthalmol* 1994;117:603-24; PMID: 8172267

Graham SL, Drance SM, Wijsman K, Douglas GR, Mikelberg FS. Ambulatory blood pressure monitoring in glaucoma. The nocturnal dip. *Ophthalmology* 1995;102:61-9; PMID: 7831043

Wang JJ, Mitchell P, Smith W. Is there an association between migraine headache and open-angle glaucoma? Findings from the Blue Mountains eye study. *Ophthalmology* 1997;104:1714-9; PMID: 9331214

[E13]

Level of evidence = C

Black ethnicity may increase risk for glaucoma.

Systematic review 1

The systematic review aimed to identify the magnitude of risk of OAG attributable to age, ethnicity, family history, myopia and diabetes. Population-based cohort and cross-sectional studies, investigating the risk of developing OAG were included, as well as meta-analyses and systematic reviews of observational population-based studies. Studies reporting populations in UK, Europe, North America, Canada or Australia were included. Hospital or clinic-based setting were excluded. The review was restricted to English language publications. The methodological quality of the included studies was assessed.

4 383 reports were identified from the search for studies on epidemiology, risk and disease progression, of which 285 were selected for full assessment for this review. 92 reports describing 27 studies met the inclusion criteria for the review.

The overall quality of each study was summarised as (A) no major flaws or (B) possible important flaws. Studies were included when they rated 'A' in all fields. Exceptions were made to include 'B' studies when no better evidence was available. In most studies (81%), participants were sampled adequately and selected from a relevant population. Suboptimal approaches to diagnose OAG (e.g. high IOP, absence of a visual test, unstandardised criteria) were used in five studies (19%).

Crude and adjusted relative risks (or odds ratios depending on study design) of OAG for the risk factors under investigation were abstracted. Where two or more studies contributed data, a random effects meta-analysis was undertaken. If both an unadjusted and adjusted ratio were reported in a study, an age- and gender-adjusted odds ratio was used in the meta-analysis. A relative risk was generated when an adjusted odds ratio was not reported and raw data were available.

The relationship between ethnicity and OAG was evaluated in only one study. This study provided a direct comparison of **prevalence between black and white ethnicity**. Age-specific prevalence rates for OAG among African-Americans ranged from 1.23% (95% CI 0.23 to 2.24) in those aged 40–49 years to 9.15% (95% CI 5.83 to 12.48) in those aged 70–79 years. The relative risk of OAG among the Baltimore over-40 years **black population compared with whites is estimated to be 3.80** (95% CI 2.56 to 5.64). The onset of disease appears to be earlier for blacks as the number of cases identified for those aged between 40 and 59 was considerably higher than that observed in whites (2.3% and 0.25%, respectively).

References

Burr JM, Mowatt G, Hernández R. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11;iii-iv, ix-x, 1-190; PMID: 17927922

Systematic review 2

Structured Medline (January 1950-January 2013) search and a hand search of references and citations of retrieved articles yielding 57 articles from 41 studies were included in the systematic review. The summary prevalence of glaucoma in the highest-quality studies was 2.6% (95% CI, 2.1%-3.1%). Among risk factors evaluated that black race increases the risk of glaucoma (OR, 2.9; 95% CI, 1.4-5.9)

References

Hollands H, Johnson D, Hollands S, Simel DL, Jinapriya D, Sharma S. Do findings on routine examination identify patients at risk for primary open-angle glaucoma? The rational clinical examination systematic review. *JAMA* 2013;309:2035-42; PMID: 23677315

Systematic review 3

The objective of the analysis of this systematic review was to determine the strength of association between age, gender, ethnicity, family history of disease and refractive error and the risk of developing glaucoma. The medical advisory secretariat conducted a computerized search of literature in English-language articles, published from January 2000 to March 2006. In addition, a search was conducted for published guidelines, health technology assessments, and policy decisions. Bibliographies of references of relevant papers were searched for additional references.

Studies including participants ≥ 20 years old, population-based prospective cohort studies, population-based cross-sectional studies when prospective cohort studies were unavailable or insufficient and studies determining and reporting the strength of association or risk-specific prevalence or incidence rates were included in the review. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to summarize the overall quality of the body of evidence.

A total of 498 citations for the period January 2000 through February 2006 were retrieved and an additional 313 were identified when the search was expanded to include articles published between 1990 and 1999. An additional 6 articles were obtained from bibliographies of relevant articles. Of these, 36 articles were retrieved for further evaluation. Upon review, 1 meta-analysis and 15 population-based epidemiological studies were accepted for this review

Only 1 cross-sectional study compared the prevalence rates of POAG between black and white participants. These data suggest that prevalent glaucoma is statistically significantly greater in a black population 50 years of age and older compared with a white population of similar age. There is an overall 4-fold increase in prevalent POAG in a black population compared with a white population. This increase may be due to a confounding variable not accounted for in the analysis. **The quality of the evidence is low.**

References

Medical Advisory Secretariat. Routine eye examinations for persons 20-64 years of age: an evidence-based analysis. *Ont Health Technol Assess Ser* 2006;6:1-81; PMID: 23074485

[E14]

Level of evidence = D

No randomized screening, diagnostic and follow-up trials reporting their clinical effectiveness or cost-effectiveness in preventing glaucoma induced visual disability have been published. The major challenge in evaluating a diagnostic test in glaucoma is the lack of a perfect reference standard. The high risk of bias of diagnostic study designs is an additional concern.

Systematic review 1

Highly sensitive systematic electronic searches for this systematic review were undertaken by December 2005. The diagnostic accuracy review of diagnostics and screening tests included 40 studies totaling more than 48 000 participants' ≥ 40 years. The primary reference standard was confirmation of OAG at follow-up examination. Also considered was diagnosis of OAG requiring treatment. **No studies were at low risk of bias.** A small subset of eight studies was judged to have higher quality. Most potential screening tests reviewed had an estimated specificity of 85% or higher. No test was clearly most accurate, with only a few, heterogeneous studies for each test.

References

Burr JM, Mowatt G, Hernández R. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11;iii-iv, ix-x, 1-190; PMID: 17927922

Systematic review 2

A systematic review through October 6, 2011 was conducted from MEDLINE®, Embase, LILACS, and CENTRAL through October 6, 2011, and MEDLINE and CENTRAL (March 2, 2011) and screening of an existing database to identify relevant systematic review.

After the Burr et al. 2007 systematic review (above), 4,960 studies were identified, of which 83 studies addressing the accuracy of screening and diagnostic tests were eligible. The sensitivity of standard automated perimetry (SAP) was higher than Goldmann tonometry, similar to the Heidelberg retina tomograph (HRT), and lower than disc photos or frequency doubling technology (FDT) visual field testing. The specificity of SAP was higher than disc photos and FDT, similar to HRT, and lower than Goldmann tonometry. Some comparisons of tests could not be performed due to variability in populations and reported thresholds. No other studies were identified.

68% of studies were at high risk of spectrum bias (not representative of those who would receive the test in practice). 6% had differential verification bias (different reference standards). The candidate tests were interpreted without knowledge of reference standard in only 29% of studies. 48% of the studies did not include an explanation of withdrawals from the study, and 46% of the studies reported the number of uninterpretable test results. Only 3 of 83 studies included a population-based sample.

References

Ervin AE, Boland MV, Myrowitz EH . Screening for Glaucoma: Comparative Effectiveness. Comparative Effectiveness Review Number 59 *AHRQ Publication* No. 12-EHC037-EF, April 2012;

http://www.effectivehealthcare.ahrq.gov/ehc/products/182/1026/CER59_Glaucoma-Screening_Final-Report_20120524.pdf

Systematic review 3

A systematic search for this systematic review was conducted up to April 2010 to identify studies evaluating 5 new technologies (confocal scanning laser ophthalmoscopy by Heidelberg Retina Tomography, optical coherence tomography [OCT], scanning laser polarimetry using GDx-VCC, frequency doubling technology, and blue-on-yellow automated perimetry). The reference standards were optic disc assessment or standard achromaticwhite-on-white perimetry. The review included cost analyses or full economic evaluation studies comparing both costs and consequences associated with these technologies.

Of the 410 unique citations retrieved by the search, 6 articles either presented a cost analysis of tests for glaucoma diagnosis or included a review of published economic studies. Of those, 3 studies presented a cost analysis of scanning lasers and OCT, mostly in terms of costs associated with the diagnostic equipment. However, differences in settings or methods made comparisons between these 3 studies difficult. One study indicated that time required to conduct the test may be an important element to consider in economic evaluations. Other reviews of economic studies of glaucoma screening identified in the search did not cite any published studies evaluating these new technologies.

Despite our extensive search, and in line with previous findings, no cost-effectiveness studies of the newer diagnostic tests could be identified.

References

Tarride JE, Burke N, Hopkins RB, Goeree R, Hodge WG. New glaucoma diagnostic technologies: a systematic review of economic studies. *Can J Ophthalmol* 2011;46:89-90; PMID: 21283168

Review 4

A non-systematic review of the literature was conducted in PubMed by October 2010 with key words Glaucoma and cost. No randomized screening, diagnostic and follow-up trials were found of the clinical effectiveness nor cost-effectiveness of the optimum test set preventing visual disability

References

Tuulonen A. Economic considerations of the diagnosis and management for glaucoma in the developed world. *Curr Opin Ophthalmol* 2011;22:102-9; PMID: 21192264

On-going Finnish randomized screening trial

The on-going randomised prospective cohort study - Northern Finland Birth Cohort (NFBC) Eye Study – trial is designed to address the following questions: what is the best combination of diagnostic tests for

detecting glaucoma in an unscreened population, what are the benefits and disadvantages of the screening to the individual and the society and is glaucoma screening both effective and cost-effective. The prevalence, incidence and risk factors of glaucoma and other eye diseases will be evaluated, as well as their impact on quality of life.

A postal questionnaire covering extensively the medical and socioeconomical background was sent to the 10 300 subjects. The effectiveness and the cost-effectiveness of glaucoma screening will be calculated. The response rate of the questionnaire was 67% (n = 6 855).

For the Eye Study the subjects were randomised to the screening group (50%) and the control group (50%). 871 randomised subjects had undergone the eye screening protocol by the end of April 2013. In the future, both groups (100%) will be examined.

The screening protocol includes automated and manifest refraction, best corrected visual acuity, central corneal thickness, intraocular pressure, Humphrey 24-2 perimetry, stereoscopic optic nerve head (ONH) photography, retinal nerve fibre layer (RNFL) photography and imaging with Scanning Laser Ophthalmoscopy (HRT), Scanning Laser Polarimetry (GDx) and Optical Coherence Tomography (OCT). Two ophthalmologists evaluate the ONH and RNFL photographs and the visual fields independently. All suspected glaucoma cases are re-evaluated by two independent glaucoma experts. HRT, GDx and OCT findings are assessed separately

References

Saarela V, Karvonen E, Stoor K, Hägg P, Luodonpää M, Kuoppala J, Taanila A, Tuulonen A. The Northern Finland Birth Cohort Eye Study: Design and baseline characteristics. *BMC Ophthalmol.* 2013 Oct 8;13:51. doi: 10.1186/1471-2415-13-51.

[E15]

Level of evidence = C

Sizeable inter- and intraobserver variability and substantial uncertainty may be observed for all tonometers, including Goldmann applanation tonometer (GAT), casting doubt on the validity of GAT as the default standard. Studies have been generally poorly reported.

Systematic review

The aim of systematic review was to compare the agreement of IOP readings of one or more tonometers in adults with the readings of GAT as the reference tonometer and to explore the factors affecting the agreement between tonometers including CCT and IOP level. Tonometry performed by any type of examiner including optometrists, ophthalmologists, nurses, technicians and patients was included. The primary outcome was the agreement between a tonometer and the reference standard. Secondary outcomes included inter- and intraobserver reliability for two observations. The quality of all included studies was assessed using a checklist.

A total of 102 studies reporting 130 comparisons involving 11 582 participants (15 525 eyes) were included. The studies took place in 26 countries in 1988-2010. The studies assessed the agreement of at least one tonometer with Goldmann Applanation Tonometer. Comparators were dynamic contour tonometer (DCT), non-contact tonometer (NCT), Ocular response analyser (ORA), Ocuton S, rebound tonometer (iCare), TonoPen, and transpalpebral tonometer. 99 studies had sufficient data for meta-analysis.

Studies were generally poorly reported. The agreement in IOP (95% limits) varied across tonometers, from 0.2 mmHg (–3.8 to 4.3 mmHg) for NCT to 2.7 mmHg (–4.1 to 9.6 mmHg) for Ocuton S. Sizeable inter- and intraobserver variability and substantial uncertainty was observed for all tonometers, including GAT, casting doubt on the validity of GAT as the default standard. Sensitivity analyses and subgroup analyses were undertaken to seek to identify sources of heterogeneity although with little light generated.

Due to magnitude of observed heterogeneity, it was not possible to undertake a subgroup analysis of CCT even on the basis of a crude dichotomy of the group for any of the studies. The exclusion of (based on reporting) lower-quality studies similarly did not provide clarity in this regard, although this perhaps reflects the substantial amount of non-reporting of key information in the studies.

References

Burr JM, Botello-Pinzon P, Takwoingi Y. Surveillance for ocular hypertension: an evidence synthesis and economic evaluation. *Health Technology Assessment* 2012;16:1-271; PMID: 22687263

[E16]

Level of evidence = D

The significance of measurements of diurnal curve on progression of glaucoma is unclear.

Systematic review

The aim of the systematic review] was conducted to determine whether the use of a diurnal tension curve (multiple IOP measurements over a minimum 8 hour duration) is more effective than not using a diurnal tension curve (single IOP measurements) to assess IOP fluctuation as a risk factor for the development or progression of glaucoma and to determine whether the use of a diurnal tension curve is beneficial for glaucoma suspects or patients with progressive glaucoma despite normal single office IOP measurements and leads to a more effective disease management strategy.

Literature search was performed on July 22, 2010 for studies published from January 1, 2006 until July 14, 2010. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with unknown eligibility were reviewed with a second clinical epidemiologist, then by a group of epidemiologists until consensus was established. The quality of evidence was assessed as high, moderate, low or very low according to GRADE methodology.

Inclusion criteria were open angle glaucoma (established or OHT high risk) in an adult population, IOP measurement by Goldmann applanation tonometry, number and timing of IOP measurements explicitly reported (e.g., 5 measurements a day for 5 visits to generate a diurnal curve or 1 measurement a day [no diurnal curve] every 3 months for 2 years). IOP parameters include fluctuation (range [peak minus trough] or standard deviation) and mean outcome measure = progression or development of glaucoma. Study reports results for ≥ 20 eyes. The outcome of interest was progression or development of glaucoma.

There is very low quality evidence (retrospective studies, patients on different treatments) for the use of a diurnal tension curve or single measurements to assess short or long-term IOP fluctuation or mean as a risk factor for the development or progression of glaucoma. There is very low quality evidence (expert opinion) whether the use of a diurnal tension curve is beneficial for glaucoma suspects or patients with progressive glaucoma, despite normal single office IOP measurements, and leads to a more effective disease management strategy.

References

Medical Advisory Secretariat. Diurnal tension curves for assessing the development or progression of glaucoma: an evidence-based analysis. *Ont Health Technol Assess Ser* 2011;11:1-40; PMID: 23074414
http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/diurnal_tension_curves_20110629.pdf

[E17]

Level of evidence = D

Although thin cornea may result in lower IOP readings than thick cornea, no reliable conversion equation exists to correct the IOP readings.

References

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Gunvant P, O'Leary DJ, Baskaran M. Evaluation of tonometric correction factors. *J Glaucoma* 2005;14:337-43; PMID: 16148580

[E18]

Level of evidence = C

Devices for measuring the central corneal thickness give variable results and may not give comparable results.

References

Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. *Survey Ophthalmol* 2001;44:367-408; PMID: 10734239

Radford SW, Lim R, Salmon JF. Comparison of Orbscan and ultrasound pachymetry in the measurement of central corneal thickness. *Eye* 2004;18:434-6; PMID: 15069445

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Rainer G, Petternel V, Findl O. Comparison of ultrasound pachymetry and partial coherence interferometry in the measurement of central corneal thickness. *J Cataract Refract Surg* 2002;28:2142-5; PMID: 12498849

[E19]

Level of evidence = D

There is no evidence that CCT (central corneal thickness) corrected IOP would improve risk prediction for development of glaucoma in ocular hypertension, or prevent glaucoma induced visual disability.

The purpose of the study was to determine if the accuracy of the baseline prediction model for the development of primary open angle glaucoma (POAG) in patients with ocular hypertension (OHT) can be improved by correcting intra ocular pressure (IOP) for central corneal thickness (CCT).

Reanalysis of the prediction model for the risk of developing POAG was carried out using the same baseline variables (age, IOP, CCT, VCDR, and PSD) except that IOP was adjusted for CCT using correction formulae. A separate Cox proportional hazards model was run using IOP adjusted for CCT by each of the 5 formulae published to date. Models were run including and excluding CCT.

The material consisted of a total of 1433 of 1636 participants randomized to OHTS who had complete baseline data for factors in the prediction model: age, IOP, CCT, vertical cup-to-disc ratio (VCDR), and pattern standard deviation (PSD).

C-statistics for prediction models that used IOP adjusted for CCT by various formulas ranged from 0.75 to 0.77, no better than the original prediction model (0.77) that did not adjust IOP for CCT.

References

Brandt JD, Gordon MO, Gao F . Adjusting intraocular pressure for central corneal thickness does not improve prediction models for primary open-angle glaucoma. *Ophthalmology* 2012;119:437-42; PMID: 21705084

[E20]

Level of evidence = D

The association between corneal thickness as an independent risk factor and glaucoma is unclear.

Systematic review

A systematic review was undertaken to identify prediction models for development of OAG that include IOP as a predictor, and to critically appraise the construction and validation of the models. Databases were searched from 1987 until January 2011 with no language restriction. Prospective studies and studies in which patients were retrospectively identified but prospectively followed up were included if: only patients with OHT were recruited, they were conducted post 1987, when reliable computerised perimetry became the standard of care, a prediction equation for the development of OAG could be obtained, the reported model included at least two variables, one of which was IOP and the performance of the model was reported in any data set (derivation or validation) of longitudinal follow-up of a cohort initially free of OAG irrespective of the length of follow-up. Adults with OHT (defined as elevated IOP but no evidence of glaucomatous optic nerve damage or visual field loss) aged ≥ 18 years were included.

The quality of included studies was assessed using a checklist that included assessment of the definition of OAG, the method of measurement of candidate predictors and how continuous predictors were used in the models.

Of 565 articles screened, 54 full-text papers were retrieved for detailed evaluation of eligibility. Forty-nine papers were excluded. Of the five included papers, four were based on the results of two RCTs, the OHTS (Ocular Hypertension Treatment Study) and the European Glaucoma Prevention Study. These provided three models for which prediction equations were available (full and reduced OHTS models and the pooled OHTS-EGPS means model). The fifth paper reported the independent validation study of the OHTS model in the Diagnostic Innovations in Glaucoma Study (DIGS) cohort.

Both the OHTS and EGPS were large prospective studies that included patients with OHT aged ≥ 30 years who had no evidence of glaucomatous damage at baseline. The OHTS randomised 1636 individuals, with an IOP 24-32 mmHg in one eye and an IOP 21-32 mmHg in the other eye, to treatment or observation. The EGPS randomised 1081 individuals with IOP ≥ 22 mmHg in at least one eye to treatment or placebo. The inclusion and exclusion criteria used in the DIGS cohort were very similar to those used by the OHTS (IOP ≥ 24 mmHg in one eye and ≥ 21 mmHg in the other eye). The original protocols of the OHTS and EGPS did not include CCT and measurements were taken later, 2–3 years after randomisation of the last patient enrolled in the studies. All patients in the DIGS had CCT measurements taken during follow-up.

In univariate analyses of the OHTS or pooled OHTS and EGPS data, statistically significant predictors for development of OAG were age, IOP, CCT, VCD ratio, horizontal cup-to-disc (C/D) ratio, PSD, history of heart disease, gender, race and diabetes mellitus. In both OHTS and EGPS, history of diabetes and heart disease were self-reported and not clinically verified. CCT was a major predictor for the development of OAG

over 5 years. For the OHTS-EGPS model, there was an increase in risk per 40- μ m decrease in corneal thickness (HR 2.04, 95% CI 1.70 to 2.45).

The authors conclude, however, that **it is unclear to what extent lower CCT is responsible for the increased risk of OAG**. Previous studies have shown that CCT tends to decrease with increasing age. It is also well known that corneal thickness influences the measurement of IOP: IOP is overestimated in thick corneas and underestimated in thin ones. Nevertheless, **there is no consensus on the clinical significance of the effect of CCT on IOP measurements**. No correlation was found between CCT and IOP in either the OHTS or the EGPS. This may be owing to exclusion of patients with normal or very low IOPs and also those with very high IOPs. In the Early Manifest Glaucoma Trial, CCT was identified as a significant predictive factor for glaucoma progression in patients with higher baseline IOP but not in those with lower baseline IOP.

Racial differences in CCT have been reported in several population studies, with individuals of African ancestry having thinner corneas, on average, than Caucasians, Hispanics or Asians. It has been suggested that black race may not be an independent risk factor because black patients tend to have higher IOP, thinner corneas and higher C/D ratios than other patients with OHT and are therefore generally at a higher risk than white patients. In the OHTS and OHTS-EGPS, when either VCD ratio or CCT was included in the multivariate model, race was no longer statistically significant.

CCT has also been shown to be a highly heritable trait. Because thinner CCT has also been found to predict progression of visual loss in patients with OAG, it is plausible that a biological link exists between aspects of the cornea that regulate its thickness and the physical and structural properties of tissues involved in glaucoma pathogenesis.

References

Burr JM, Botello-Pinzon P, Takwoingi Y. Surveillance for ocular hypertension: an evidence synthesis and economic evaluation. *Health Technology Assessment* 2012;16:1-271; PMID: 22687263

[E21]

Level of evidence = C

Although spectral domain optical coherence tomography may provide better test-retest variability of the circumpapillary retinal nerve fiber layer and disc morphometric parameters, all systems need improvement in their test-retest variability measurement capabilities.

Review

The author reports test-retest variability from 52 studies including planimetry from disc images, confocal scanning laser ophthalmoscope (HRT), scanning laser polarimeter (GDx), spectral domain optical coherence tomography (SD OCT), ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT).

In analyzing disease progression, either trend-type or event-type analysis is used. The confirmation of deterioration requires clear evidence which change from baseline exceeds the variability attributable to both the patient and the instrument, i.e. assessment of the test-retest variability is indispensable in determining the optimal frequency of performing imaging test.

The test-retest variability of a system is estimated e.g. by calculating the coefficient of variation (CV), intraclass correlation coefficient (ICC), and minimum detectable changes (MDC). Coefficient of variation (CV) values < 10% are considered capable of indicating good reproducibility. Intraclass correlation coefficient (ICC) 1 means perfect reproducibility (test-retest variability = 0). ICC ≥ 0.9 is considered almost perfect and ICC ≥ 0.75 as a cut-off for good reproducibility. Minimum detectable change (MDC) can be calculated on the ICC and standard deviation (SD) of measurement results.

	Number of studies	CV min	CV max	ICC min	ICC max
Disc planimetry	5	3	12	0.67	0.94
HRT	9	2	11	0.85	0.99
GDx	5	2	13	0.84	0.99
SD-OCT	23	1	11	0.62	0.99
UBM	3	5	10	-	-
AS-OCT	7	5	10	0.61	1.0

In HRT, test-retest variability has been extensively studied and reported to depend on patient age, severity of glaucoma, image quality, cylindrical error, lens opacity, surface geometry and reference plane. The rim area change in progressive eyes is reported to vary -0.005 - 0.012 mm² per year. In order to detect 80% of a yearly change of -0.012 mm² with HRT, 16 examinations are needed over 4 years which produces

30% false positives. If one takes 8 examinations over 4 years, 60% of a yearly change of -0.012 mm^2 will be detected with 20% false positives.

In GDx test-retest variability is reported to be worse in more advanced stages of glaucoma. 50% of progressing eyes with 95% specificity can be detected using the fast mode analysis of GDx Guided Progression Analysis (GPA).

Although the SD-OCT seems to provide better test-retest variability of the circumpapillary retinal nerve fiber layer (RNFL) and disc morphometric parameters, the systems need improvement in their test-retest variability measurement capabilities. Conservative estimate of MDC would be around $4 \mu\text{m}$. When $50 \mu\text{m}$ (difference between normal and advanced glaucoma) is divided by $4 \mu\text{m}$, glaucoma progression can be divided 13 stages, i.e. the same as with visual fields in the EMGT study (difference between normal and advanced glaucoma -25 db divided by the mean yearly change of 2 dB indiatinf progression).

Although knowing the test-retest variability would be indispensable in determining the optimal frequency of performing imaging tests, in every-day clinical work it seems currently impossible to take into account the large number of parameters and their largely variable reproducibility.

References

Araie M. Test-retest variability in structural parameters measured with glaucoma imaging devices. *Jpn J Ophthalmol* 2013;57:1-24; PMID: 23138681

[E22]

Level of evidence = D

The clinical value of imaging instrument as an addition to gonioscopy is unclear.

The objective was to assess the published literature to determine whether anterior segment imaging provides sufficient information to be considered a substitute for gonioscopy. Literature searches of the PubMed and Cochrane Library databases were last conducted on July 6, 2011. The searches yielded 371 unique citations. Members of the Ophthalmic Technology Assessment Committee Glaucoma Panel reviewed the titles and abstracts of these articles and selected 134 of possible clinical significance for further review of which 79 studies met the inclusion criteria. The level of evidence was assessed using the scheme adopted by the American Academy of Ophthalmology.

Quantitative and qualitative parameters defined from ultrasound biomicroscopy (UBM), anterior segment optical coherence tomography (OCT), Scheimpflug photography, and the scanning peripheral anterior chamber depth analyzer (SPAC) demonstrate a strong association with the results of gonioscopy. There is substantial variability in the type of information obtained from each imaging method. Imaging of structures posterior to the iris is possible only with UBM. Direct imaging of the anterior chamber angle (ACA) is possible using UBM and OCT. The ability to acquire OCT images in a completely dark environment allows greater sensitivity in detecting eyes with appositional angle closure. Noncontact imaging using OCT, Scheimpflug photography, or SPAC makes these methods more attractive for large-scale PAC screening than contact imaging using UBM.

Authors' conclusions: Although there is evidence suggesting that anterior segment imaging provides useful information in the evaluation of PAC, none of the imaging methods provides sufficient information about the ACA anatomy to be considered a substitute for gonioscopy.

References

Smith SD, Singh K, Lin SC, Chen PP, Chen TC, Francis BA, et al. Evaluation of the anterior chamber angle in glaucoma: a report by the american academy of ophthalmology. *Ophthalmology* 2013 Oct;120(10):1985-1997

[E23]

Level of evidence = B

No distinct parameters of the optic nerve head (e.g. cup/disc –ratio) seem to separate glaucoma subjects from healthy individuals.

References

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[E24]

Level of evidence = C

The inter-observer congruency (kappa statistics) in evaluating disc images in cross-sectional studies may vary between 0.5 to 0.9 (on average 0.7).

Study 1

An online survey, including questions relating to qualification, practice environment, and diagnostic methods was completed by 1256 optometrists. Based on their responses, 208 (17%) were selected to undertake an online disc assessment exercise. Optometrists evaluated the same disc images previously assessed by European ophthalmologists as part of the European Optic Disc Assessment Trial (EODAT); the task was to state if the disc appeared healthy or glaucomatous. There were 110 stereoscopic disc images, of which 40 were healthy, 48 glaucomatous, and six ocular hypertensive, with 16 duplicate images. Sensitivity, specificity and overall accuracy were calculated and compared between optometrist groups and with the EODAT ophthalmologists using permutation analysis.

Median sensitivity was 0.92 (95% CI: 0.70, 1.00) and median specificity was 0.74 (95% CI: 0.62, 0.88). Median overall accuracy was 80% (95% CI: 67%, 88%). Agreement between optometrists was moderate (Fleiss' κ : 0.57). Optometrists with higher qualifications did not have overall higher sensitivity than those without ($p = 0.23$), but had higher specificity ($p = 0.001$) and higher overall accuracy ($p < 0.001$). Optometrists displayed higher sensitivity but lower specificity than the EODAT ophthalmologists.

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Hadwin SE, Redmond T, Garway-Heath DF et al. Assessment of optic disc photographs for glaucoma by UK optometrists: the Moorfields Optic Disc Assessment Study (MODAS). *Ophthalmic Physiol Opt* 2013;33:618-24; PMID: 23634792

Study 2

The purpose of the study was to determine the diagnostic accuracy of judging optic disc photographs for glaucoma by ophthalmologists. A total of 243 of 875 (27%) invited ophthalmologists in 11 European countries classified 40 healthy eyes and 48 glaucomatous eyes with varying severity of the disease on stereoscopic slides. Duplicate slides were provided for determining intraobserver agreement.

The intraobserver agreement (kappa) varied between -0.13 and 1.0 and was on average good (0.7). The overall diagnostic accuracy of ophthalmologists was 81% (standard deviation [SD], 6.8; range, 61%-94%).

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Reus NJ, Lemij HG, Garway-Heath DF, Airaksinen PJ, Anton A, Bron AM, Faschinger C, Holló G, Iester M, Jonas JB, Mistlberger A, Topouzis F, Zeyen TG. Clinical assessment of stereoscopic optic disc

photographs for glaucoma: the European Optic Disc Assessment Trial. *Ophthalmology*. 2010 Apr;117(4):717-23. doi: 10.1016/j.ophtha.2009.09.026. Epub 2010 Jan 4.

Study 3

Two hundred seven subjects (109 glaucoma and 98 normal subjects) were evaluated to study the agreement of optic disc measurements obtained with the Cirrus high-density optical coherence tomography (HD-OCT) and the Heidelberg retina tomograph (HRT) and compare the intervisit, test-retest variability between the instruments.

One eye from each individual was selected randomly for optic disc imaging by the Cirrus HD-OCT and the HRT. Areas of the optic disc and the cup, cup volume, vertical cup-to-disc ratio and cup-to-disc area ratio were compared between the instruments. The OCT measurements were corrected for ocular magnification using the Littman's formula. The measurement agreement was evaluated with the Bland-Altman plots. The intervisit test-retest variability was examined in 17 randomly selected glaucoma patients who underwent optic disc imaging weekly for 8 consecutive weeks. The intraclass correlation coefficients (ICC) and the reproducibility coefficients of the optic disc parameters were computed.

The OCT measured smaller optic disc and rim areas and greater cup volume, vertical cup-to-disc ratio and cup-to-disc area ratio than the HRT did (all with $P < 0.001$). There were proportional biases in the Bland-Altman plots between OCT and HRT optic disc measurements except for rim area and cup-to-disc area ratio. The 95% limits of agreement of rim area ranged between -0.28 and 0.88 mm² before, and between -0.22 and 0.92 mm² after correction for ocular magnification. **Optic disc assessment by spectral-domain OCT and confocal scanning laser ophthalmoscopy demonstrates poor agreement.**

References

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Earlier studies with supporting the evidence

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Sommer A, Quigley HA, Robin AL . Evaluation of nerve fiber layer assessment. *Arch Ophthalmol* 1984;102:1766-71; PMID: 6508617

**[E25]****Level of evidence = D**

The evaluation of *progression* from disc images shows large variability (agreement between 54–92%, on average 72%).

References

Chee RI, Silva FQ, Ehrlich JR, Radcliffe NM. Agreement of flicker chronoscopy for structural glaucomatous progression detection and factors associated with progression. *Am J Ophthalmol* 2013;155:983-90; PMID: 23462231

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[E26]

Level of evidence = D

There may be large variations in sensitivity and specificity of clinical and digital structural examinations which depend on the comparison test. The risk of bias in study designs is significant.

Systematic review

A systematic review was conducted through October 6, 2011 and existing databases were screened to identify relevant systematic reviews. The quantity, quality, and consistency of the body of available evidence was assessed for answering the question 'What is the predictive value of screening tests for open-angle glaucoma?'

One systematic review (Burr et al., 2007) addressed the diagnostic test accuracy of candidate screening tests for the detection of OAG. Burr et al. (2007) conducted a diagnostic test accuracy review of candidate diagnostic and screening tests for OAG. Highly sensitive systematic electronic searches were undertaken by December 2005. The investigators included 40 studies totaling more than 48,000 participants 40 years of age and older and those at high risk for the development of OAG based on demographic characteristics or comorbidities. The focus was on studies of participants likely to be encountered in a routine screening setting. The primary reference standard was confirmation of OAG at followup examination. Also considered was diagnosis of OAG requiring treatment. No studies were at low risk of bias. A small subset of eight studies was judged to have higher quality.

After the Burr et al. 2007 systematic review, 4,960 studies were identified, of which 83 studies addressing the accuracy of screening tests were eligible. The sensitivity of standard automated perimetry (SAP) was higher than Goldmann tonometry, similar to the Heidelberg retina tomograph (HRT), and lower than disc photos or frequency doubling technology (FDT) visual field testing. The specificity of SAP was higher than disc photos and FDT, similar to HRT, and lower than Goldmann tonometry. Some comparisons of tests could not be performed due to variability in populations and reported thresholds. No other studies were identified.

68% of studies were at high risk of spectrum bias (not representative of those who would receive the test in practice). 6% had differential verification bias (different reference standards). The candidate tests were interpreted without knowledge of reference standard in only 29% of studies. 48% of the studies did not include an explanation of withdrawals from the study, and 46% of the studies reported the number of uninterpretable test results. Only 3 of 83 studies included a population-based sample.

1. Tests of Optic Nerve Structure

1.1. Heidelberg Retina Tomograph II

Evidence From Burr et al., 2007

HRT II was a diagnostic test of interest in 3 studies. Using the common criterion of one or more results that are borderline or outside normal limits, the pooled sensitivity was 86 percent (95% credible interval [CrI], 55 to 97) and the pooled specificity was 89 percent (95% CrI, 66 to 98).

Evidence From Primary Studies

Seventeen primary studies included measures of diagnostic accuracy for HRT II. Two studies specifically focused on detecting early or moderate glaucoma. One study enrolled 60 participants with glaucoma (30 with early defects and 30 with moderate visual field defects) and 60 healthy volunteers. AUC values were reported to be in the range of 0.474 (disc area ratio parameter) to 0.852 (vertical cup-to-disc ratio parameter). Another study enrolled 70 participants with early or moderate glaucoma and 70 healthy volunteers. The range of sensitivity across 12 parameters was from 47 percent (RNFL cross-sectional area) to 74 percent (linear cup/disc area ratio), and the range of specificity was from 47 percent (mean RNFL thickness) to 71 percent (cup shape measure). The remaining 15 studies explored comparisons of HRT II with other devices, such as the GDx with VCC (variable corneal compensation), OCT, HRT III, and FDT. Overall, HRT II was found not to perform as well as GDx VCC, OCT, or FDT. HRT II and HRT III were found to have a similar diagnostic profile. Three of the included studies concluded that HRT II was not an appropriate tool for population-based glaucoma screening studies.

1.2. Heidelberg Retina Tomograph III

Evidence From Primary Studies

Eleven studies examined the diagnostic accuracy of HRT III. One study identified 81 participants with early visual field loss (out of 247 participants with glaucoma) and 142 healthy volunteers. Early visual field loss was defined as a mean deviation less than 5dB. The sensitivity of the Glaucoma Probability Score for distinguishing eyes with early field loss from healthy eyes was 68 percent, and that of the Moorfields Regression Analysis was 72 (at a fixed specificity of 92 percent). The investigators concluded: "Moorfields Regression Analysis and Glaucoma Probability Score have similar ability to detect glaucomatous changes, and typically agree. The relative ease and sensitivity of the operator-independent Glaucoma Probability Score function of the HRT III may facilitate glaucoma screening."

Another study compared four imaging methods for their ability to distinguish early glaucoma from healthy eyes. 46 eyes of 46 participants with early OAG and 46 eyes from healthy volunteers were enrolled. Sensitivity (parameter: reference height) ranged from 4 to 70 percent (Frederick S. Mikelberg discriminant

function and Reinhard O. W. Burk discriminant function) when holding the specificity of the test constant at 95 percent.

2. Ophthalmoscopy

Evidence From Burr et al., 2007

Burr et al. (2007) included seven studies addressing the diagnostic accuracy of ophthalmoscopy. Using a common cutoff point of a vertical cup-to-disc ratio greater than or equal to 0.7, pooled sensitivity for the five studies with this common criterion was 60 percent (95% CrI, 34 to 82 percent), and specificity was 94 percent (95% CrI, 76 to 99). The diagnostic odds ratio (DOR) was 25.7 (95% CrI, 5.79 to 109.50), suggesting a 26-fold higher odds of a positive test among those with glaucoma than those without glaucoma.

3. Optical Coherence Tomography (OCT)

Evidence From Primary Studies

Of the 47 included studies that investigated the diagnostic accuracy of OCT, 34 considered the Stratus OCT, 10 included the Cirrus OCT, 6 considered the RTVue OCT, 2 included the Spectralis OCT, 2 examined the OTI OCT, and 1 included the OTI Spectral OCT/SLO. Across the 34 studies that examined the Stratus OCT, all were at high risk of spectrum bias because those with known disease as well as those with healthy eyes were enrolled in the studies. The sample size ranged from 26 to 95 participants with glaucoma or suspected glaucoma and 37 to 128 healthy volunteers, with one study also enrolling 130 participants with ocular hypertension. For the parameter average RNFL thickness, the range of sensitivity was 24 to 96 percent, suggesting appreciable heterogeneity among the studies. The range of specificity was 66 to 100 percent.

4. Optic Disc Photography

Evidence From Burr et al., 2007

There were six studies of optic disc photography. The range of sensitivity was from 65 to 77 percent, and the range of specificity was from 59 to 98 percent.

Evidence From Primary Studies

Two studies of the diagnostic accuracy of optic disc photography and one study of cup-to-disc ratio measurement as measured by an ophthalmologist using a slit-lamp biomicroscope and 78 Diopter lens were included. Danesh-Meyer et al. (2006) included participants with OAG as well as glaucoma suspects and healthy volunteers. The AUC (comparison of those deemed to have glaucoma and borderline disease vs. normal) was 0.84 (95% confidence interval [CI], 0.74 to 0.92) for the cup-to-disc ratio and 0.95 (95% CI, 0.80 to 0.98) for the Disc Damage Likelihood Score, suggesting that the Disc Damage Likelihood Score is a more effective means of discriminating people with and without disease. The diagnostic accuracy of cup-to-disc

ratio measurement from the Francis et al. (2011) study is described in the section on FDT C-20 perimetry [E37].

5. RNFL Photography

Evidence From Burr et al., 2007

The common cut-off point for the four included studies was diffuse and/or localized defect observed on RNFL photographs. The pooled diagnostic odds ratio was 23.1 (95% CrI, 4.41 to 123.50), and the pooled sensitivity and specificity were 75 and 88 percent, respectively.

Evidence From Primary Studies

Two studies examined the accuracy of RNFL photography. One study analyzed RNFL photographs of 72 glaucoma and 48 healthy participants. Results showed the RNFL defect score II, with an AUC of 0.75 ($p < 0.001$), was the best parameter for discriminating early glaucoma from healthy eyes (sensitivity, 58.3 percent; specificity, 95.8 percent). Another study compared RNFL photography with the GDx with VCC in 42 participants with OAG, 32 persons suspected of having OAG, and 40 healthy volunteers. The sensitivities of the global RNFL score were 36 and 81%, respectively, for fixed specificities of 95 and 80%. At a fixed specificity of 95%, the sensitivity of the Nerve Fiber Indicator was 71% versus the 36% reported above for red-free photos. Overall, the global RNFL score determined from red-free photos did not perform as well as scanning laser polarimetry. The AUC was 0.91 for the GDx with VCC Nerve Fiber Indicator versus 0.84 for the global RNFL score.

6. Scanning Laser Polarimetry (GDx)

Evidence From Primary Studies

Twenty-seven studies included an investigation of the GDx with VCC. The aim of eight studies was to discriminate early glaucoma from no disease. In the studies that focused on early OAG, the range of sensitivity across all comparisons and cutoffs for the most frequently reported parameter—Temporal, Superior, Nasal, Inferior, Temporal average—was 30 to 82%. Specificity was fixed at 80, 90, or 95% in three studies, and the lowest reported specificity was 66%. The range in sensitivity for the nerve fiber indicator parameter across all comparisons and cutoffs was from 28 to 93%. The lowest specificity reported was 53 percent or was fixed at 80, 90, or 95%.

Three studies examined the GDx with enhanced corneal compensation (ECC). The sample sizes of the included studies ranged from 63 to 92 glaucoma participants and 41 to 95 healthy volunteers. One study compared the AUCs for GDx with VCC and GDx with ECC, and reported that GDx with ECC performed significantly better than GDx with VCC for the parameters Temporal, Superior, Nasal, Inferior, Temporal average, Superior average, and Inferior average ($p = <0.01$). Two other studies and concurred that imaging with ECC appears to improve the ability to diagnose OAG.



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[E27]

Level of evidence = D

The sensitivity and specificity of visual field examinations vary considerably depending on the selected reference standard. The study designs indicate a high risk of bias.

Systematic review

A systematic review was conducted through October 6, 2011 and existing databases were screened to identify relevant systematic reviews. The quantity, quality, and consistency of the body of available evidence was assessed for answering the question 'What is the predictive value of screening tests for open-angle glaucoma?'

One systematic review (Burr et al., 2007) addressed the diagnostic test accuracy of candidate screening tests for the detection of OAG. Burr et al. (2007) conducted a diagnostic test accuracy review of candidate diagnostic and screening tests for OAG. Highly sensitive systematic electronic searches were undertaken by December 2005. The investigators included 40 studies totaling more than 48 000 participants 40 years of age and older and those at high risk for the development of OAG based on demographic characteristics or comorbidities. The focus was on studies of participants likely to be encountered in a routine screening setting. The primary reference standard was confirmation of OAG at followup examination. Also considered was diagnosis of OAG requiring treatment. No studies were at low risk of bias. A small subset of eight studies was judged to have higher quality.

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Humphrey Visual Field Analyzer (HFA) - Evidence From Primary Studies

Ten studies examined the diagnostic accuracy of the HFA. Of these, six examined HFA Short Wavelength Automated Perimetry; two tested HFA-SAP, (SAP)-SITA, and HFA SAP-Full Threshold (FT); four examined HFA-SITA-Standard; and one tested the HFA SITA-Fast protocol. The HFA Short Wavelength Automated Perimetry testing protocol (the most frequently reported) included 25 to 286 participants with

glaucoma and 22 to 289 healthy volunteers across the six included studies. Sensitivity across all comparisons and cutoffs for the mean deviation ranged from 25.9 to 83 percent. Specificity ranged from 80 to 95.2 percent. Cutoff points ranged from -5.42 to -11.06 dB.

SAP Suprathreshold Test - Evidence From Burr et al., 2007

Nine studies, including the Baltimore Eye Survey and the Blue Mountains Eye Study, examined the SAP suprathreshold test. Although the sensitivity and specificity were similar for the Baltimore and Blue Mountains studies, there was significant heterogeneity among the included studies. The range in sensitivity was 25 to 90 percent; the range in specificity was 67 to 96 percent.

SAP Threshold Test -Evidence From Burr et al., 2007

Among the five studies analyzed for SAP threshold, both Humphrey 30-2 and 24-2 threshold and Octopus 500 were evaluated. The pooled sensitivity was 88 percent, and specificity was 80 percent for the common cutoff point. (The definition of the common cutoff point differed by included study, but is defined in Burr et al.)

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[E28]

Level of evidence = C

If the diagnosis of glaucoma is defined only by the visual field examination methods, the clinical significance of a single abnormal visual field may be small.

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[E29]

Level of evidence = C

In clinical 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, e.g. over 80% of disc haemorrhages may be missed during clinical examination.

Study

The purpose of the study was to compare the rates of detection of optic disc hemorrhages by clinical examination and by review of optic disc photographs at the Optic Disc Reading Center (ODRC) in the annual disc photographs of the Ocular Hypertension Treatment Study (OHTS). Both eyes of 1618 participants were examined for optic disc hemorrhages every 6 months by clinical examination, with dilated fundus examinations every 12 months, and by annual review of stereoscopic disc photographs at the ODRC. Median follow-up was 96.3 months.

Stereophotography-confirmed glaucomatous optic disc hemorrhages were detected in 128 eyes of 123 participants before the POAG end point. Twenty-one cases (16%) were detected by both clinical examination and review of photographs, and 107 cases (84%) were detected only by review of photographs ($P < 0.0001$).

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[E30]

Photography of the nerve fibre layer may support the diagnosis glaucoma.

Level of evidence = C

Study 1

The agreement of angular locations of retinal nerve fiber layer (RNFL) defect margins in glaucomatous eyes using red-free fundus photographs were compared to Cirrus high-definition optical coherence tomography (OCT) RNFL deviation and thickness maps. 380 RNFL defects with clear margins in red-free fundus photographs were overlaid on the OCT deviation and thickness maps. A reference line was drawn between the disc center and the macular center. Lines were also drawn between the optic disc center and the point where the RNFL defect margins crossed the OCT scan circle. The angle between the reference and defect-margin lines defined the angular location of the defect margin.

The angular locations of proximal and distal RNFL defect margins on OCT thickness maps showed good agreement with red-free fundus photographs. However, OCT deviation maps showed greater angular locations for both proximal and distal RNFL defect margins compared with red-free fundus photographs, especially in eyes with higher myopia ($p < 0.05$). This finding should be considered when evaluating RNFL defects using OCT maps.

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Study 2

The ability of clock-hour, deviation, and thickness maps of Cirrus high-definition spectral-domain optical coherence tomography (HD-OCT) in detecting retinal nerve fiber layer (RNFL) defects identified in red-free fundus photographs in eyes with early glaucoma (mean deviation > -6.0 dB) was investigated in a cross-sectional study. 295 eyes with glaucomatous RNFL defects with clear margins observed in red-free fundus photographs and 200 age-, sex-, and refractive error-matched healthy eyes were enrolled.

The width and location of RNFL defects were evaluated by using the red-free fundus photograph. When a RNFL defect detected by red-free fundus photograph did not present as (1) yellow/red codes in the clock-hour map, (2) yellow/red pixels in the deviation map, or (3) blue/black areas in the thickness map, the event was classified as a misidentification of a photographic RNFL defect by Cirrus HD-OCT. In healthy eyes, the presence of false-positive RNFL color codes of Cirrus HD-OCT maps was investigated.

The prevalence of and factors associated with the (1) misidentification of photographic RNFL defects by Cirrus HD-OCT in eyes with glaucoma and (2) false-positive RNFL color codes of Cirrus HD-OCT maps in healthy eyes were assessed.

Among the 295 red-free fundus photographic RNFL defects from 295 eyes with glaucoma, 83 (28.1%), 27 (9.2%), and 0 (0%) defects were misidentified in the clock-hour, deviation, and thickness maps of Cirrus HD-OCT, respectively. Fifty-six defects (19.0%) were misidentified only in the clock-hour map and 27 (9.2%) in both the clock-hour and deviation maps. The misidentification of photographic RNFL defects by Cirrus HD-OCT was associated with a narrower width and a temporal location of RNFL defects ($P < 0.05$). Among the 200 healthy eyes, 25 (12.5%), 30 (15.0%), and 12 (6.0%) eyes had false-positive RNFL color codes in clock-hour, deviation, and thickness maps of Cirrus HD-OCT, respectively.

Among the clock-hour, deviation, and thickness maps obtained with Cirrus HD-OCT, the thickness map showed the best diagnostic ability in detecting photographic RNFL defects. The RNFL thickness map may be a useful tool for the detection of RNFL defects in eyes with early glaucoma.

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Study 3

The objective of the cross-sectional, observational study was to determine whether focal abnormalities of the lamina cribrosa are present in glaucomatous eyes with localized retinal nerve fiber layer (RNFL) defects. 20 eyes of 14 subjects with localized RNFL defects detected by stereophotographs and 40 eyes of 25 age-matched healthy subjects had stereoscopic optic disc photography and in vivo lamina cribrosa imaging using enhanced depth imaging optical coherence tomography (EDI-OCT).

Of 20 eyes with a localized RNFL defect, 15 (75%) had \geq lamina cribrosa defect compared with only 1 of 40 healthy eyes (3%). The largest area lamina cribrosa defect was present in a radial line EDI-OCT scan corresponding with a localized RNFL defect in 13 of 15 eyes (87%). There was good agreement between graders as to whether an eye had an LC defect ($\kappa = 0.87$; 95% confidence interval [CI], 0.73-1.00; $P < 0.001$) and the location of the largest defect ($\kappa = 0.72$; 95% CI, 0.44-1.00; $P < 0.001$).

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Study 4

39 patients (48 eyes) with localized RNFLDs by fundus photography and 48 age-matched control individuals were included into the study. The individuals underwent spectral domain OCT of the retinal nerve layer. In OCT, a localized RNFLD was defined as a dipping of the retinal nerve fiber layer thickness curve into the red-colored band of the graph, measured at a peripapillary circle with a diameter of 3.46 mm.

In the 48 eyes of the study group, 63 localized RNFLDs were seen on the fundus photographs. On the OCTs, 58 of these 63 localized RNFLDs were detected, whereas 5 defects were not detected. Two localized RNFLDs seen on the OCTs were not found on the corresponding fundus photographs. The resulting sensitivity and specificity of OCT for detecting localized RNFLDs were 92% and 96%, respectively. The overall agreement rate between both methods was 94% (90/96), and the κ value was 0.90 ($P < 0.001$). The results of both techniques correlated with each other for the determination of the location (Pearson correlation coefficient (r)=0.99; $P < 0.001$) and the width of the localized RNFLDs (201 ± 123 degrees vs. 207 ± 115 degrees; $r=0.93$; $P < 0.001$).

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Study 5

Four selected glaucoma eyes with visual field defects and retinal nerve fibre layer (RNFL) defects in photography were compared to Stratus optical coherence tomography (OCT) images. The RNFL defects were not picked up by the OCT algorithm or pseudo-colour images. However, defects seemed to be present in OCT grey-scale and raw data images in all four eyes

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[E31]

Level of evidence = D

There is insufficient experience on the use of nerve fiber layer photography in population based screening studies.

On-going population-based study in Finland

The on-going randomised prospective cohort study - Northern Finland Birth Cohort (NFBC) Eye Study – trial is designed to address the following questions: what is the best combination of diagnostic tests for detecting glaucoma in an unscreened population, what are the benefits and disadvantages of the screening to the individual and the society and is glaucoma screening both effective and cost-effective. The prevalence, incidence and risk factors of glaucoma and other eye diseases will be evaluated, as well as their impact on quality of life.

A postal questionnaire covering extensively the medical and socioeconomical background was sent to the 10 300 subjects. The effectiveness and the cost-effectiveness of glaucoma screening will be calculated. The response rate of the questionnaire was 67% (n = 6 855).

For the Eye Study the subjects were randomised to the screening group (50%) and the control group (50%). 871 randomised subjects had undergone the eye screening protocol by the end of April 2013. In the future, both groups (100%) will be examined.

The screening protocol includes automated and manifest refraction, best corrected visual acuity, central corneal thickness, intraocular pressure, Humphrey 24-2 perimetry, stereoscopic optic nerve head (ONH) photography, retinal nerve fibre layer (RNFL) photography and imaging with Scanning Laser Ophthalmoscopy (HRT), Scanning Laser Polarimetry (GDx) and Optical Coherence Tomography (OCT). Two ophthalmologists evaluate the ONH and RNFL photographs and the visual fields independently. All suspected glaucoma cases are re-evaluated by two independent glaucoma experts. HRT, GDx and OCT findings are assessed separately

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[E32]

Level of evidence = D

Although numerous qualitative and quantitative methods have been developed to evaluate visual field progression, the superiority of any of them has been confirmed in prevailing glaucoma patients' quality of life.

Review 1

To obtain an overview of all methods to assess glaucomatous visual field progression, a systematic literature search was performed in April 2009 (PubMed, EMBASE and all databases and registers of the Cochrane Library). A total of 2450 articles were identified. Based on predefined exclusion criteria, studies reporting on patients with glaucoma who were followed for a minimum of 1 year with the use of standard visual field examinations were included so that progression could be assessed. 412 articles were included. From this search, 21 articles that used the Humphrey Visual Field Analyzer (HFA) and studied mean follow-up IOP as a prognostic factor for glaucomatous visual field progression were included. The reproducibility of progression methods in patients with glaucoma was evaluated by performing a second systematic search in PubMed in April 2009.

Ten Questions and Answers

1. How many methods can we choose from to assess visual field progression?

A total of **301 different methods were used in 412 articles**. **Fifteen different perimeters** were found to have been used to assess progression in the literature. **As the majority of 222 studies (54%) reported HFA, increasing to 77% of the articles published since 2000, the review focused on HFA**. HFA methods were further classified into qualitative and quantitative methods. A qualitative method implies that the ophthalmologist decides on the occurrence of progression, whereas a quantitative method uses numeric units for defining progression. Qualitative methods were used 32 times (8%), and quantitative methods, 355 times (92%). Quantitative methods that calculate a rate of progression were used 166 times (47% of quantitative methods). However, most of these studies dichotomized the rate of progression because they aimed to compare different progression methods or estimated treatment effects in a large group of patients. Therefore, even these methods did not really quantify the rate of progression needed for decision making in individual patients.

2. Which method to assess visual field progression can predict the loss of QoL?

The prediction of loss in QoL has not been shown for any method. The ultimate goal of glaucoma management is to prevent the loss of QoL. A method to assess progression should therefore identify patients who will lose vision-related QoL in the future if treatment is not intensified. Although this constitutes the essential goal of monitoring progression, it has not been addressed in empirical research. Empirical research

should ideally randomize patients to different monitoring strategies with a subsequent long follow-up period to evaluate differences in QoL. Future studies should address this issue with the inclusion of methods quantifying the rate of progression.

3. What is the gold standard to assess glaucomatous visual field progression?

There is no gold standard to assess visual field progression.

4. Which methods have been compared with a substitute gold standard of visual field progression or stability?

Several methods have been compared with a substitute gold standard to assess visual field progression. **There is much variation in several accuracy measures within studies and between studies. There seems to be no superior method**, although some have a lower diagnostic odds ratio when compared with other methods within one study.

5. Which methods have been compared with other parameters of disease progression?

One study that used progressive optic disc cupping as a reference standard was found (the Advanced Glaucoma Intervention Study, AGIS).

6. Which methods give a good prediction of future visual field loss?

One way to investigate the sustainability of progression is to use the outcomes after a limited number of follow-up years to predict outcomes after a longer period, both using the same baseline as a reference. Several methods have shown high sustainability (AGIS, CIGTS, EMGT, CNTGS and pointwise linear regression analysis methods). Instead of looking at the sustainability of positive test results, one study used correlations to validate the continuous Visual Field Index (VFI) rate, i.e. whether the VFI rate in the initial 3.3 years could reliably predict the VFI after a mean follow-up time of 8.2 years. A correlation coefficient of 0.78 was found when the predicted VFI was compared with the actual last VFI.

7. Which methods have shown to be related with a presumed prognostic factor of glaucomatous progression?

In total, 20 different methods have been studied in relation with mean intraocular pressure (IOP) in 21 articles. Thirteen methods (65%) found a positive relationship between mean IOP and glaucomatous visual field progression. Six of these methods (30%) showed a statistically significant positive difference ($p < 0.05$) in mean IOP between the progressive and non-progressive groups.

8. Which methods have shown to be reproducible?

No studies about the reproducibility of methods to assess visual field progression **have been conducted**. 21 articles studying **cross-sectional** reproducibility of visual field measures derived from the HFA. In general, these studies showed that mean deviation (MD) values have a higher reproducibility than point wise values.

9. Taking into account the evidence above, which method should we select from the 301 available methods?

The selection from 301 methods was limited to 48 different methods for which data on validity were present. Excluding the different cut-off points, the selection was limited to twelve methods (AGIS, CIGTS, PLR, MD, Glaucoma Change Probability (GCP), EMGT, VFI, Threshold Noiseless Trend (TNT), Werner, clinical scoring system (CSS), CNTGS, and subjective methods).

Methods based on the VFI, MD, GCP or EMGT may be usable, because the required information is available on the printed output of the HFA. Among them, the EMGT method is the only method that has shown to correlate with mean IOP during follow-up. Methods based on MD and EMGT seem to perform well in some studies although they probably overestimated the accuracy of methods. The odds ratio of the EMGT method was relatively low in the other studies.

Qualitative methods could also be useful, although the interpretation of results is dependent on the capacity of the observer. This may cause high interobserver variability. These methods have frequently been used as a substitute for a gold standard. In these cases, however, the assessment was based on the judgement of more than one observer. Qualitative methods have also shown to correlate well with mean IOP, but these findings could be biased because these qualitative assessments were not masked for other clinical information.

10. In the end, what do we really want to know?

Comments of authors:

The current evidence base is not perfect but seems to be fair for a few methods that have been validated. As numerous methods are available, one should probably stop developing many new methods to assess visualfield progression. **The ultimately relevant question, whether using one method to monitor patients is superior to another in preventing loss of QoL, has not been answered. Methods that quantify the rate of visual field progression seem to be the most appropriate for guiding subsequent medical actions in individual patients, because they can be used to estimate individual risk of lifetime visual disability.** This should ideally be studied in prospective studies with long follow-up periods.

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[E33]

Level of evidence = C

The incidence of visual field progression varies considerably and depends mainly on selected methodology (82% of the heterogeneity).

Systematic review

A systematic computerized search was performed in PubMed, EMBASE, and all databases and registers of The Cochrane Library, in April 2009. The search was limited to articles in English, Dutch, French, or German. A total of 2450 articles were identified. All titles and abstracts were screened, and articles were excluded based on predefined exclusion criteria. Of the remaining 782 articles that were studied completely, 48 articles fulfilled the selection criteria. The selected studies had to follow patients with glaucoma for minimally 1 year with the use of conventional visual field examinations.

Twelve articles that studied 30 methods in ten studies were included in the meta-analysis. All methods were named and classified in six groups according to their main characteristics.

1. Glaucoma progression analysis (GPA)

- similar to the visual field endpoint in the EMGT study
- an event analysis based on pattern deviation values and is included in the HFA software.
- When significant deterioration ($p < 0.05$) is seen on the pattern deviation probability maps of the GPA printouts in the same three or more points on three consecutive follow-up tests, the software interprets this as likely progression.

2. Group (AGIS & CIGTS)

- Two methods that were based on the AGIS method, use a scoring system to grade each visual field in the follow-up period.
- The AGIS score is based on the actual decibel deviations at the total deviation plot, while the CIGTS algorithm is based on the p-values obtained from the total deviation probability plot.
- Both scoring systems range from 0 to 20, with 0 representing no field loss and 20 end-stage disease.
- Visual field series are considered to be progressive if the score has a minimal increase of four (with the AGIS method) or three points (with the CIGTS method) and is confirmed by two additional tests.

3. Point-wise linear regression (PLR)

- a linear regression analysis is performed in different individual locations at the visual field.

4. Linear regression analysis with visual field indices

- MD
- Visual field index (VFI) is calculated by the software of the HFA. Each location on the visual field contributes to the VFI, although it is more heavily weighted to central areas of the visual field. A location that is not significantly ($p < 0.05$) depressed on the pattern deviation probability map is considered to have a 100% sensitivity. The VFI is expressed as one percentage, where 100% represents a normal

visual field and 0% represents a perimetrically blind eye. The HFA software performs a linear regression analysis of the VFI against time.

5. Combined a PLR and a linear regression analysis of the MD value

- The methods in this group were variants of the threshold noiseless trend (TNT) program
- The TNT program filters perimetric results and takes into account dependency relations in the visual field.
- Moreover, it combines linear regression analyses of the MD, the cumulative defect curve, and different locations at the visual field.
- Suspected progression is seen for the first time that one of these parameters indicates progression. If this result is repeated by two consecutive examinations or if two or more parameters indicate progression, TNT indicates definite progression

6. Clinical group - methods based on clinical judgement

- Classified in this group were methods based on entirely subjective assessments of visual fields by multiple observers, who had to agree on progression while they were blinded for other clinical data.
- Other methods in this group used certain algorithms for the assessment of visual fields, for example based on the clinical judgement of scotoma's.
- One clinical method was based on nonparametric ranking of MD values. This method objectifies the commonly practised method of monitoring glaucoma patients with the use of MD values. A visual field series is considered progressive as the MD value of a follow-up visual field is worse than the MD of the worse of two baseline fields. This has to be confirmed on at least two visual fields.

Population characteristics

- In total, 1 040 eyes of 948 patients with glaucoma were studied in the ten studies included.
- All patients were derived from western countries, with mean baseline MD values ranging from -3.3 to -10.4 dB, and mean age ranging from 58 to 73 years.
- An average of 1.7 visual fields per year were analysed in the studies.
- Patients received various treatments during the follow-up period.

The mean estimated incidence proportion of progression

- 0.21 (95% confidence interval (CI) 0.15, 0.26) in 6 years, indicating that on average 21% of the study eyes progressed in 6 years (**range from 2% to 62% in 6 years, depending on the method**)
- The incidence proportions of progression according to 30 methods ranged from 0.02 (CI -0.02, 0.05) to 0.62 (CI 0.47, 0.78).
- GPA was the most frequently studied method, with six studies in this meta-analysis. With an incidence proportion of 0.16 (CI 0.14, 0.19), the GPA is in the middle of the ranking of all 30 methods.
- The AGIS based methods and most of the methods based on linear regression analysis with indices showed lower incidence proportions than the GPA method.

- Methods that are based on clinical judgement or the TNT program showed higher incidences than the GPA.

Factors associated with incidence of progression

- **Follow-up time was significantly associated with the incidence of progression**, with an increase in the incidence proportion of approximately 2.1 per cent points per extra follow-up year ($p < 0.001$).
- **Baseline MD was also significantly associated with the incidence of progression**, increasing the incidence proportion by 0.9 per cent points per extra dB of MD loss ($p = 0.025$). No accelerating (quadratic) relationships between these two predictors and the incidence proportions were found ($p = 0.93$ and $p = 0.77$, respectively).
- **Approximately 82% of the heterogeneity in this analysis can be accounted for by the variety of methods used in studies.** The rest of the heterogeneity was explained by the mean baseline MD value and the mean follow-up time.

Comment of authors

The results of the model can only be generalized for clinically treated glaucoma patients with a mean baseline MD value around -7 dB and a mean follow-up time of 6 years. The estimates of progression should be corrected by adding 0.9% to the incidence or by subtracting 0.9% from the incidence, for each dB decrease and increase in baseline MD value, respectively. In the same way, the incidences should be corrected by adding 2.1% for each year extra follow-up. The chosen method accounted for nearly all differences in the incidence of progression that we found in the included studies, with the exception of the part that can be explained by the baseline MD value and the follow-up time.

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[E34]

Level of evidence = B

Visual field examination seems to be dependent on the patient's response, which shows variation both during and between the tests.

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[E35]

Level of evidence = D

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

1. Review: PubMed by October 2010 with key words Glaucoma and cost*

No randomized screening trials were found of the clinical effectiveness or cost-effectiveness of screening for preventing visual disability. Simulation models of cost-effectiveness of systematic screening for glaucoma in Finland and in UK agree partly and suffer from unreliability of input data to be able to draw definitive conclusions.

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2. Finnish simulation model 2

An organized screening program was modeled and compared to opportunistic case finding using a simulation model in a population aged 50–79 years at 5 year intervals. The cost of one QALY gained by screening was €9023 (5% discount rate). During 20 years, in the population of 1 million the cumulative costs exceeding opportunistic case finding in Finland were €30 million avoiding 930 years of visual disability in 701 persons. The results were sensitive to the estimates of specificity of screening tests, screening cost, discount rate, follow-up cost, prevalence of suspected glaucoma and prevalence of glaucoma.

An organized screening program could be a cost-effective strategy especially in older age groups in Finland. Also patients with glaucoma diagnosis were screened in the model. Therapy was not initiated or was withdrawn from patients with ocular hypertension, i.e. only manifest glaucoma was treated. The threshold specificities of diagnostic tests for screening being less costly and more efficient were 96-98%.

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3. Systematic review and UK simulation model

The model simulated that screening might be cost-effective in a 50-year-old cohort at a prevalence of 4% with a 10-year screening interval. General population screening at any age would not be cost-effective. Selective screening of groups with higher prevalence (family history, black ethnicity) might be worthwhile, although this would only cover 6% of the population. Extension to include other at-risk cohorts (e.g. myopia and diabetes) would include 37% of the general population, but the prevalence is then too low for screening to be considered cost-effective. In addition to prevalence, the cost-effectiveness of the screening program was highly sensitive to the perspective on costs. In this model, cost-effectiveness was not particularly sensitive to the accuracy of screening tests. False-positives were not considered in the model.

References

Burr JM, Mowatt G, Hernández R. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess* 2007;11;iii-iv, ix-x, 1-190; PMID: 17927922

4. Systematic review by October 2011

MEDLINE®, Embase, LILACS, and CENTRAL through October 6, 2011, and MEDLINE and CENTRAL (March 2, 2011) and screened an existing database to identify relevant systematic reviews. There is limited evidence on the effects of screening for OAG.

References

Ervin AE, Boland MV, Myrowitz EH . Screening for Glaucoma: Comparative Effectiveness. Comparative Effectiveness Review Number 59 *AHRQ Publication* No. 12-EHC037-EF, April 2012; http://www.effectivehealthcare.ahrq.gov/ehc/products/182/1026/CER59_Glaucoma-Screening_Final-Report_20120524.pdf

5. Australian simulation model

The results suggested the if diagnosis rates of opportunistic case finding could be improved by educating clinicians (without considering costs of training), it would be associated with a rise in eye care costs as more people were treated. Simultaneously, disability adjusted life years (DALYs) would decrease.

References

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6. Study

In the UK the real-life impact of evidence-based NICE indicated no improvement in accuracy for detecting an abnormal IOP and there was a **reduction** in accuracy in detecting an abnormal optic disc.



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7. Study

The post-NICE guideline rising number of referrals did not lead to indentifying more glaucoma patients.

References

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[E36]

Level of evidence = A

Measurement of the intraocular pressure is insufficient for glaucoma screening.

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[E37]

Level of evidence = C

Frequency doubling technology perimetry (FDT) may be feasible in screening for glaucoma. The sensitivity and specificity vary considerably depending on the comparison test. The study designs indicate a high risk of bias.

Systematic review

A systematic review was conducted through October 6, 2011 and existing databases were screened to identify relevant systematic reviews. The quantity, quality, and consistency of the body of available evidence was assessed for answering the question 'What is the predictive value of screening tests for open-angle glaucoma?'

One systematic review (Burr et al., 2007) addressed the diagnostic test accuracy of candidate screening tests for the detection of OAG. Burr et al. (2007) conducted a diagnostic test accuracy review of candidate diagnostic and screening tests for OAG. Highly sensitive systematic electronic searches were undertaken by December 2005. The investigators included 40 studies totaling more than 48,000 participants 40 years of age and older and those at high risk for the development of OAG based on demographic characteristics or comorbidities. The focus was on studies of participants likely to be encountered in a routine screening setting. The primary reference standard was confirmation of OAG at followup examination. Also considered was diagnosis of OAG requiring treatment. No studies were at low risk of bias. A small subset of eight studies was judged to have higher quality.

After the Burr et al. 2007 systematic review, 4,960 studies were identified, of which 83 studies addressing the accuracy of screening tests were eligible. The sensitivity of standard automated perimetry (SAP) was higher than Goldmann tonometry, similar to the Heidelberg retina tomograph (HRT), and lower than disc photos or frequency doubling technology (FDT) visual field testing. The specificity of SAP was higher than disc photos and FDT, similar to HRT, and lower than Goldmann tonometry. Some comparisons of tests could not be performed due to variability in populations and reported thresholds. No other studies were identified.

68% of studies were at high risk of spectrum bias (not representative of those who would receive the test in practice). 6% had differential verification bias (different reference standards). The candidate test were interpreted without knowledge of reference standard in only 29% of studies. 48% of the studies did not include an explanation of withdrawals from the study, and 46% of the studies reported the number of uninterpretable test results. Only 3 of 83 studies included a population-based sample

FDT (C-20-1) Perimetry

Evidence From Burr et al., 2007

The pooled sensitivity and specificity results for the three studies that included FDT (C-20-1) perimetry and the common diagnostic criterion of one abnormal test point were high (92 and 94%, respectively).

Evidence From Primary Studies

Four studies discussed the accuracy of FDT C-20 perimetry. One study enrolled 130 participants with ocular hypertension and 48 healthy volunteers. Using a cutoff of a cluster of at least four points with a sensitivity outside 95% normal limits, or three points outside 98% normal limits, or at least one point outside 99% normal limits, investigators determined the sensitivity of FDT to be 31% and its specificity 73% among the subset of 32 participants with glaucomatous optic neuropathy (of the 130 with ocular hypertension). The investigators concluded that FDT might not be an ideal test for participants with early defects. Another study enrolled 35 participants with known OAG and 35 age- and sex-matched controls with no evidence of glaucoma. Investigators used FDT, noncontact tonometry, and a questionnaire individually and in all possible combinations to determine the accuracy of single and combination tests. FDT's sensitivity was 58% and its specificity was 99%. Overall, FDT was determined to be the best among the candidate single and combination tests in the study, despite fair sensitivity for detecting OAG.

One study enrolled glaucoma patients who had never experienced perimetry prior to the study. The investigators reported that 21 (33% percent) of the 64 participants with glaucoma were identified as having early disease, but data were not provided for this subgroup. Sensitivity and specificity were 86 and 74%, respectively, for the presence of at least one abnormal location and 83 and 83 percent, respectively, for two or more abnormal locations, regardless of severity.

One study conducted population-based screening of 6,082 Latinos age 40 years and older as part of the Los Angeles Latino Eye Study (LALES) to determine the diagnostic accuracy of candidate screening tests performed alone or in combination.⁸¹ Participants completed Humphrey Visual Field testing in addition to FDT C-20-1, GAT, and central corneal thickness and cup-to-disc ratio measurements. Diagnostic test accuracy outcomes were assessed for the general population as well as high-risk subgroups, defined as persons who were 65 years and older, those with a family history of glaucoma, and persons with diabetes. Of the 6,082 participants screened, 4.7 percent (286) were diagnosed as having OAG. Based on three glaucoma diagnosis definitions (glaucomatous optic nerve appearance, glaucomatous visual field loss, glaucomatous optic nerve and visual field loss), the test parameters vertical cup-to-disc ratio ≥ 0.5 , glaucomatous optic nerve and visual field loss, the test parameters vertical cup-to-disc regardless of the definition of glaucoma (98%). HVF mean deviation < 5 percent had the highest sensitivity (78%) using the definition of optic nerve defects only, while the HVF glaucoma hemifield test had the highest sensitivity under the other two definitions (90%) for glaucomatous visual field loss and 90% for both field loss and optic nerve damage). Specific results for the FDT C-20-1 were as follows (sensitivity/specificity, definition of glaucoma):

59% /79% glaucomatous optic nerve appearance only; 68%/80%, glaucomatous visual field loss only; 67% /79%, both glaucomatous optic nerve appearance and visual field loss. The investigators reported similar results when high-risk subgroups were analyzed and concluded that “these results suggest that screening of high-risk groups based on these criteria may not improve over screening of the general population over age 40.”

FDT (C-20-5) Perimetry

Evidence From Burr et al., 2007

Five studies of FDT (C-20-5) with significant heterogeneity using the common cutoff point of one abnormal test point were included. The range of sensitivity was 7 to 100%; the specificity range was 55 to 89%.

FDT 24-2 Perimetry

Evidence From Primary Studies

Five studies examined the diagnostic accuracy of FDT 24-2 threshold tests using the Humphrey Matrix Perimeter. All studies included participants with known glaucoma and healthy volunteers, and we judged these studies to be at high risk of spectrum bias. The range of sample size was 25 to 174 glaucomatous eyes and 15 to 164 healthy eyes. Sensitivities and specificities were reported for the parameters mean deviation, pattern standard deviation, and glaucoma hemifield test outside of normal limits. There was appreciable heterogeneity in the estimates of sensitivity at 80%, 90%, and 95% specificity that may be attributed to a number of factors, including different patient populations and variations in cutoff points. The sensitivity was 55% for the mean deviation and 94% at 80% fixed specificity. Two studies reported 39 and 87% at 90% fixed specificity, and 32 and 82% at fixed 95% specificity, respectively. Sensitivity and specificity for pattern standard of deviation (PSD) and glaucoma hemifield test are reported with their cutoff points in the evidence tables in Appendix C of the full report.

Two studies reported the AUC for the mean deviation parameter (0.69 for both studies with $p < 0.04$ and 95% CI, 0.564 to 0.815, respectively). The AUCs for PSD were 0.66 ($p = 0.09$) and 0.733 (95% CI, 0.618 to 0.848).

FDT 30-2 Perimetry

Evidence From Primary Studies

Two studies discussed the detection of early glaucoma using the FDT 30-2 threshold test with the Humphrey Matrix Perimeter. Both studies enrolled OAG participants with early visual field loss and healthy controls. The mean deviation and PSD were judged to be good parameters for distinguishing between eyes with early disease and eyes with no known defects. The mean deviations were 0.795 and 0.750 and the PSDs were 0.808 and 0.934, respectively. Both study groups, however, determined that the best parameter

for distinguishing eyes with early glaucoma from healthy eyes was the number of points that have p less than 5% in the pattern deviation plot, with an AUC of 0.985 (95% CI, 0.943 to 0.998) and 0.990 ($p < 0.001$).

FDT N-30 Perimetry

Evidence From Primary Studies

Four studies examined the accuracy of the FDT N-30 threshold test. One study focused on the detection of early glaucoma among a sample of 75 participants with OAG, 87 with ocular hypertension, 67 with glaucomatous optic neuropathy, and 90 healthy volunteers. At the best cutoff of less than -0.78, the sensitivity of the mean deviation parameter was 61% and the specificity was 74% for distinguishing early OAG from healthy eyes. At the best cutoff of greater than 3.89, the sensitivity of the PSD was 76% and the specificity was 88%. Another study focused on the detection of early disease among a sample of 52 participants with early OAG and 53 healthy volunteers. The sensitivity of mean deviation for distinguishing early OAG from healthy eyes at the best cutoff (less than -1.12) was 67% and the specificity was 74%. At the best cutoff of greater than 3.97, the sensitivity of the parameter PSD was 96% and the specificity was 85%.

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[E38]

Level of evidence = B

Lowering of IOP seems to prevent development of glaucoma in ocular hypertension.

Meta-analysis (Including Ocular Hypertension Treatment Study)

A meta-analysis was performed to assess the effectiveness of pressure lowering treatment to delay the development of glaucoma in ocular hypertension, as well as progression of manifest open angle glaucoma. Medline, Embase, and the Cochrane Library were used as data sources. Eligible studies were randomised controlled trials with a concurrent untreated control group and information on time to glaucomatous changes to visual field and optic disc. Trial reports were reviewed independently by two investigators in an unblinded standardised manner.

Meta-analysis of trials in ocular hypertension showed a significant preventive effect of reducing intraocular pressure on progression to glaucoma (hazard ratio 0.56, 95% confidence interval 0.39 to 0.81, $P = 0.01$; number needed to treat 12). Pooled data of studies in manifest glaucoma showed a significant delay of visual field deterioration (0.65, 0.49 to 0.87, $P = 0.003$; NNT = 7), with subgroup analysis showing a larger effect in patients with raised pressure and a reduced effect in normal tension glaucoma (subgroup comparison: not significant).

Lowering intraocular pressure in patients with ocular hypertension or manifest glaucoma is beneficial in reducing the risk of visual field loss in the long term.

References

Maier PC, Funk J, Schwarzer G, Antes G, Falck-Ytter YT. 1. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ*. 2005 Jul 16;331(7509):134. Epub 2005 Jul; PMID:15994659, PMCID:PMC558697

Randomized Controlled Trial

Randomized, double-masked, controlled clinical trial (The European Glaucoma Prevention Study, EGPS) was undertaken to evaluate the efficacy of reduction of intraocular pressure (IOP) by dorzolamide in preventing or delaying primary open-angle glaucoma (POAG) in patients affected by ocular hypertension (OHT).

1081 patients (≥ 30 years) were enrolled by 18 European centers. The inclusion criteria were IOP 22-29 mmHg; 2 normal and reliable visual fields (on the basis of mean deviation and corrected pattern standard deviation or corrected loss variance of standard 30/II Humphrey or Octopus perimetry); normal optic disc as determined by the Optic Disc Reading Center. Patients were randomized to treatment with dorzolamide or placebo (the vehicle of dorzolamide). Efficacy end points were visual field, optic disc changes, or both. A visual field change during follow-up had to be confirmed by 2 further positive tests. Optic disc change was

defined on the basis of the agreement of 2 of 3 independent observers evaluating optic disc stereo slides. The safety end point was an IOP of more than 35 mmHg on 2 consecutive examinations.

During the course of the study, the mean percent reduction in IOP in the dorzolamide group was 15% after 6 months and 22% after 5 years. Mean IOP declined by 9% after 6 months and by 19% after 5 years in the placebo group. At 60 months, the cumulative probability of converting to an efficacy end point was 13.4% in the dorzolamide group and 14.1% in the placebo group (hazard ratio, 0.86; 95% confidence interval [CI], 0.58-1.26; $P = 0.45$). The cumulative probability of developing an efficacy or a safety end point was 13.7% in the dorzolamide group and 16.4% in the placebo group (hazard ratio, 0.73; 95% CI, 0.51-1.06; $P = 0.1$).

Although dorzolamide reduced IOP throughout the 5 years of the trial, the EGPS failed to detect a statistically significant difference between medical therapy and placebo in reducing the incidence of POAG among a large population of OHT patients at moderate risk for developing POAG. Placebo also significantly and consistently lowered IOP.

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Other studies supporting the evidence

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[E39]

Level of evidence = B

Lowering of IOP seems to delay the progression of glaucomatous abnormalities in open angle glaucoma.

Systematic review

Systematic review searched for systematic reviews published by March 2011 as well primary studies without imposed language, sample size, or date restrictions up to 30 July 2012:

- Treatments currently used for OAG, including medical, laser, and incisional surgery were examined in studies with participants aged ≥ 40 years who had primary or suspected OAG.
- Evidence from additional primary studies that were published after the date of the last search conducted for systematic reviews.

The risk of bias, consistency, directness, and precision of the body of evidence was assessed. The search found 11 258 publications, of which 379 were eligible. Also 169 systematic reviews were identified, of which 23 remained eligible for inclusion after screening. These systematic reviews also included all but 86 of the primary studies identified. Because of appreciable variability in interventions, follow-up intervals, or assessments of outcomes, **the focus was on qualitative rather than quantitative synthesis.**

High-level evidence suggests that medical, laser, and surgical treatments decrease intraocular pressure and that medical treatment and trabeculectomy reduce the risk for optic nerve damage and visual field loss compared with no treatment.

No systematic reviews of medical or surgical interventions for OAG were identified directly addressing visual impairment. Primary studies that met inclusion criteria were identified. However, none were of sufficient duration or size to identify outcomes that plausibly could be related to visual impairment due to glaucoma

The limitations included heterogeneous outcome definitions and measurements among the included studies; exclusion of many treatment studies that did not stratify results by glaucoma type.

Medical and surgical treatments for open-angle glaucoma lower intraocular pressure and reduce the risk for optic nerve damage over the short to medium term. **Which treatments best prevent visual disability and improve patient-reported outcomes is unclear.**

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[E40]

Level of evidence = D

Although there is high-level evidence that treatment decreases IOP and reduce the risk of structural and functional progression in OHT and glaucoma compared to no treatment, [E38](B), [E39](B), the *direct* effects of treatments on *visual impairment* and the comparative efficacy of different treatments are not clear. Which treatments improve patient-reported outcomes is also unclear.

Based on the economic *simulation models* in the US, UK, Holland, and China, treating glaucoma appears to be cost effective compared to 'no treatment'. There is uncertainty whether to treat none, some or all patients with ocular hypertension. When treated, the cost-effectiveness models of different therapeutic interventions give variable results.

Comment

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

Systematic review

Systematic review searched for systematic reviews published by March 2011 as well primary studies without imposed language, sample size, or date restrictions up to 30 July 2012.

- Treatments currently used for OAG, including medical, laser, and incisional surgery were examined in studies with participants aged ≥ 40 years who had primary or suspected OAG.
- Evidence from additional primary studies that were published after the date of the last search conducted for systematic reviews.
- The risk of bias, consistency, directness, and precision of the body of evidence was assessed.
- The search found 11 258 publications, of which 379 were eligible. Also 169 systematic reviews were identified, of which 23 remained eligible for inclusion after screening. These systematic reviews also included all but 86 of the primary studies identified.
- Because of appreciable variability in interventions, follow-up intervals, or assessments of outcomes, the focus was on qualitative rather than quantitative synthesis.

High-level evidence suggests that medical and surgical treatments for open-angle glaucoma lower intraocular pressure and reduce the risk for optic nerve damage over the short to medium term. Which treatments best prevent visual disability and improve patient-reported outcomes is unclear. The limitations included heterogeneous outcome definitions and measurements among the included studies; exclusion of many treatment studies that did not stratify results by glaucoma type.

No systematic reviews of medical or surgical interventions for OAG were identified directly addressing visual impairment. Primary studies that met inclusion criteria were identified. However, none were of sufficient duration or size to identify outcomes that plausibly could be related to visual impairment due to glaucoma.

References

Boland MV, Ervin EM, Friedman DS . Comparative effectiveness of treatments for open angle glaucoma. *Ann Intern Med* 2013;158:271-9; PMID: 23420235

Study 1 (external validation of the OHTS-EGPS model for predicting the 5-year risk of open-angle glaucoma in ocular hypertensives)

The study independently evaluated and compared the performance of the Ocular Hypertension Treatment Study-European Glaucoma Prevention Study (OHTS-EGPS) prediction equation for estimating the 5-year risk of open-angle glaucoma (OAG) in four cohorts of adults with ocular hypertension. Data from two randomised controlled trials and two observational studies were analysed individually to assess transferability of the prediction equation between different geographical locations and settings. To make best use of the data and to avoid bias, missing predictor values were imputed using multivariate imputation by chained equations. Using the OHTS-EGPS risk prediction equation, predicted risk was calculated for each patient in each cohort.

Analyses were based on 393, 298, 188 and 159 patients for the Rotterdam, Moorfields, Dunfermline, and Nottingham cohorts, respectively. The discriminative ability was good, with c-indices between 0.69 and 0.83. In calibration analyses, **the risk of OAG was generally overestimated, although for the Rotterdam cohort the calibration slope was close to 1 (1.09, 95% CI 0.72 to 1.46), the ideal value when there is perfect agreement between predicted and observed risks.** The OHTS-EGPS risk prediction equation has predictive utility, but further validation in a population-based setting is needed.

References

Takwoingi Y, Botello AP, Burr JM, Azuara-Blanco A, Garway-Heath DF, Lemij HG, Sanders R, King AJ, Deeks JJ; Surveillance for Ocular Hypertension Study Group(Burr J, Botello A, Takwoingi Y, Hernández R, Vazquez-Montes M, Elders A, Asaoka R, Banister K, van der Schoot J, Fraser C, King A, Lemij H, Sanders R, Vernon S, Tuulonen A, Kotecha A, Glasziou P, Garway-Heath D, Crabb D, Vale L, Azuara-Blanco A, Perera R, Ryan M, Deeks J, Cook J). External validation of the OHTS-EGPS model for predicting the 5-year risk of open-angle glaucoma in ocular hypertensives. *Br J Ophthalmol.* 2014 Mar;98(3):309-14. doi: 10.1136/bjophthalmol-2013-303622. Epub 2013 Dec 19.

Review

Review of the literature

- PubMed by October 2010 with key words Glaucoma and cost
- There is uncertainty whether to treat none, some or all patients with ocular hypertension. When treated, the conclusions for cost-effectiveness of different interventions are not congruent.
- It is likely that the blindness rates in modeling studies have different estimates.

References

Tuulonen A. Economic considerations of the diagnosis and management for glaucoma in the developed world. *Curr Opin Ophthalmol* 2011;22:102-9; PMID: 21192264

Simulation model

An economic simulation model determining the cost-effectiveness of treating NTG with IOP lowering therapy to prevent progressive visual field loss.

- Transitional probabilities were derived from the Collaborative Normal Tension Glaucoma Study and cost data obtained from the literature and the Medicare fee schedule.
- The extra cost of treating all patients with NTG over a 10-year period in the US was \$34,225 per QALY, patients with disc hemorrhage US \$24,350, migraine US \$25,533, and females US \$27,000 per QALY.
- The cost-effectiveness of treating all NTG patients was sensitive to cost fluctuation of medications, choice of utility score associated with disease progression, and insensitive to cost of consultations and laser/surgery

References

Li EY, Tham CC, Chi SC, Lam DS. Cost-effectiveness of treating normal tension glaucoma. *Invest Ophthalmol Vis Sci* 2013;54:3394-9; PMID: 23599342

Systematic review and simulation model

The UK Health Technology Assessment compared five alternative surveillance and treatment pathways in OHT.

- The two most intensive pathways were based on the NICE guidelines (check-ups from every 4-12 - month to 6-24 -month intervals depending on initial risk), two further pathways followed biennial follow-up schemes differing in location (surveillance either in hospital or in primary care), and in the fifth 'Treat all' pathway, all IOPs > 21 mmHg were treated with prostaglandins. In 'Treat all' pathway, IOP was measured annually in community optometry with referral to a hospital only if IOP reduction was <15%.
- The results of the model indicated no clear benefit from intensive monitoring in OHT. 'Treat all' was the least and 'NICE intensive' was the most costly pathway.
- Compared to 'Treat all' –strategy, however, the pathway with 2-year check ups in an eye hospital (and treatment with > 5% glaucoma risk in 5 years) reduced the incidence of conversion to glaucoma and

provided more QALYs. However, simultaneously this pathway cost considerably more - above the limit of the society's willingness to pay in the UK.

- For the cost-benefit analysis the biennial hospital pathway was the only pathway relative to 'no surveillance' that had a positive net benefit.
- The results of the UK model were sensitive treatment adherence. Due to sparse evidence, the UK model (based on expert opinion) assumed adherence of 50% in 'Treat all' pathway and 75% in the other four monitoring pathways.

References

Burr JM, Botello-Pinzon P, Takwoingi Y. Surveillance for ocular hypertension: an evidence synthesis and economic evaluation. *Health Technology Assessment* 2012;16:1-271; PMID: 22687263

Systematic reviews and simulation models (Holland)

An economic simulation model in Holland (built on systematic evaluation of literature)

- The results suggested that treating **all** OHT patients with IOP > 21 mmHg would be cost saving compared to watchful waiting – even if 43% of the simulated untreated OHT patients never converted to glaucoma in their entire lifetime.
- Non-adherence to the medication was not considered in the model. It was assumed that including adherence would have a small impact of the outcomes but would have unnecessarily increased the complexity of the model.
- In eyes with manifest glaucoma, in lieu of 'guessing' the initial target pressure and redefining it according to rate of progression, the model suggested to aim at a standard IOP < 15 mmHg in **all** glaucoma patients - even if it the model indicated that 72% would need direct combination therapy and 46% would require glaucoma surgery.
- According to the model, these simplified strategies would **decrease** demand for intensive monitoring,

References

van Gestel A. Glaucoma management. Economic evaluations based on a patient level simulation model. *Ipskamp Drukkers*, Enschede, Holland, 2012. ISBN 978-94-6191-403-3

[E41]

Level of evidence = C

The prevalence of visual disability among screened populations may vary between 0.03% and 2.4% while some registry-based retrospective studies have reported clearly higher prevalence rates compared to cross-sectional screening studies (visual disability in both eyes in 15% within 15 years and 22% in 20 years, visual disability in one eye in 9% in 10 years and 54% in 20 years).

Screening studies

Fleming C, Whitlock E, Beil T . Primary care screening for ocular hypertension and primary open-angle glaucoma. Evidence synthesis 2005;34, Contract No. 290-02-0024, *Oregon Evidence-Based Practice Center*; Bookshelf ID: NBK42905;PMID: 20722130

Hirvelä H. Visual function and ocular disease in the elderly. Acta Universitatis Ouluensis Medica, D327, 1995, Oulu

Jonasson F, Thordarson K. Prevalence of ocular disease and blindness in a rural area in the eastern region of Iceland during 1980 through 1994. *Acta Ophthalmol* 1987;182:40-3; PMID: 2837059

Coffey M, Reidy A, Wormald R, Xian WX, Wright L, Courtney P. Prevalence of glaucoma in the west of Ireland. *Br J Ophthalmol* 1993;77:17-21; PMID: 8435391

Dielemans I, Vingerling JR, Wolfs RC . The prevalence of primary open-angle glaucoma in a population-based study in the Netherlands. The Rotterdam study. *Ophthalmology* 1994;101:1851-5; PMID: 7800368

Sommer A, Tielsch JM, Katz J . Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol* 1991;109:1090-5; PMID: 1867550

Sommer A, Tielsch JM, Katz J . Racial differences in the cause-specific prevalence of blindness in east Baltimore. *N Engl J Med* 1991;325:1412-7; PMID: 1922252

Quigley HA, Tielsch JM, Katz J, Sommer A. Rate of progression in open-angle glaucoma estimated from cross-sectional prevalence of visual field damage. *Am J Ophthalmol* 1996;122:355-63; PMID: 8794708

Retrospective and registry base studies

Ang GS, Eke T. Lifetime visual prognosis for patients with primary open-angle glaucoma. *Eye* 2007;21:604-608; PMID:16485015

Peters D, Bengtsson B, Heijl A. Lifetime risk of blindness in open-angle glaucoma. *Am J Ophthalmol* 2013;156:724-730; doi: 10.1016/j.ajo.2013.05.027. Epub 2013 Aug 7; PMID:23932

Peters D, Bengtsson B, Heijl A. Factors associated with lifetime risk of open-angle glaucoma. *Acta Ophthalmologica* 2013; doi10.1111/aos.12203; PMID:23837818

Forsman E, Kivelä T, Vesti E. Lifetime visual disability in open-angle glaucoma and ocular hypertension. *J Glaucoma* 2007;16:313-319; PMID:17438426

Hattenhauer MG, Johnson DH, Ing HH . The probability of blindness from open-angle glaucoma. *Ophthalmology* 1998;105:2099-104; PMID: 9818612

King AJ, Reddy A, Thompson JR, Rosenthal AR. The rates of blindness and of partial sight in glaucoma patients. *Eye* 2001;14:613-9; PMID: 11040909

Blomdahl S, Calissendorff BM, Tengroth B, Wallin O. Blindness in glaucoma patients. *Acta Ophthalmol Scand* 1997;75:589-91; PMID: 9469562

Chen PP. Blindness in patients with treated open angle-galucoma. *Ophthalmology* 2003;110:726-33; PMID: 12689894

Ederer F, Gaasterland DA, Dally LG, Kim J . The Advanced Glaucoma Intervention Study (AGIS): 13. Comparison of treatment outcomes within race: 10-year results. *Ophthalmology* 2004;111:651-64; PMID: 15051195

Kwon YH, Kim CS, Zimmerman MB, Alward WL, Hayreh SS. Rate of visual field loss and long-term visual outcome in primary open-angle. *Am J Ophthalmol* 2001;132:47-56; PMID: 11438053

[E42]

Level of evidence = C

Variation on IOP may not increase risk of progression in ocular hypertensive patients.

References

Bengtsson B, Heijl A. A long-term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. *J Glaucoma* 2005;14:135-8; PMID: 15741815

Bengtsson B, Heijl A. Diurnal IOP fluctuation: not an independent risk factor for glaucomatous visual field loss in high-risk ocular hypertension. *Graefes Arch Clin Exp Ophthalmol* 2005;243:513-8; PMID: 15756577

[E43]

Level of evidence = D

The evidence of neuroprotective effects of medications is missing.

Systematic review

Neuroprotection for glaucoma refers to any intervention intended to prevent optic nerve damage or cell death. The objective of the review was to systematically examine the evidence regarding the effectiveness of neuroprotective agents for slowing the progression of OAG in adults.

Systematic literature review was conducted through October 16, 2012 including registries of trials. No date or language restrictions were used. RCT's in which topical or oral treatments were used for neuroprotection in adults with OAG were selected. Minimum follow up time was 4 years.

One trial was identified for this review. Two studies comparing memantine to placebo are currently awaiting classification until additional study details are provided.

One multi-center RCT of adults with low-pressure glaucoma (Low-pressure Glaucoma Treatment Study, LoGTS) conducted in the USA was included. The primary outcome was visual field progression after 4 years of treatment with either brimonidine or timolol. Of the 190 adults enrolled in the study, 12 (6%) were excluded after randomization and 77 (41%) did not complete 4-year follow up. The rate of attrition was unbalanced between groups with more participants dropping out of the brimonidine group (55%) than the timolol group (29%). Of those remaining in the study at 4 years, participants assigned to brimonidine showed less visual field progression than participants assigned to timolol (5/45 participants in the brimonidine group compared with 18/56 participants in the timolol group). Since no information was available for the 12 participants excluded from the study, or the 77 participants who dropped out of the study, the authors were unable to draw any conclusions from these results as the participants for whom data are missing may or may not have progressed. The mean IOP was similar in both groups at the 4-year follow up among those for whom data were available: 14.2 mmHg (standard deviation (SD) = 1.9) among the 43 participants in the brimonidine group and 14.0 mmHg (SD = 2.6) among the 48 participants in the timolol group. Among the participants who developed progressive visual field loss, IOP reduction $\geq 20\%$ was not significantly different between groups: 4/9 participants in the brimonidine group and 12/31 participants in the timolol group. The study authors did not report data for visual acuity or vertical cup-disc ratio. The most frequent adverse event was ocular allergy to study drug, which occurred more frequently in the brimonidine group (20/99 participants) than the timolol group (3/79 participants).

Although neuroprotective agents are intended to act as pharmacological antagonists to prevent cell death, this trial did not provide evidence that they are effective in preventing retinal ganglion cell death, and thus preserving vision in people with OAG. Further clinical research is needed to determine whether neuroprotective agents may be beneficial for individuals with OAG. Such research should focus outcomes important to patients, such as preservation of vision, and how these outcomes relate to cell death and optic nerve damage. Since OAG is a chronic, progressive disease with variability in symptoms, RCTs designed to



measure the effectiveness of neuroprotective agents would require long-term follow up (more than four years) in order to detect clinically meaningful effects.

References

Sena DF, Lindsley K. Neuroprotection for treatment of glaucoma in adults. *Cochrane Database Syst Rev* 2013;(2):CD006539; PMID: 23450569

[E44]

Level of evidence = B

Medical therapy reduces IOP and prostaglandins reduce IOP more than other monotherapies.

Systematic reviews comparing timolol with travoprost and latanoprost showed prostaglandin analogues to be more effective at decreasing IOP. Two systematic reviews concluded that bimatoprost 0.03% decreased IOP more effectively than did latanoprost at 3 months (risk difference [RD], 12 [95% CI, 4 to 21]), although this difference was not present at 1 and 6 months. Two reviews concluded that mean IOP reduction was similar with travoprost and latanoprost. For the comparison of bimatoprost with travoprost, one review reported a significant difference in favor of bimatoprost at 3 or more months of follow-up (weighted mean difference, 0.88 [CI, 0.13 to 1.63]), whereas another review concluded that bimatoprost and travoprost were similarly effective (weighted mean difference, 0.08 [CI 0.62 to 0.79]).

All but 3 of the studies assessing medical treatments for decreasing IOP were included in systematic reviews. Two studies examined brand and generic latanoprost and found that both decreased IOP equivalently, by 6 to 7 mm Hg. A single study also showed that latanoprost (7.5 mm Hg) and the combination of brimonidine–timolol (7.0 mm Hg) both decreased IOP by the same amount.

The strength of evidence from these 3 most recent trials was judged to be low. However, with the addition of the consistent high-quality systematic reviews, the conclusion that topical glaucoma medications decrease IOP is wellsupported, as is the conclusion that prostaglandin agents are superior to other monotherapies with regard to decreasing IOP.

References

Boland MV, Ervin EM, Friedman DS. Comparative effectiveness of treatments for open-angle glaucoma. *Ann Intern Med* 2013;158:271-9; PMID: 23420235



[E45]

Level of evidence = C

Prostaglandins with or without preservatives seem to lower IOP similarly: travoprost.

References

Lewis RA, Katz GJ, Weiss MJ . Travoprost 0.004% with and without bentsakonium chloride: A comparison of safety and efficacy. *J Glaucoma* 2007;16:98-103; PMID: 17224758

Gross RL, Peace JH, Smith SE . Duration of IOP reduction with travoprost BAK-free solution. *J Glaucoma* 2008;17:217-22; PMID: 18414108



[E46]

Level of evidence = C

Prostaglandins with or without preservatives seem to lower IOP similarly: latanoprost.

References

Rouland JF, Traverso CE, Stalmans I . Efficacy and safety of preservative-free latanoprost eyedrops, compared with BAK-preserved latanoprost in patients with ocular hypertension or glaucoma. *Br J Ophthalmol* 2013;97:196-200; PMID: 23203707



[E47]

Level of evidence = C

Prostaglandins with or without preservatives seem to lower IOP similarly: tafluprost.

References

Habi A, Varma R, Tsai JC . Randomized clinical trial of the efficacy and safety of preservative-free tafluprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2012;153:1187-96; PMID: 22310086



[E48]

Level of evidence = B

Latanoprost and tafluprost seem to lower IOP equally effectively.

References

Uusitalo H, Pillunat LE, Ropo A. Efficacy and safety of tafluprost 0.0015% versus latanoprost 0.005% eye drops in open-angle glaucoma and ocular hypertension: 24-month results of a randomized, double-masked phase III study. *Acta Ophthalmol* 2010;88:12-9; PMID: 20420586

Ranno S, Sacchi M, Brancato C, Gilardi D, Lembo A, Nucci P. A prospective study evaluating IOP changes after switching from a therapy with prostaglandin eye drops containing preservatives to nonpreserved tafluprost in glaucoma patients. *Sci World J* 2012;2012:804730; PMID: 22606063



[E49]

Level of evidence = C

Bimatoprost may lower IOP somewhat more than tafluprost.

References

Ranno S, Sacchi M, Brancato C, Gilardi D, Lembo A, Nucci P. A prospective study evaluating IOP changes after switching from a therapy with prostaglandin eye drops containing preservatives to nonpreserved tafluprost in glaucoma patients. *Sci World J* 2012;2012:804730; PMID: 22606063

[E50]

Level of evidence = C

Bimatoprost may lower IOP somewhat more travoprost and latanoprost.

References

Eyawo O, Nachega J, Lefebvre P . Efficacy and safety of prostaglandin analogues in patients with predominantly primary open-angle glaucoma or ocular hypertension: a meta-analysis. *Clin Ophthalmol* 2009;3:447-56; PMID: 19684868

van der Valk R, Webers CA, Lumley T, Hendrikse F, Prins MH, Schouten JS. A network meta-analysis combined direct and indirect comparisons between glaucoma drugs to rank effectiveness in lowering intraocular pressure. *J Clin Epidemiol* 2009;62:1279-83; PMID: 19716679

Faridi UA, Saleh TA, Ewings P . Comparative study of three prostaglandin analogues in the treatment of newly diagnosed cases of ocular hypertension, open-angle and normal tension glaucoma. *Clin Experiment Ophthalmol* 2010;38:678-82; PMID: 20456437

[E51]

Level of evidence = C

Travoprost may lower IOP somewhat more than tafluprost.

References

Schnober D, Hofmann G, Maier H, Scherzer ML, Ogundele AB, Jasek MC. Diurnal IOP-lowering efficacy and safety of travoprost 0.004% compared with tafluprost 0.0015% in patients with primary open-angle glaucoma or ocular hypertension. *Clin Ophthalmol* 2010;4:1459-63; PMID: 21191441

Ranno S, Sacchi M, Brancato C, Gilardi D, Lembo A, Nucci P. A prospective study evaluating IOP changes after switching from a therapy with prostaglandin eye drops containing preservatives to nonpreserved tafluprost in glaucoma patients. *Sci World J* 2012;2012:804730; PMID: 22606063

[E52]

Level of evidence = B

Brimonidine seems to lower IOP somewhat less than timolol within 12 months.

References

Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. *Arch Ophthalmol* 1997;115:847-52; PMID: 9230823

LeBlanc RP. Twelve-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in patients with glaucoma or ocular hypertension. Brimonidine Study Group 2. *Ophthalmology* 1998;105:1960-7; PMID: 9787370

Katz LJ. Brimonidine tartrate 0.2% twice daily vs timolol 0.5% twice daily: 1-year results in glaucoma patients. Brimonidine Study Group. *Am J Ophthalmol* 1999;127:20-6; PMID: 9932994



[E53]

Level of evidence = B

Topical carbonic dehydrase inhibitors seem to lower IOP less than timolol.

References

Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group. *Arch Ophthalmol* 1995;113:1009-16; PMID: 7639651

March WF, Ochsner KI. The long-term safety and efficacy of brinzolamide 1.0% (Azopt) in patients with primary open-angle glaucoma or ocular hypertension. The Brinzolamide Long-Term Therapy Study Group. *Am J Ophthalmol* 2000;129:136-43; PMID: 10682964

**[E54]****Level of evidence = A**

The combination of prostaglandin and timolol lower IOP on an average 2 mmHg more than timolol alone, and 1 mmHg more than prostaglandin alone.

References

Quaranta L, Biagioli E, Riva I, Rulli E, Poli D, Katsanos A, Floriani I. Prostaglandin analogs and timolol-fixed versus unfixed combinations or monotherapy for open-angle glaucoma: a systematic review and meta-analysis. *J Ocul Pharmacol Ther.* 2013;29(4):382-389. doi: 10.1089/jop.2012.0186; PMID:23231442

Aptel F, Cucherat M, Denis P. Efficacy and tolerability of prostaglandin-timolol fixed combinations: a meta-analysis of randomized clinical trials. *Eur J Ophthalmol.* 2012;22(1):5-18. doi: 10.5301/ejo.5000009; PMID:22167538

[E55]

Level of evidence = C

The combination drugs may have somewhat lower efficacy than the same drugs in different bottles but the clinical difference is small.

References

Quaranta L, Biagioli E, Riva I, Rulli E, Poli D, Katsanos A, Floriani I. Prostaglandin analogs and timolol-fixed versus unfixed combinations or monotherapy for open-angle glaucoma: a systematic review and meta-analysis. *J Ocul Pharmacol Ther.* 2013;29(4):382-389. doi: 10.1089/jop.2012.0186; PMID:23231442

Cox JA, Mollan SP, Bankart J, Robinson R. Efficacy of antiglaucoma fixed combination therapy versus unfixed components in reducing intraocular pressure: a systematic review. *Br J Ophthalmol.* 2008;92(6):729-734. doi: 10.1136/bjo.2008.139329; PMID:18460539

Holló G, Hommer A, Antón López A, Ropo A. Efficacy, safety, and tolerability of preservative-free fixed combination of tafluprost 0.0015%/timolol 0.5% versus concomitant use of the ingredients. *J Ocul Pharmacol Ther.* 2014 Apr 16. [Epub ahead of print]. PMID: 24738883



[E56]

Level of evidence = B

The combination of prostaglandin and timolol seem to be somewhat more effective dosed in the evening than in the morning.

References

Quaranta L, Biagioli E, Riva I, Rulli E, Poli D, Katsanos A, Floriani I. Prostaglandin analogs and timolol-fixed versus unfixed combinations or monotherapy for open-angle glaucoma: a systematic review and meta-analysis. *J Ocul Pharmacol Ther.* 2013;29(4):382-389. doi: 10.1089/jop.2012.0186; PMID: 23231442

Webers CA, Beckers HJ, Zeegers MP, Nuijts RM, Hendrikse F, Schouten JS. The intraocular pressure-lowering effect of prostaglandin analogs combined with topical β -blocker therapy: a systematic review and meta-analysis. *Ophthalmology.* 2010 Nov;117(11):2067-74.e1-6. doi: 10.1016/j.ophtha.2010.03.024; PMID:20619459



[E57]

Level of evidence = C

Dorzolamid-timolol combination seems to lower IOP as much as brinzolamide-timolol combination.

References

Manni G, Denis P, Chew P . The safety and efficacy of brinzolamide 1%/timolol 0.5% fixed combination versus dorzolamide 2%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. *J Glaucoma* 2009;18:293-300; PMID: 19365194



[E58]

Level of evidence = C

Brimonidine-timolol combination seems to lower IOP 1 mmHg more than timolol alone and 2.8 (2.5-3) mmHg more than brimonidine alone.

References

Strohmaier K, Snyder E, DuBiner H, Adamsons I. The efficacy and safety of the dorzolamide-timolol combination versus the concomitant administration of its components. Dorzolamide-Timolol Study Group. *Ophthalmology* 1999;106:1-9; PMID: 10598691

[E59]

Level of evidence = C

A single study showed that latanoprost (7.5 mm Hg) and the combination of brimonidine–timolol (7.0 mm Hg) both may both decrease IOP by the same amount.

Systematic reviews comparing timolol with travoprost and latanoprost showed prostaglandin analogues to be more effective at decreasing IOP. Two systematic reviews concluded that bimatoprost 0.03% decreased IOP more effectively than did latanoprost at 3 months (risk difference [RD], 12 [95% CI, 4 to 21]), although this difference was not present at 1 and 6 months. Two reviews concluded that mean IOP reduction was similar with travoprost and latanoprost. For the comparison of bimatoprost with travoprost, one review reported a significant difference in favor of bimatoprost at 3 or more months of follow-up (weighted mean difference, 0.88 [CI, 0.13 to 1.63]), whereas another review concluded that bimatoprost and travoprost were similarly effective (weighted mean difference, 0.08 [CI 0.62 to 0.79]).

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The strength of evidence from these 3 most recent trials was judged to be low. However, with the addition of the consistent high-quality systematic reviews, the conclusion that topical glaucoma medications decrease IOP is wellsupported, as is the conclusion that **prostaglandin agents are superior to other monotherapies with regard to decreasing IOP.**

References

Boland MV, Ervin EM, Friedman DS . Comparative effectiveness of treatments for open-angle glaucoma. *Ann Intern Med* 2013;158:271-9; PMID: 23420235

**[E60]****Level of evidence = C****The treatment compliance with glaucoma medication is poor.**

A literature search in the databases MEDLINE, EMBASE, CINAHL, PsychInfo, and Cochrane and reference lists was conducted. Thirty-four articles describing 29 original quantitative studies, in English, German, French, or Dutch, were included. Studies on noncompliance in drug trials were excluded.

The proportions of patients who deviate from their prescribed medication regimen ranged from 5% to 80%. The impact of noncompliance on clinical outcome has not yet been established. There are no determinants sensitive and specific enough to identify potential noncompliers accurately.

References

Olthoff CM, Schouten JS, van de Borne BW, Webers CA. Noncompliance with ocular hypertensive treatment in patients with glaucoma or ocular hypertension. An evidence-based review. *Ophthalmology* 2005;112:953-61; PMID: 15885795

Norell SE. Improving medication compliance: a randomised clinical trial. *Br Med J* 1979;2:1031-3; PMID: 519269

[E61]

Level of evidence = D

It is unclear whether patient education and guidance may improve compliance.

Systematic review 1

The objective was to summarise the effects of interventions for improving adherence to ocular hypotensive therapy in people with ocular hypertension (OHT) or glaucoma. Search by June 2012 included CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO, PsycEXTRA, Web of Science, ZETOC, OpenGrey, mRCT, ClinicalTrials.gov, and ICTRP. RCTs and quasi-RCTs that compared interventions to improve adherence to ocular hypotensive

Sixteen trials (1565 participants) met the inclusion criteria. Seven studies investigated some form of patient education. In six of these studies this education was combined with other behavioural change interventions including tailoring daily routines to promote adherence to eye drops. Eight studies compared different drug regimens (one of these trials also compared open and masked monitoring) and one study investigated a reminder device. **The studies were of variable quality and some were at considerable risk of bias; in general, the length of follow-up was short at less than six months with only two studies following up to 12 months.**

As different interventions and outcomes were reported, it was not possible to produce an overall estimate of effect. **There was some evidence from three studies that education combined with personalised interventions, that is, more complex interventions, improved adherence to ocular hypotensive therapy.** There was weak evidence as to whether people on simpler drug regimens were more likely to adhere and persist with their ocular hypotensive therapy. A particular problem was the interpretation of cross-over studies, which in general were not reported correctly. One study investigated a reminder device and monitoring but the study was small and inconclusive.

Authors' conclusion: Although complex interventions consisting of patient education combined with personalised behavioural change interventions, including tailoring daily routines to promote adherence to eye drops, may improve adherence to glaucoma medication, **overall there is insufficient evidence to recommend a particular intervention.**

References

Waterman H, Evans JR, Gray TA, Henson D, Harper R. Interventions for improving adherence to ocular hypotensive therapy. *Cochrane Database Syst Rev.* 2013 Apr 30;4:CD006132. doi: 10.1002/14651858.CD006132.pub3.

Systematic review 2

Adherence to prescribed glaucoma medications is often poor, and proper adherence can be challenging for patients. Systematic review of the literature identified 8 studies using educational interventions to improve glaucoma medication adherence. Overall, **five of the eight studies found that educational interventions lead to a significant improvement in medication adherence, and two additional studies found a trend towards improvement.** More rigorous studies grounded in Health Behavior Theory with adequately powered samples and longer follow-up are needed.

Adherence to prescribed glaucoma medications is often poor, and proper adherence can be challenging for patients. Systematic review of the literature identified 8 studies using educational interventions to improve glaucoma medication adherence. Overall, five of the eight studies found that educational interventions lead to a significant improvement in medication adherence, and two additional studies found a trend towards improvement. More rigorous studies grounded in Health Behavior Theory with adequately powered samples and longer follow-up are needed.

References

Newman-Casey PA, Weizer JS, Heisler M, Lee PP, Stein JD. Systematic review of educational interventions to improve glaucoma medication adherence. *Semin.Ophthalmol.* 2013 May;28(3):191-201

[E62]

Level of evidence = C

Allergic reactions and adverse effects of glaucoma treatment seem to be common.

Contact allergy is caused by almost all topical glaucoma medications; pilocarpin, beta blockers: timolol, befunolol, betaxolol, levobunolol, carteol, metipranolol, carboanhydrase inhibitors, adrenergics, prostaglandin analogues, preservatives (BAK, bentsalcon chloride), parabens, thimerosal (Holdiness 2001, Butler 1995, Costagliola 2001, Jerstad 2002, Cusano 1993, Gaspari 1993, Manni 2004, Aalto-Korte 1998, Vilaplana 2000, Tosti 1988, Hätinén et al 1985).

Adverse effects are common. In the Collaborative Normal-Tension Glaucoma Study (CNTGS) (CNTS Glaucoma Group 1998) 23 of 66 treated eyes (35%) developed **cataract**, compared with 11 of 79 eyes in the control group (14%) ($p = 0.0011$), relative risk (RR) 2.5, CL 1.32-4.75. The highest incidence of cataracts (16 of 33) occurred in surgically treated eyes, RR 3.48, CL 1.82-6.68. The rate of cataract formation in untreated eyes was lower than surgically treated eyes ($p=0.0001$) but was not different from medically treated eyes ($p=0.18$). In another study the risk of cataract formation was compared in medically treated vs. untreated eyes. In the EMGT study (2002), cataract development was more likely in the group treated with ALT (Argon Laser Trabeculoplasty) plus betaxolol than in untreated subjects ($p=0.002$), and the risk of cataracts related to treatment increase over time ($p=0.02$).

Ocular symptoms, such as dryness, tearing and itching, were frequently reported. In the Ocular Hypertension Treatment Study (OHTS) (Kass et al 2002) ocular symptoms occurred in 57% of treated patients and 47% of control subjects, NNH (number needed to harm) 10, $p<0.001$. Other symptoms such as darkening of the eyelids or eyelash growth, were reported in 23% of treated patients vs. 18% of control subjects (NNH 10, $p<0.001$). Patients were treated by prostaglandin analogues, most often by latanoprost and betablockers.

The CIGTS trial (Lichter et al 2001) reported **intraoperative and postoperative complication for surgical trabeculectomy** in 524 participants. Intraoperative complication included bleeding in the anterior chamber (7.1%) and conjunctival buttonhole defects (1.0%). Complications within 30 days postoperative were: 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 (10.9%). Over time, the cataract extraction rate in the surgery group remained significantly higher than in the medication group ($p=0.0001$).

In the OHTS study (Kass et al 2002), there were no observed differences between the treated and untreated participants in total hospitalizations, worsening of pre existing conditions, or mortality. Serious psychiatric adverse effects were reported in 5.5% (44 of 800) vs. 3.4% (27 of 802) in the control group ($p=0.05$), RR 1.63, CL 1.02-2.61. Serious genitourinary adverse effects occurred in 1.5% (12 of 800) of the treatment group vs. 0.5% (4 of 802) in the control group ($p=0.04$), RR 3.01, CL 0.97-9.29.

Comment:

The glaucoma treatment studies were identified from MEDLINE, Cochrane Library and from HUCS Skin and allergy Hospital. The database search about possible adverse effects to various glaucoma medications consisted of 224 abstracts and titles from 1998 to 2004.

There are no high quality prospective studies concerning adverse effects and the adverse effects are often told as secondary outcomes in big glaucoma treatment studies.

There are only few studies, where the allergic reactions are verified by allergy tests. Another problem is that we may have an allergic reaction in the eye caused by glaucoma medication but the skin tests used for eye drops are not sensitive enough compared to the eye. Further problems are test medications, which usually are eye drops used by the patients. They are tested in most instances "as is" on the back skin. The back skin 5mm thick and the lid skin 0.5mm. This causes a fundamental difference in sensitivity, which is further amplified by very sensitive cornea and conjunctiva.

The treatment options include topical medications, systemic medications, laser surgery, and incisional surgery, alone or in combination. No data exists about sensitivity and specificity in suspected ocular allergies caused by topical glaucoma medication.

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Heijl A, Leske MC, Bengtsson B . Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol* 2002;120:1268-79; PMID: 12365904

[E63]

Level of evidence = B

Although timolol seems to cause systemic side-effects which can be serious, it seems to be locally tolerated better than prostaglandin analogues.

Systemic adverse effects

A historical cohort study by Kirwan . was performed to determine the incidence of airways obstruction in subjects with no previous history of airways obstruction, following treatment with topical beta antagonists for glaucoma for the period 1993–7.

For selective topical beta antagonists 12 of 324 treated subjects developed airways obstruction, compared with 112 of 9 094 controls (adjusted hazard rate 3.0, 95% confidence interval 1.6 to 5.4). For non-selective topical beta antagonists, the corresponding figures were 69 of 2321 subjects compared with the same control group (adjusted hazard rate 2.2, CI 95% 1.6 to 3.0). There was no significant difference between groups, $p = 0.47$, chi(2) test, both being associated with a significantly increased risk of airways obstruction.

Selective topical beta antagonists do appear to have an excess risk of airways obstruction in this population setting and should be subject to the same prescribing caveats as unselective topical beta antagonists.

References

Kirwan JF, Nightingale JA, Bunce C, Wormald R. Do selective topical beta antagonists for glaucoma have respiratory side effects? *Br J Ophthalmol* 2004;88:196-8; PMID: 14736772

Waldock et al recruited 141 newly diagnosed glaucoma patients who underwent a full ocular, cardiovascular, and respiratory examination, including an electrocardiogram (ECG) and spirometry.

At the initial examination, 17 patients (13%) had ECG evidence of first degree heart block, seven were prescribed latanoprost, six with brimonidine, and four with betaxolol. Eight patients were found to have a respiratory wheeze, four were prescribed brimonidine and the other four latanoprost. They were reviewed 3 months later. One eye of each patient was randomly chosen for analysis, performed using analysis of variance and the chi(2) test.

Timolol was associated with lowered pulse rates and reductions in the spirometry measurements. 41% of patients using brimonidine complained of systemic side effects and over 55% of patients using betaxolol complained of ocular irritation including dry eye. 28% of patients required an alteration in their glaucoma management.

References

Waldock A, Snape J, Graham CM. Effects of glaucoma medications on the cardiorespiratory and intraocular pressure status of newly diagnosed glaucoma patients. *Br J Ophthalmol* 2000;84:710-3; PMID: 10873979

Additional information of topical beta-blockers as the cause of bronchoconstriction or bradycardia in http://www.ebmeds.org/ebmeds/ebmeds_home.asp?mode=scripts&submode=view&id=scr00597&country=UK

Local side-effects

Twelve studies involving 3048 patients with open-angle glaucoma or ocular hypertension were included **in the meta-analysis comparing timolol with prostaglandin analogs**. Participants received either travoprost, other prostaglandin analog or timolol.

Ocular hyperaemia was the most common side-effect of prostaglandin analogues. The combined results suggested that **travoprost 0.004% caused a higher percentage of ocular hyperaemia than timolol 0.5%** (OR = 6.76, 95% CI 4.93-9.25, $P < 0.00001$), **or latanoprost 0.005%** (OR = 2.03, 95% CI 1.49-2.75, $P = 0.00001$) **and travoprost 0.0015%** (OR = 1.64, 95% CI 1.32-2.04, $P = 0.00001$). However, there was no statistically significant difference between travoprost 0.004% and bimatoprost 0.03% (OR = 0.65, 95% CI 0.42-1.00, $P = 0.05$) in hyperaemia.

There was an **increased incidence of pigmentation with travoprost 0.004% when compared to timolol 0.5%** (OR = 11.06, 95% CI 2.07-59.08, $P = 0.005$). There was no statistically significant difference between travoprost 0.004% and latanoprost 0.005% (OR = 0.74, 95% CI 0.38-1.46, $P = 0.4$) in iris pigmentation.

Travoprost 0.004% caused a **higher percentage of eyelash changes than timolol 0.5%** (OR = 38.81, 95% CI 20.65-72.93, $P < 0.00001$). There was also an increased incidence of eyelash changes with travoprost 0.004% than latanoprost 0.005% (OR = 3.82, 95% CI 2.50-5.84, $P < 0.00001$), or travoprost 0.0015% (OR = 1.79, 95% CI 1.40-2.27, $P < 0.00001$).

References

Li N, Chen XM, Zhou Y. Travoprost compared with other prostaglandin analogues or timolol in patients with openangle glaucoma or ocular hypertension: Meta-analysis of randomized controlled trials. *Clin Exp Ophthalmol* 2006;34:755-64; PMID: 17073898

In a meta-analysis comparing latanoprost with timolol in patients with open-angle glaucoma, **latanoprost caused hyperaemia and iris pigmentation more often than timolol** (RR = 2.20, 95% CI 1.33-3.65). The number needed to harm was 21 (CI 14-42) when compared to timolol. Moreover, of 478 patients who were treated with latanoprost, 21 (4.39%) developed iris pigmentation. In contrast, none of the patients treated with timolol showed this effect (0/387). **Four studies compared systemic adverse reactions to timolol versus latanoprost, such as their effects on systolic blood pressure and heart**

rate. Timolol caused slowing of heart rate after 3 or 6 months of treatment, and this returned to the baseline level after switching to latanoprost.

References

Zhang WY, Po AL, Dua HS, Azuara-Blanco A. Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. *Br J Ophthalmol* 2001;85:983-90; PMID: 11466259

In a **systematic review comparing timolol with brimonidine** (α_2 adrenergic agonist), **prostaglandin analogs** (travoprost, latanoprost), **other β adrenergic antagonists, and placebo there was a twofold increase in the odds of participant drop out due to drug-related adverse events among participants randomized to timolol versus betaxolol** (OR. 2.40; 95% CI, 1.04-5.53, five trials), and the odds of dropping out were lower among participants randomized to timolol when compared to those receiving brimonidine (OR, 0.21; 95% CI 0.14-0.31, three trials). As to the **comparison of timolol with prostaglandin analogs, participants receiving either travoprost or latanoprost had six times the odds and twice the odds** (OR, 6.76, CI 4.93-9.25 and OR 2.03, CL 1.49-2.75), respectively, of dropping out of the study due to conjunctival hyperemia, compared to patients receiving timolol. Both drugs also significantly increased iris pigmentation (travoprost OR 11.06, CI 2.07-59.08 and latanoprost OR 8.01, CI 1.87-34.30).

References

Boland MV, Ervin AM, Friedman DS . Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013;158:271-9; PMID: 23420235

[E64]

Level of evidence = C

Topical anti-glaucoma medications may cause meibomian gland dysfunction.

Arita et al. examined 71 eyes of 71 glaucoma patients (group 1) receiving one type of antiglaucoma eye drops, 61 eyes of 61 glaucoma patients (group 2) receiving two types of antiglaucoma eye drops, and 30 eyes of 30 glaucoma patients (group 3) receiving three types of antiglaucoma eye drops. Controls comprised 75 eyes of 75 healthy volunteers. Subjective symptoms were evaluated by questionnaire, and lid margin and superficial punctate keratopathy were evaluated by slit lamp examination. Meibomian glands of upper and lower eyelids were observed and scored using noncontact meibography (meiboscope). Tear film break-up time (BUT) was measured and meibum was graded.

Lid margin abnormality, superficial punctate keratopathy, meiboscope, and meibum scores were significantly higher in glaucoma patients than in controls ($P < 0.001$). BUT and Schirmer scores were significantly lower in glaucoma patients than in controls ($P < 0.001$). Subgroup analysis of the parameters in group 1 revealed no significant difference between patients receiving prostaglandin and those receiving β -blockers, or among groups 1, 2, and 3. Multivariate regression analysis demonstrated that meiboscope significantly correlated with lid margin abnormality score ($P = 0.007$) and BUT ($P = 0.045$) in group 1; with BUT ($P = 0.004$), symptom score ($P = 0.003$), and age ($P = 0.026$) in group 2; and with lid margin abnormality score ($P = 0.001$) in group 3.

Long-term use of antiglaucoma eye drops was associated with alterations in meibomian gland morphology and function.

References

Arita R, Itoh K, Maeda S, Maeda K, Furuta A, Tomidokoro A, Aihara M, Amano S. Comparison of the long-term effects of various topical antiglaucoma medications on meibomian glands. *Cornea*. 2012 Nov;31(11):1229-34. doi: 10.1097/ICO.0b013e31823f8e7d.

[E65]

Level of evidence = B

Ocular hyperaemia is common adverse effect of prostaglandin analogs.

Twelve studies involving 3048 patients with open-angle glaucoma or ocular hypertension were included in the meta-analysis comparing timolol with prostaglandin analogs. Participants received either travoprost, other prostaglandin analog or timolol.

Ocular hyperaemia was the most common side-effect of prostaglandin analogues. The combined results suggested that travoprost 0.004% caused a higher percentage of ocular hyperaemia than timolol 0.5% (OR = 6.76, 95% CI 4.93-9.25, $P < 0.00001$), or latanoprost 0.005% (OR = 2.03, 95% CI 1.49-2.75, $P = 0.00001$) and travoprost 0.0015% (OR = 1.64, 95% CI 1.32-2.04, $P = 0.00001$). However, there was no statistically significant difference between travoprost 0.004% and bimatoprost 0.03% (OR = 0.65, 95% CI 0.42-1.00, $P = 0.05$) in hyperaemia.

References

Li N, Chen XM, Zhou Y. Travoprost compared with other prostaglandin analogues or timolol in patients with openangle glaucoma or ocular hypertension: Meta-analysis of randomized controlled trials. *Clin Exp Ophthalmol* 2006;34:755-64; PMID: 17073898

In a meta-analysis comparing latanoprost with timolol in patients with open-angle glaucoma, latanoprost caused hyperaemia and iris pigmentation more often than timolol (RR = 2.20, 95% CI 1.33-3.65). The number needed to harm was 21 (CI 14-42) when compared to timolol.

References

Zhang WY, Po AL, Dua HS, Azuara-Blanco A. Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. *Br J Ophthalmol* 2001;85:983-90; PMID: 11466259

A systematic review compared timolol with brimonidine (α_2 adrenergic agonist), prostaglandin analogs (travoprost, latanoprost), other β adrenergic antagonists, and placebo. As to the comparison of timolol with prostaglandin analogs, participants receiving either travoprost or latanoprost had six times the odds and twice the odds (OR, 6.76, CI 4.93-9.25 and OR 2.03, CL 1.49-2.75), respectively, of dropping out of the study due to conjunctival hyperemia, compared to patients receiving timolol.



References

Boland MV, Ervin AM, Friedman DS . Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013;158:271-9; PMID: 23420235

[E66]

Level of evidence = B

Increased iris pigmentation may be a common adverse effect of prostaglandin analogs.

Twelve studies involving 3048 patients with open-angle glaucoma or ocular hypertension were included in the meta-analysis comparing timolol with prostaglandin analogs. Participants received either travoprost, other prostaglandin analog or timolol.

There was an increased incidence of iris pigmentation with travoprost 0.004% when compared to timolol 0.5% (OR = 11.06, 95% CI 2.07-59.08, P = 0.005). There was no statistically significant difference between travoprost 0.004% and latanoprost 0.005% (OR = 0.74, 95% CI 0.38-1.46, P = 0.4) in iris pigmentation.

References

Li N, Chen XM, Zhou Y. Travoprost compared with other prostaglandin analogues or timolol in patients with openangle glaucoma or ocular hypertension: Meta-analysis of randomized controlled trials. *Clin Exp Ophthalmol* 2006;34:755-64; PMID: 17073898

In a meta-analysis comparing latanoprost with timolol in patients with open-angle glaucoma, latanoprost caused hyperaemia and iris pigmentation more often than timolol (RR = 2.20, 95% CI 1.33-3.65). The number needed to harm was 21 (CI 14-42) when compared to timolol. Moreover, of 478 patients who were treated with latanoprost, 21 (4.39%) developed iris pigmentation. In contrast, none of the patients treated with timolol showed this effect (0/387).

References

Zhang WY, Po AL, Dua HS, Azuara-Blanco A. Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. *Br J Ophthalmol* 2001;85:983-90; PMID: 11466259

A systematic review compared timolol with brimonidine (α_2 adrenergic agonist), prostaglandin analogs (travoprost, latanoprost), other β adrenergic antagonists, and placebo. As to the comparison of timolol with travoprost or latanoprost, both drugs significantly increased iris pigmentation (travoprost OR 11.06, CI 2.07-59.08 and latanoprost OR 8.01, CI 1.87-34.30).

References

Boland MV, Ervin AM, Friedman DS. Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013;158:271-9; PMID: 23420235

The 5-year, randomized, open-label safety study (Goldber et al. 2008) compared once-daily latanoprost with usual care, defined as any commercially available IOP-reducing medication except latanoprost. The study was conducted at 406 centers in 14 countries. Patients were excluded if they had previously been or currently were being treated with latanoprost or another prostaglandin. In all, 5893 patients were randomized, and 5854 (99.3%) received at least one dose of study medication.

The first subject visit occurred 1999, and the last was on 2005. In the total safety population, 3936 (67%) patients were randomized to latanoprost, and 2707/3936 (69%) completed the study. 1918 patients were initially randomized to usual care, and 1285/1918 (67%) completed the study. At baseline, approximately 95% of patients were receiving IOP-reducing medications, with 78% being treated with β -adrenergic antagonists and 20% receiving topical carbonic anhydrase inhibitors.

Among patients ever treated with latanoprost, investigators judged that 577/4638 (12%) had increased iris pigmentation compared to those who used any other IOP reducing agent.

References

Goldberg I, Li XY, Selaru D, Paggiarino D. A 5-year, randomized, open-label safety study of latanoprost and usual care in patients with open-angle glaucoma or ocular hypertension. *Eur J Ophthalmol* 2008;18:408-16; PMID: 18465724

[E67]

Level of evidence = B

Prostaglandin analogs seem to cause hyperpigmentation of the periorbital skin and excessive growth of eyelashes.

Meta-analysis

Twelve studies involving 3048 patients with open-angle glaucoma or ocular hypertension were included in the meta-analysis comparing timolol with prostaglandin analogs. Participants received either travoprost, other prostaglandin analog or timolol.

Travoprost 0.004% caused a higher percentage of **eyelash changes** than timolol 0.5% (OR = 38.81, 95% CI 20.65-72.93, P < 0.00001). There was also an increased incidence of eyelash changes with travoprost 0.004% than latanoprost 0.005% (OR = 3.82, 95% CI 2.50-5.84, P < 0.00001), or travoprost 0.0015% (OR = 1.79, 95% CI 1.40-2.27, P < 0.00001).

References

Li N, Chen XM, Zhou Y. Travoprost compared with other prostaglandin analogues or timolol in patients with openangle glaucoma or ocular hypertension: Meta-analysis of randomized controlled trials. *Clin Exp Ophthalmol* 2006;34:755-64; PMID: 17073898

Study 1

The 5-year, randomized, open-label safety study compared once-daily latanoprost with usual care, defined as any commercially available IOP-reducing medication except latanoprost. The study was conducted at 406 centers in 14 countries. Patients were excluded if they had previously been or currently were being treated with latanoprost or another prostaglandin. In all, 5893 patients were randomized, and 5854 (99.3%) received at least one dose of study medication.

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References

Goldberg I, Li XY, Selaru D, Paggiarino D. A 5-year, randomized, open-label safety study of latanoprost and usual care in patients with open-angle glaucoma or ocular hypertension. *Eur J Ophthalmol* 2008;18:408-16; PMID: 18465724

Study 2

The study of Inoue et al. (2012) included 250 eyes from 250 patients diagnosed with primary open-angle glaucoma or ocular hypertension who were treated with either latanoprost, travoprost, tafluprost, bimatoprost, or isopropyl unoprostone for >3 months in only one eye. Photographs of both eyes were obtained, and the images were assessed by three ophthalmologists who were masked to treatment type. The existence of eyelid pigmentation and eyelash bristles was judged, and images of the left and right eyes were compared. Subjective symptoms regarding the existence of eyelid pigmentation and eyelash bristles were investigated through a questionnaire.

There was no significant difference between the five types of medications with regard to **eyelid pigmentation** ($P=0.537$). Use of isopropyl unoprostone resulted in a significantly lower incidence of eyelash bristles ($P<0.0001$). The questionnaire investigation showed that eyelid pigmentation and eyelash bristles were significantly more frequent with travoprost (42% and 42%, respectively) and bimatoprost (58% and 60%, respectively), and latanoprost (30% and 28%, respectively) and tafluprost (22% and 34%, respectively) and unoprostone (12% and 8%, respectively) compared with other three medications ($P<0.0001$). The appearance frequency of eyelid pigmentation was similar among the five types of PG analogs studied, but eyelash bristles appeared less frequently with isopropyl unoprostone use.

References

Inoue K, Shiokawa M, Higa R. Adverse periocular reactions to five types of prostaglandin analogs. *Eye (Lond.)* 2012;26:1465-72; PMID: 23037910

Study 3

In another meta-analysis comparing latanoprost with timolol in patients with open-angle glaucoma, latanoprost caused hyperaemia and iris pigmentation more often than timolol (RR = 2.20, 95% CI 1.33-3.65). The number needed to harm was 21 (CI 14-42) when compared to timolol. Of 478 patients who were treated with latanoprost, 21 (4.39%) developed iris pigmentation. In contrast, none of the patients treated with timolol showed this effect (0/387).

References

Zhang WY, Po AL, Dua HS, Azuara-Blanco A. Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension. *Br J Ophthalmol* 2001;85:983-90; PMID: 11466259

[E68]

Level of evidence = C

Treatment with prostaglandin analogues may be related to a small risk of macular oedema, uveitis and corneal changes.

Study 1

This 5-year, randomized, open-label safety study (Goldberg et al 2008) compared once-daily latanoprost with usual care, defined as any commercially available IOP-reducing medication except latanoprost. The study was conducted at 406 centers in 14 countries. Patients were excluded if they had previously been or currently were being treated with latanoprost or another prostaglandin. In all, 5893 patients were randomized, and 5854 (99.3%) received at least one dose of study medication.

The first subject visit occurred 1999, and the last was on 2005. In the total safety population, 3936 (67%) patients were randomized to latanoprost, and 2707/3936 (69%) completed the study. 1918 patients were initially randomized to usual care, and 1285/1918 (67%) completed the study. At baseline, approximately 95% of patients were receiving IOP-reducing medications, with 78% being treated with β -adrenergic antagonists and 20% receiving topical carbonic anhydrase inhibitors.

In the total safety population, the 5-year incidence of macular, iritis/uveitis, or corneal erosions was low and ($\leq 2.7\%$) and comparable for patients randomized to latanoprost or usual care; latanoprost vs. usual care 2.4%/1.9%, incidence of **iritis/uveitis** 2.5%/2.2%, incidence of **corneal erosions** 2.7%/2.2%. Kaplan-Meier estimates indicated a low risk (≤ 3.17) for each of three events at 5 years. Rates of these events in the total latanoprost and initial treatment populations were consistent with those for the total safety population.

References

Goldberg I, Li XY, Selaru D, Paggiarino D. A 5-year, randomized, open-label safety study of latanoprost and usual care in patients with open-angle glaucoma or ocular hypertension. *Eur J Ophthalmol* 2008;18:408-16; PMID: 18465724

Study 2

Denis (2010) conducted an open label uncontrolled 3-month study of once-daily use of 0.005 percent latanoprost in 258 ophthalmology practices that included 600 participants with OHT or OAG. Keratitis was reported in 0.8% of patients.

References

Denis P, Baudouin C, Bron A. First-line latanoprost therapy in ocular hypertension or open-angle glaucoma patients: a 3-month efficacy analysis stratified by initial intraocular pressure. *BMC Ophthalmol* 2010;10:4; PMID: 20181282

[E69]

Level of evidence = C

Prostaglandin analogs may cause periorbitopathy.

Study 1

Doran et al (2012) described an unexpected side effect of prostaglandin analogues, prostaglandin associated periorbitopathy (PAP). The characteristic features are: upper lid ptosis, deepening of the upper lid sulcus, involution of dermatochalasis, periorbital fat atrophy, mild enophthalmos, inferior scleral show, increased prominence of lid vessels, tight eyelids.

References

Doran M, Berke SJ, Pasquale LR. What clinicians need to know about prostaglandin-associated periorbitopathy. *EyeNet* 2012; 3:31-33.

Filippopoulos T, Paula JS, Torun N, Hatton MP, Pasquale LR, Grosskreutz CL. Periorbital changes associated with topical bimatoprost. *Ophthalm Plast Reconstr Surg*. 2008;24(4):302-307; doi: 10.1097/IOP.0b013e31817d81df; PMID:18645437

Peplinski LS, Albani Smith K. Deepening of lid sulcus from topical bimatoprost therapy. *Optom Vis Sci*. 2004;81(8):574-577; PMID:15300114

Tappeiner C, Perren B, Iliev ME, Frueh BE, Goldblum D. [Orbital fat atrophy in glaucoma patients treated with topical bimatoprost. Can bimatoprost cause enophthalmos?]. *Klin Monbl Augenheilkd*. 2008;225(5):443-445; doi: 10.1055/s-2008-1027362; PMID:18454393

Jayaprakasam A, Ghazi-Nouri S. Periorbital fat atrophy - an unfamiliar side effect of prostaglandin analogues. *Orbit*. 2010;29(6) 357-359; doi: 10.3109/01676830.2010.527028; PMID:21158579

Park J, Cho HK, Moon JI. Changes to upper eyelid orbital fat from use of topical bimatoprost, travoprost, and latanoprost. *Jpn J Ophthalmol*. 2011;55(1): 22-27; doi: 10.1007/s10384-010-0904-z. Epub 2011 Feb 18; PMID:21331688

Study 2

Kucukevcilioglu et al. investigated prostaglandin associated periorbitopathy (PAP) in 105 patients using bimatoprost, latanoprost or travoprost for more than one month. The other eye was used as a control. Statistically significant differences were found among the groups regarding the presence of all PAP findings ($p < 0.05$). Periorbital fat loss was the most frequent finding and was observed in nearly all PAP patients except those who were relatively young. The overall frequency of PAP was 93% in the bimatoprost group, 41% in the latanoprost group, and 70% in the travoprost group. The frequency of deepening of the upper lid sulcus was 80% in the bimatoprost group, 16% in the latanoprost group, and 45% in the travoprost group. The frequency of milder changes (the presence of either only periorbital fat loss, or dermatochalasis

involution, or both) was higher in the latanoprost group (62%) than in the travoprost (36%) and bimatoprost (7%) groups.

References

Kucukevcilioglu M, Bayer A, Uysal Y, Altinsoy HI. Prostaglandin associated periorbitopathy in patients using bimatoprost, latanoprost and travoprost. *Clin Experiment Ophthalmol*. 2013 Jul 12. doi: 10.1111/ceo.12163. [Epub ahead of print]; PMID:23844550

Study 3

Sakata et al. investigated deepening of the upper eyelid sulcus (DUES), one symptom of prostaglandin-associated periorbitopathy. The open-label prospective study investigated the incidence and factors associated with DUES in Japanese glaucoma patients initially treated with benzalkonium chloride (BAK)-preserved tafluprost. Tafluprost was instilled in one eye. Facial photographs and subjective reports of DUES were obtained at intervals over 6 months. 43 eyes of 43 glaucoma patients (24 men and 19 women) were evaluated. Mean IOP before treatment was 16.6 ± 2.7 and after treatment, 14.1 ± 2.3 mmHg ($P < 0.001$). The objective rate of DUES was 9% (4/43) at 2 months, 14% (6/43) at 4 months and 14% (6/43) at 6 months. During this period, only one patient self-reported DUES. No significant association was found between DUES occurrence and other systemic or ocular factors.

References

Sakata R, Shirato S, Miyata K, Aihara M. Incidence of deepening of the upper eyelid sulcus on treatment with a tafluprost ophthalmic solution. *Jpn J Ophthalmol*. 2014 Jan 7. [Epub ahead of print]; doi: 10.1007/s10384-013-0299-8. Epub 2014 Jan 7; PMID:24390604

Study 4

Choi et al. investigated in vitro the potential mechanisms by which topical prostaglandin analogs could induce orbital fat volume reduction and cause deep superior sulcus syndrome. Human orbital adipose precursors were treated in vitro for 24 h (day 1) with prostaglandin F₂α (PGF₂α), latanoprost, travoprost, bimatoprost, and tafluprost in their commercial formulations (1:100 dilution). Latanoprost, travoprost, bimatoprost, and tafluprost inhibited human preadipocyte differentiation and intracellular lipid accumulation. Morphologic and metabolic changes in orbital adipocytes caused by PGF₂α analogs may be a possible pathophysiologic explanation of superior eyelid deepening in patients with glaucoma.

References

Choi HY, LeeJE, Lee JW, Park HJ, Jung JH. In vitro study of antiadipogenic profile of latanoprost, travoprost, bimatoprost, and tafluprost in human orbital preadipocytes. *J Ocul Pharmacol Ther*. 2012 Apr;28(2):146-52. doi: 10.1089/jop.2011.0160. Epub 2011 Nov 22; PMID:22107041, PMCID:PMC3315164

[E70]

Level of evidence = D

The thinning effect of prostaglandin analogues on CCT is not confirmed.

The IOP-lowering effect of topical prostaglandin analogues (PGAs) was examined in relation to central corneal thickness (CCT). 75 subjects were enrolled in this post hoc analysis of a randomized prospective trial. The mean age was 63 ± 11 years; 48 were Caucasian. The mean CCT was 562 ± 41 μm . At repeated measures, ANCOVA analysis showed a significant effect of both baseline IOP ($p < 0.0001$) and CCT ($p = 0.003$) on IOP. At week 12, a regression analysis of the effect of CCT on baseline IOP showed that for every 10 μ increase in CCT there was 0.3 mm Hg less IOP decrease from baseline.

It was found a statistically significantly association between a lower mean IOP and a thinner cornea when baseline IOP is controlled for. The magnitude of the relationship is small but may be clinically significant in patients with either very thin or very thick corneas.

References

Birt CM, Buys YM, Kiss A, Trope GE; Toronto Area Glaucoma Society. The influence of central corneal thickness on response to topical prostaglandin analogue therapy. *Can J Ophthalmol* 2012;47:51-4; PMID: 22333852

The long-term effect of latanoprost was evaluated on central corneal thickness (CCT) in patients with normal tension glaucoma (NTG). This was a **retrospective study** and included 166 eyes of 166 patients [128 with NTG and 38 with glaucoma suspect, suspicious discs with normal visual fields, and an intraocular pressure (IOP) ≤ 21 mmHg as the control group]. Patients with newly diagnosed NTG and who had not had previous topical glaucomatous treatment were followed ≥ 24 months and received latanoprost 0.005% monotherapy once a day. CCT measurements were performed with an ultrasound pachymeter. CCT measurements before treatment and 24 months after treatment were analyzed.

There were no significant differences between the latanoprost group and the control group with respect to sex, age, baseline IOP, and CCT. A statistically significant reduction in the mean CCT was observed in the latanoprost group [536 ± 38 vs. 530 ± 36 μm ($n = 128$), $P < 0.01$], but not in the control group [543 ± 40.2 vs. 543 ± 37.0 μm ($n = 38$), $P = 0.786$]. Long-term use of latanoprost may decrease the CCT in patients with NTG.

References

Kim HJ, Cho BJ. Long-term effect of latanoprost on central corneal thickness in normal tension glaucoma. *J Ocul Pharmacol Ther* 2011;27:73-6; PMID: 21091278

[E71]

Level of evidence = D

Topical prostaglandin analogs (PGAs) may cause gastrointestinal adverse effects.

Study 1

Cai et al. 2013, performed a molecular genetic analysis on the patient reported by Yu et al., who developed nausea, vomiting and diarrhea after topical application of travoprost and latanoprost, but not bimatoprost, and then speculated that the mechanism underlying the gastro-intestinal distress secondary to PGA topical application should be attributed to their stimulation of smooth muscles of the gastric and intestinal tract via prostanoid receptors. To further verificate the speculation, other three glaucoma patients who exhibited different gastro-intestinal responses to different PGA medications were enrolled.

The results suggested that the relative expression level of FP receptor, versus EP receptors, might be associated with the severity of gastro-intestinal effects incurred by PGAs. Owing to the differed expression levels of FP receptor, the responses of various patients to different PGAs can be variable.

References

Cai S, Zhou X, Yan N, Liu X, Li X. Possible mechanism for the gastro-intestinal adverse effects upon topical application of Prostaglandin F₂α analogs. *Med Hypotheses*. 2013;80:32-5; PMID: 23098372

Study 2 (case report)

References

Yu M, Chen X, Jia, Liu X. Travoprost and latanoprost, but not bimatoprost, induced nausea, vomiting and diarrhoea. *BMC Case Rep* 2009;2009. pii: bcr08.2008.0618. doi: 10.1136/bcr.08.2008.0618. Epub 2009 Feb 26; PMID: 21686721

Study 3

Three cases with proven gastrointestinal disturbances due to latanoprost have been described. All these three patients had severe gastrointestinal adverse effects after initiating treatment with prostaglandin analogues; first patient developed esophageal spasm, regurgitation, constipation, and generalized malaise. The second patient noted a burning sensation in his stomach, heartburn, and an acid aftertaste. The third patient developed nausea, vomiting, and dizziness. The adverse effects in all 3 patients were confirmed with unmasked challenge-rechallenge tests, and all the patients were given at least 2 additional prostaglandin analogues.



References

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[E72]

Level of evidence = C

Compression of the nasolacrimal duct may reduce some side-effects.

In a pilot study the effect of bilateral inferior punctal occlusion on the ocular hypotensive effect was evaluated after topically applied timolol using silicone punctal plugs. A randomized, double-masked, cross-over clinical trial was conducted, comparing the ocular hypotensive effect of timolol maleate 0.25 percent, both with and without occlusion of the inferior punctum with the Freeman silicone punctal plug. Following a 2-week washout of topical medication, 17 subjects with early primary open-angle glaucoma or ocular hypertension received one drop of timolol 0.25 percent in each eye with or without punctal plugs in place. Blood pressure, resting pulse rate, and intraocular pressure were measured both before timolol instillation and at intervals of 1, 2, 4, 8, and 12 hours following drop instillation. Following a 2-week washout period, the subjects were evaluated with the alternative treatment. There was no statistically significant difference ($p = 0.648$) in IOP levels between treatment groups .

References

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Twenty patients with primary open angle glaucoma who have been treated with identical antiglaucoma eye drops in both eyes were examined. Silicone punctal plugs were used to occlude the inferior punctum of one eye, in order to block the nasolacrimal canal. The intraocular pressures and effects of the medical therapy before and after punctal occlusion were compared. Punctal occlusion significantly decreased the intraocular pressure with an average of 2.00 +/- 0.43 mmHg in the plugged eyes ($p < 0.001$). The intraocular pressure in the unplugged control eyes did not change significantly ($p > 0.05$) after punctal occlusion of the fellow treated eye.

References

Aritürk N, Oge I, Erkan D, Süllü Y, Sahin M. The effects of nasolacrimal canal blockage on topical medications for glaucoma. *Acta Ophthalmol Scand* 1996;74:411-3; PMID: 8883562

In a study silicone punctal plugs were used to occlude the inferior punctum of one eye in each of 19 patients treated with identical antiglaucoma eyedrops in both eyes. The intraocular pressures before and after punctal occlusion were compared. The eyes with the punctal plugs showed a statistically significant ($p < 0.0001$) decrease in pressure of 1.32 mm Hg after punctal occlusion when compared to that of the fellow



control unplugged eyes. The intraocular pressures in the plugged eyes decreased an average of 1.82 mm Hg after punctal occlusion when compared to before punctal occlusion ($p = .001$).

References

Huang TC, Lee DA. Punctal occlusion and topical medications for glaucoma. *Am J Ophthalmol* 1989;107:151-5; PMID: 2913809

In Finnish studies there has been shown that temporary occlusion of nasolacrimal puncta decreases the systemic absorption of the glaucoma medication.

Kaila T, Huupponen R, Salminen L. Effects of eyelid closure and nasolacrimal duct occlusion on the systemic absorption of ocular timolol in human subjects. *J Ocul Pharmacol* 1986;2:365-9; PMID: 3503120

Urtti A, Salminen L. Minimizing systemic absorption of topically administered ophthalmic drugs. *Surv Ophthalmol* 1993;37:435-56; PMID: 8100087

[E73]

Level of evidence = B

Laser and medical therapy seem to induce similar IOP lowering effect.

Systematic review 1

The systemic review compare selective laser trabeculoplasty (SLT) to other glaucoma treatment options in terms of their intraocular pressure (IOP)-lowering effect. Searches performed on PubMed, Cochrane Central Register of Controlled Trials, Ovid, EMBASE, metaRegister of Controlled Trials, and ClinicalTrials.gov. Only randomised controlled trials (RCTs) were included. The main outcome measure was the change in IOP from baseline.

Of 23 RCTs with 17 meeting the inclusion criteria. Three trials compared 360degree SLT to medical therapy and found no difference between the two treatment options. Three trials indicate no difference between 360degree SLT and medical therapy, with one of the trials indicating greater IOP reduction with latanoprost over 90degree and 180degree SLT. There were no RCTs identified that compared SLT to surgery.

References

McAlinden C. Selective laser trabeculoplasty (SLT) vs other treatment modalities for glaucoma: systematic review. *Eye* 2014 Mar;28(3):249-258; doi: 10.1038/eye.2013.267. Epub 2013 Dec 6; PMID:24310236 [PubMed - in process] PMCID:PMC3965810 [Available on 2015/3/1]

Systematic review 2

The purpose of the systematic review and meta-analysis was to evaluate the efficacy and tolerability of selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT). Six clinic studies, all of which were random controlled trials, were selected through extensive searches of PubMed, Cochrane Library, Embase, and meeting abstracts. Efficacy measures were weighted by mean differences for intraocular pressure (IOP), as well as change of number of glaucoma medications and relative risks (RRs) for therapeutic IOP responses.

There was no significant difference in therapeutic IOP responses between SLT and ALT, with a pooled RR of 0.84 (95% CI, 0.51-1.38). When compared in patients with previous failed laser treatment (ALT or SLT), WMD was 1.48 (95% CI, 0.75-2.21). Patients who received SLT took fewer glaucoma medications after operations than those who received ALT, with a WMD of 0.29 (95% CI, 0.01-0.56). The frequencies of anterior chamber flare and IOP peak after operation were similar comparing SLT and ALT, with pooled RRs of 0.90 (95% CI, 0.74-1.11) and 0.90 (95% CI, 0.45-1.82), respectively.

References

Wang H, Cheng JW, Wei RL, Cai JP, Li Y, Ma XY. Meta-analysis of selective laser trabeculoplasty with argon laser trabeculoplasty in the treatment of open-angle glaucoma. *Canadian Journal of Ophthalmology* 2013 Jun;48(3):186-192; doi: 10.1016/j.jcjo.2013.01.001; PMID:23769780

Six RCTs

Randomized controlled trials (RCTs) comparing SLT versus ALT were searched through August 2013. The main outcome measure was IOP, and secondary outcomes included the number of glaucoma medications, the success rate, and adverse events. Six RCTs, involving 482 eyes treated with laser trabeculoplasty, were included in the meta-analysis. For all patients (including first and previous laser trabeculoplasty), no significant difference in IOP lowering was observed between SLT and ALT at one hour ($P = 0.40$), one week ($P = 0.72$), one month ($P = 0.37$), six months ($P = 0.08$), one year ($P = 0.34$), two years ($P = 0.58$), three years ($P = 0.34$), four years ($P = 0.47$), and five years ($P = 0.50$). A statistically significant difference in favor of SLT was found when comparing the IOP reduction at three months after intervention (weighted mean difference (WMD): 1.19 mmHg [0.41; 1.97]; $I(2)=0\%$; $P = 0.003$).

For patients who were naive to laser, there was no significant difference of reduction in IOP comparing SLT with ALT at any time point. In patients' previous LT, no statistically significant difference in IOP reduction was found at six months (WMD: 1.92 mmHg [-0.91; 4.74]; $I(2) = 77.3\%$; $P = 0.18$). There was no significant difference in the reduction in the number of glaucoma medications, the success rate, or adverse event rates between the two treatments.

References

Wang W, He M, Zhou M, Zhang X. Selective laser trabeculoplasty versus argon laser trabeculoplasty in patients with open-angle glaucoma: a systematic review and meta-analysis. *PLoS ONE* [Electronic Resource] 2013;8(12):e84270; doi: 10.1371/journal.pone.0084270. eCollection 2013; ID:24367649 [PubMed - in process], PMID:PMC3868565

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[E74]

Level of evidence = B

Argon and selective laser trabeculoplasty seem to induce similar IOP lowering effect.

Systematic review 1

The systemic review compare selective laser trabeculoplasty (SLT) to other glaucoma treatment options in terms of their intraocular pressure (IOP)-lowering effect. Searches performed on PubMed, Cochrane Central Register of Controlled Trials, Ovid, EMBASE, metaRegister of Controlled Trials, and ClinicalTrials.gov. Only randomised controlled trials (RCTs) were included. The main outcome measure was the change in IOP from baseline.

An initial search of PubMed identified 23 RCTs with 17 meeting the inclusion criteria. Nine RCTs compared 180degree SLT to 180degree argon laser trabeculoplasty (ALT) and one trial compared 360degree SLT to 360degree ALT, all reporting no difference in terms of IOP reduction from baseline. **In terms of the IOP lowering effect, there was no difference between SLT and ALT.**

References

McAlinden C. Selective laser trabeculoplasty (SLT) vs other treatment modalities for glaucoma: systematic review. *Eye* 2014 Mar;28(3):249-258; doi: 10.1038/eye.2013.267. Epub 2013 Dec 6; PMID:24310236 [PubMed - in process], PMID:PMC3965810[Available on 2015/3/1]

Systematic review 2

The purpose of the systematic review and meta-analysis was to evaluate the efficacy and tolerability of selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT). Six clinic studies, all of which were random controlled trials, were selected through extensive searches of PubMed, Cochrane Library, Embase, and meeting abstracts. Efficacy measures were weighted by mean differences for intraocular pressure (IOP), as well as change of number of glaucoma medications and relative risks (RRs) for therapeutic IOP responses.

There was no significant difference in therapeutic IOP responses between SLT and ALT, with a pooled RR of 0.84 (95% CI, 0.51-1.38). When compared in patients with previous failed laser treatment (ALT or SLT), WMD was 1.48 (95% CI, 0.75-2.21). Patients who received SLT took fewer glaucoma medications after operations than those who received ALT, with a WMD of 0.29 (95% CI, 0.01-0.56). The frequencies of anterior chamber flare and IOP peak after operation were similar comparing SLT and ALT, with pooled RRs of 0.90 (95% CI, 0.74-1.11) and 0.90 (95% CI, 0.45-1.82), respectively.

References

Wang H, Cheng JW, Wei RL, Cai JP, Li Y, Ma XY. Meta-analysis of selective laser trabeculoplasty with argon laser trabeculoplasty in the treatment of open-angle glaucoma. *Canadian Journal of Ophthalmology* 2013 Jun;48(3):186-192; doi: 10.1016/j.cjjo.2013.01.001, PMID:23769780

Six RCTS

Randomized controlled trials (RCTs) comparing SLT versus ALT were searched through August 2013. The main outcome measure was IOP, and secondary outcomes included the number of glaucoma medications, the success rate, and adverse events. Six RCTs, involving 482 eyes treated with laser trabeculoplasty, were included in the meta-analysis. **For all patients (including first and previous laser trabeculoplasty), no significant difference in IOP lowering was observed between SLT and ALT at one hour (P = 0.40), one week (P = 0.72), one month (P = 0.37), six months (P = 0.08), one year (P = 0.34), two years (P = 0.58), three years (P = 0.34), four years (P = 0.47), and five years (P = 0.50).** A statistically significant difference in favor of SLT was found when comparing the IOP reduction at three months after intervention (weighted mean difference (WMD): 1.19 mmHg [0.41; 1.97]; I(2)=0%; P = 0.003).

For patients who were naive to laser, there was no significant difference of reduction in IOP comparing SLT with ALT at any time point. In patients' previous LT, no statistically significant difference in IOP reduction was found at six months (WMD: 1.92 mmHg [-0.91; 4.74]; I(2) = 77.3%; P = 0.18). **There was no significant difference in the reduction in the number of glaucoma medications, the success rate, or adverse event rates between the two treatments.**

References

Wang W, He M, Zhou M, Zhang X. Selective laser trabeculoplasty versus argon laser trabeculoplasty in patients with open-angle glaucoma: a systematic review and meta-analysis. *PLoS ONE* [Electronic Resource] 2013;8(12):e84270; doi: 10.1371/journal.pone.0084270. eCollection 2013; ID:24367649 [PubMed - in process], PMID:PMC3868565

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[E75]

Level of evidence = D

According to short-term follow-up studies in refractory glaucoma, transscleral laser cyclophotocoagulation may lower IOP but the need for repeated treatments is frequent.

References

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Kosoko O, Gaasterland D, Pollack I, Enger C. Long-term outcome of initial ciliary ablation with contact diode laser transscleral cyclophotocoagulation for severe glaucoma. *Ophthalmology* 1996;103:1294-302; PMID: 8764801



[E76]

Level of evidence = D

Patients should be treated with additional IOP lowering medication prior to cyclophotocoagulation in order to avoid postoperative pressure spikes.

References

Immonen I, Puska P, Raitta C. Transscleral contact krypton laser cyclophotocoagulation for treatment of glaucoma. *Ophthalmology* 1994;10:876-82; PMID: 8190474

Yap-Veloso MI, Simmons RB, Echelman DA, Gonzales TK, Veira WJ, Simmons RJ. Intraocular pressure control after contact transscleral diode cyclophotocoagulation in eyes with intractable glaucoma. *J Glaucoma* 1998;7:319-28; PMID: 9786561

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[E77]

Level of evidence = B

Although surgical treatment seems to reduce intraocular pressure more than medical (or laser treatment [E78], B), the rate of progression seems to be somewhat less after surgery only in far advanced glaucoma. Initially, surgically treated patients complain more about local eye problems and need more cataract surgery than medically treated patients. However, after five years the need for cataract surgery does not differ between the two groups.

References

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[E78]

Level of evidence = B

Surgical treatment seems to reduce intraocular pressure more than laser treatment.

References

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[E79]

Level of evidence = B

The visual field defects may progress in spite of decreased IOP also after surgery. It has not been possible to determine any clear cut-off IOP, which would prevent progression in surgically treated patients.

References

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[E80]

Level of evidence = C

Mitomycin C may improve the lowering of IOP one year after trabeculectomy in eyes with high risk for fibrosis and in eyes without previous surgery.

Literature through March 2005 was undertaken in the Cochrane systematic review. Randomised trials of intraoperative MMC were compared to placebo in trabeculectomy surgery. 11 trials, involving a total of 698 participants, were included. Mitomycin C appeared to reduce the relative risk of failure of trabeculectomy both in eyes at high risk of failure (relative risk 0.32, 95% confidence interval 0.20 to 0.53) and those undergoing surgery for the first time (relative risk 0.29, 95% confidence interval 0.16 to 0.53). No significant effect on failure was noted in the group undergoing trabeculectomy combined with cataract extraction. Mean IOP was significantly reduced at 12 months in all three participant groups receiving MMC compared to placebo. No significant increase in permanent sight-threatening complications was detected. However, none of the trials were large enough or of sufficient duration to address the long-term risk of bleb infection and endophthalmitis which has been reported in observational studies. Some evidence exists that MMC increases the risk of cataract.

References

Wilkins M, Indar A, Wormald R, Bunce C. Intra-operative mitomycin C for glaucoma surgery. *Cochrane Database Syst Rev* 2005;(4):CD002897; PMID: 11279773



[E81]

Level of evidence = C

The success rate of nonpenetrating surgery may be better when using Mitomycin C without increased rate of complications.

References

Cheng JW, Cai JP, Li Y, Wei RL. Intraoperative Mitomycin C for nonpenetrating glaucoma surgery. A systematic review and meta-analysis. *J Glaucoma* 2011;20:322-6; PMID: 20577107

[E82]

Level of evidence = C

Postoperative injections of 5-FU may reduce surgical failures and intraocular pressure at one year in the primary trabeculectomy group and high-risk group. Complications may be more common after 5-FU injections. The methodological quality of the trials was not high.

This update of a Cochrane review, first published in 2000, and updated in 2009 and 2014, assessed the effects of both intraoperative application and postoperative injections of 5-FU in eyes of people undergoing surgery for glaucoma at one year. Search methods: CENTRAL, Ovid MEDLINE, Ovid OLDMEDLINE, EMBASE, mRCT, ClinicalTrials.gov, and ICTRP by July 2013. RCTs of intraoperative application and postoperative 5-FU injections were compared with placebo or no treatment in trabeculectomy for glaucoma. Standard methodological procedures expected by The Cochrane Collaboration were used. Trial investigators were contacted for missing information.

The participants were divided into three separate subgroup populations (high risk of failure, combined surgery and primary trabeculectomy) and the interventions were divided into three subgroups of 5-FU injections (intraoperative, regular dose postoperative and low dose postoperative). Twelve trials, which randomised 1319 participants, were included in the review. As far as can be determined from the trial reports, the methodological quality of the trials was not high, including a high risk of detection bias in many. Of note, only one study reported low-dose postoperative 5-FU and this paper was at high risk of reporting bias. All studies were a minimum of one year long.

A significant reduction in surgical failure in the first year after trabeculectomy was detected in eyes at high risk of failure and those undergoing surgery for the first time receiving regular-dose 5-FU postoperative injections (RR 0.44, 95% confidence interval (CI) 0.29 to 0.68 and 0.21, 0.06 to 0.68, respectively). No surgical failures were detected in studies assessing combined surgery.

No difference was detected in the low-dose postoperative 5-FU injection group in patients undergoing primary trabeculectomy (RR 0.93, 95% CI 0.70 to 1.24). Perioperative 5-FU in patients undergoing primary trabeculectomy significantly reduced risk of failure (RR 0.67, 95% CI 0.51 to 0.88). This translates to a number needed to treat for an additional beneficial outcome of 4.1 for the high risk of failure patients, and 5.0 for primary trabeculectomy patients receiving postoperative 5-FU.

Intraocular pressure was also reduced in the primary trabeculectomy group receiving intraoperative 5-FU (mean difference (MD) -1.04, 95% CI -1.65 to -0.43) and regular-dose postoperative 5-FU (MD -4.67, 95% CI -6.60 to -2.73). No significant change occurred in the primary trabeculectomy group receiving low-dose postoperative 5-FU (MD -0.50, 95% CI -2.96 to 1.96). Intraocular pressure was particularly reduced in the high risk of failure population receiving regular-dose postoperative 5-FU (MD -16.30, 95% CI -18.63 to -13.97). No difference was detected in the combined surgery population receiving regular-dose postoperative 5-FU (MD -1.02, 95% CI -2.40 to 0.37).

Whilst no evidence was found of an increased risk of serious sight-threatening complications, other complications are more common after 5-FU injections. None of the trials reported on the participants' perspective of care.

Authors' conclusions: Postoperative injections of 5-FU are now rarely used as part of routine packages of postoperative care but are increasingly used on an ad hoc basis. The small but statistically significant reduction in surgical failures and intraocular pressure at one year in the primary trabeculectomy group and high-risk group must be weighed against the increased risk of complications and patient preference.

References

Green E, Wilkins M, Bunce C, Wormald R. 5-Fluorouracil for glaucoma surgery. *Cochrane Database of Systematic Reviews* 2014;2:001132; doi: 10.1002/14651858.CD001132.pub2; PMID:24554410



[E83]

Level of evidence = C

Beta radiation with trabeculectomy may prevent scarring.

References

Kirwan JF, Rennie C, Evans JR. Beta radiation for glaucoma surgery. *Cochrane Database Syst Rev* 2012;(6):CD003433; PMID: 22696336

[E84]

Level of evidence = B

Although during 5 years the IOP decreases equally in previously operated eyes undergoing surgery for Baerwaldt shunt and trabeculectomy, the success rate after shunt operation seems be better.

References

Gedde SJ, Schiffman JC, Feuer WJ, Parrish RK, Heuer DK, Brandt JD, Tube versus Trabeculectomy Study Group. The Tube Versus Trabeculectomy study: design and baseline characteristics of study patients. *Am J Ophthalmol* 2005;140:275-87; PMID: 16086949

Gedde SJ, Schiffman JC, Feuer WJ . Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. *Am J Ophthalmol* 2012;153:789-803; PMID: 22245458

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**[E85]****Level of evidence = B**

During 1–3 years follow-up the efficacy of various shunts seems similar. During one-year follow-up, shunts without valves induce lower IOP than those with valves. However, the risk of complications and additional surgery seems higher.

References

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[E86]

Level of evidence = C

Limited evidence indicates that short-term control of IOP may be better with trabeculectomy than viscocanalostomy while no difference was found for deep sclerectomy.

Review 1

The Objectives was to compare the effectiveness of non-penetrating trabecular surgery compared with conventional trabeculectomy in people with glaucoma. Search methods, extended tp September 2013, included CENTRAL, Ovid MEDLINE, Ovid OLDMEDLINE (January 1946 to September 2013), EMBASE, LILACS,mRCT, ClinicalTrials.gov and ICTRP. Selection criteria: RCTs and quasi-RCTs on participants undergoing standard trabeculectomy for open-angle glaucoma compared to non-penetrating surgery, specifically viscocanalostomy or deep sclerectomy, with or without adjunctive measures. Standard methodological procedures expected by The Cochrane Collaboration were used.

Five studies with a total of 311 eyes (247 participants) of which 133 eyes (participants) were quasi-randomised. One hundred and sixty eyes which had trabeculectomy were compared to 151 eyes that had non-penetrating glaucoma surgery (of which 101 eyes had deep sclerectomy and 50 eyes had viscocanalostomy). The confidence interval (CI) for the odds ratio (OR) of success (defined as achieving target eye pressure without eye drops) does not exclude a beneficial effect of either deep sclerectomy or trabeculectomy (OR 0.98, 95% CI 0.51 to 1.88). The odds of success in viscocanalostomy participants was lower than in trabeculectomy participants (OR 0.33, 95% CI 0.13 to 0.81). The odds ratio for achieving target eye pressure with or without eye drops was imprecise and was compatible with a beneficial effect of either trabeculectomy or non-penetrating filtration surgery (NPFS) (OR 0.79, 95% CI 0.35 to 1.79).

Operative adjuvants were used in both treatment groups; more commonly in the NPFS group compared to the trabeculectomy group but no clear effect of their use could be determined.

Although the studies were too small to provide definitive evidence regarding the relative safety of the surgical procedures we noted that there were relatively fewer complications with non-filtering surgery compared to trabeculectomy (17% and 65% respectively). Cataract was more commonly reported in the trabeculectomy studies.

None of the five trials used quality of life measure questionnaires. The methodological quality of the studies was not good. **Most studies were at high risk of bias** in at least one domain and for many, **there was lack of certainty due to incomplete reporting.**

Authors' conclusions: This review provides some limited evidence that control of IOP is better with trabeculectomy than viscocanalostomy. For deep sclerectomy, we cannot draw any useful conclusions. This may reflect surgical difficulties in performing non-penetrating procedures and the need for surgical experience.

References

Eldaly MA, Bunce C, ElSheikha Ola Z, Wormald R. Non-penetrating filtration surgery versus trabeculectomy for open-angle glaucoma. *Cochrane Database Systematic Reviews 2*; 2014. doi: 10.1002/14651858.CD007059.pub2, PMID:24532137

Review 2

The objective was to compare the hypotensive effect and safety of nonpenetrating surgery (NPS) and trabeculectomy (TE) in terms of intraocular pressure (IOP) reduction and incidence of complications. The search by March 2013 included MEDLINE and EMBASE databases. The considered interventions were TE, deep sclerectomy (DS), viscocanalostomy, and canaloplasty. The primary outcome was the mean between-group difference in the reduction in diurnal IOP from baseline to the 6- or 12-month follow-up evaluation.

Eighteen articles, accounting for 20 comparisons, were selected for data extraction and analysis. Analysis of the 6-month follow-up data showed that the pooled estimate of the mean between-group difference was -2.15 mm Hg (95% CI, -2.85 to -1.44) in favor of TE. There was no difference between the NPS subgroups. In the subgroup antimetabolite analysis, the addition of mitomycin C to TE and DS decreased the difference in the reduction in IOP (TE and DS without mitomycin C: -2.65 mm Hg [95% CI, -3.90 to -1.39]; TE and DS with mitomycin C: -0.83 mm Hg [95% CI, -2.40 to 0.74]).

In the subgroup analysis by implant addition, no significant difference induced by DS with or without drainage devices was detected (test for subgroup differences: $\chi^2(1) = 0.24$; $P = .62$).

The absolute risk of hypotony, choroidal effusion, cataract, and flat or shallow anterior chamber was higher in the TE group than in the NPS group.

Authors' conclusion: Trabeculectomy seems to be the most effective surgical procedure for reducing IOP in patients with open-angle glaucoma. However, it was associated with a higher incidence of complications when compared with NPS.

References

Rulli E, Biagioli E, Riva I, Gambirasio G, De Simone I, Floriani I, et al. Efficacy and safety of trabeculectomy vs nonpenetrating surgical procedures: a systematic review and meta-analysis. *JAMA Ophthalmology* 2013 Dec;131(12):1573-1582; doi: 10.1001/jamaophthalmol.2013.5059; PMID:24158640

**[E87]****Level of evidence = D**

Although the studies were too small to provide definitive evidence regarding the relative safety of the surgical procedures, there may be relatively fewer complications with non-filtering surgery compared to trabeculectomy.

References

Rulli E, Biagioli E, Riva I, Gambirasio G, De Simone I, Floriani I, et al. Efficacy and safety of trabeculectomy vs nonpenetrating surgical procedures: a systematic review and meta-analysis. *JAMA Ophthalmology* 2013 Dec;131(12):1573-1582; doi: 10.1001/jamaophthalmol.2013.5059; PMID:24158640

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Chai C, Loon SC. Meta-analysis of viscocanalostomyt versus trabeculectomy in uncontrolled glaucoma. *J Glaucoma* 2010;19:519-27; PMID: 20179632



[E88]

Level of evidence = D

The evidence of collagen implant in the success rate of non-penetrating surgery is unclear.

References

Cheng JW, Wei RL, Cai JP, Li Y. Efficacy and tolerability of nonpenetrating filtering surgery with and without implant in treatment of open angle glaucoma. A quantitative evaluation of the evidence. *J Glaucoma* 2009;18:233-7; PMID: 19295379

[E89]

Level of evidence = D

There is no solid evidence of the optimum monitoring schemes (e.g., frequency and timing of visits, technologies to be used for detecting progression) for patients with manifest glaucoma and ocular hypertension. Some modeling and retrospective studies suggest that more treatment could allow less frequent monitoring visits in ocular hypertension and stable glaucoma. One RCT suggests that shared care may save costs.

Finnish retrospective study of the impact resource utilization on quality of life and clinical findings

The cost data of glaucoma patients were retrospectively collected and compared in two cities in Finland during 11 years. The patients were examined at the end of follow-up period. In addition, general health related quality of life questionnaire was evaluated. Intensive monitoring frequency, treatment and spending did not lead to better quality of life in glaucoma patients, i.e. 28% higher medication costs, 46% higher diagnostic testing and follow-up costs, 3 times more laser therapies and twice more surgery between the two cities. There was actually a statistically significant counter-intuitive difference in the early glaucoma group, i.e. patients using more resources reported **worse** quality of life.

References

Hagman J. Comparison of resource utilization in the treatment of open angle glaucoma in two cities Finland: is more better? Thesis. *Acta Ophthalmologica* 2013;91:1-47; PMID: 23621767

Systematic review and UK simulation model

The UK Health Technology Assessment compared five alternative surveillance and treatment pathways in OHT.

- The two most intensive pathways were based on the NICE guidelines (check-ups from every 4-12 - month to 6-24 -month intervals depending on initial risk), two further pathways followed biennial follow-up schemes differing in location (surveillance either in hospital or in primary care), and in the fifth 'Treat all' pathway, all IOPs > 21 mmHg were treated with prostaglandins. In 'Treat all' pathway, IOP was measured annually in community optometry with referral to a hospital only if IOP reduction was <15%.
- The results of the model indicated no clear benefit from intensive monitoring in OHT. 'Treat all' was the least and 'NICE intensive' was the most costly pathway.
- Compared to 'Treat all' –strategy, however, the pathway with 2-year check ups in an eye hospital (and treatment with > 5% glaucoma risk in 5 years) reduced the incidence of conversion to glaucoma and provided more QALYs. However, simultaneously this pathway cost considerably more - above the limit of the society's willingness to pay in the UK.
- For the cost-benefit analysis the biennial hospital pathway was the only pathway relative to 'no surveillance' that had a positive net benefit.

References

Burr JM, Botello-Pinzon P, Takwoingi Y. Surveillance for ocular hypertension: an evidence synthesis and economic evaluation. *Health Technology Assessment* 2012;16:1-271; PMID: 22687263

Systematic review and simulation model (Holland)

An economic simulation model in Holland (built on systematic evaluation of literature)

- The results suggested that treating **all** OHT patients with IOP > 21 mmHg would be cost saving compared to watchful waiting – even if 43% of the simulated untreated OHT patients never converted to glaucoma in their entire lifetime.
- In eyes with manifest glaucoma, in lieu of 'guessing' the initial target pressure and redefining it according to rate of progression, the model suggested to aim at a standard IOP < 15 mmHg in **all** glaucoma patients - even if it the model indicated that 72% would need direct combination therapy and 46% would require glaucoma surgery. According to the model, these simplified strategies would **decrease** demand for intensive monitoring.
- Non-adherence to the medication was not considered in the model. It was assumed that including adherence would have a small impact of the outcomes but would have unnecessarily increased the complexity of the model.

References

van Gestel A. Glaucoma management. Economic evaluations based on a patient level simulation model. *Ipskamp Drukkers*, Enschede, Holland, 2012. ISBN 978-94-6191-403-3

Simulation model

The report aims to **determine if identification of progression would be improved by clustering tests at the beginning and end of the 2-year period**. Published recommendations suggest three visual field tests per year are required to identify rapid progression in a **newly diagnosed** glaucomatous patient over 2 years.

Computer-simulated "patients" were given a rapid VF (mean deviation [MD]) loss of -2 dB/year with added MD measurement variability. Linear regression of MD against time was used to estimate progression. One group of "patients" was measured every 6 months, another every 4 months, whereas the wait-and-see group were measured either 2 or 3 times at both baseline and at the end of a 2-year period. Stable "patients" (0 dB/year) were generated to examine the effect of the follow-up patterns on false-positive (FP) progression identification.

By 2 years, 58% and 82% of rapidly progressing patients were correctly detected using evenly spaced 6- and 4-month VFs, respectively. This **power of detection significantly improved to 62% and 95% with the wait-and-see approach** ($P < 0.001$). When compared with evenly spaced VFs, **the rate of MD loss was better estimated by the wait-and-see approach, but average detection time was slightly slower**.

Evenly spaced testing incurred a significantly higher FP rate: up to 5.9% compared with only 0.4% in wait-and-see ($P < 0.001$).

Authors' conclusions: Compared with an evenly spaced follow-up, wait-and-see identifies more "patients" with rapid VF progression with fewer FPs, making it particularly applicable to clinical trials.

References

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Simulation model (Australia)

An economic simulation model of alternative options for the organization and delivery of clinical services in the ophthalmology department of a public hospital in Australia.

- The data were sourced from routinely collected waiting and appointment lists, patient record data, and the published literature.
- Patient-level costs and quality-adjusted life years were estimated for a range of alternative scenarios, including combinations of alternate follow-up times, booking cycles, and treatment pathways.
- The model shows that a) extending booking cycle length from 4 to 6 months, b) extending follow-up visit times by 2 to 3 months, and c) using laser in preference to medication are more cost-effective than current practice at the study clinic.

References

Crane GJ, Kymes SM, Hiller JE . Using discrete-event simulation to evaluate alternative service delivery and organizational scenarios for hospital-based glaucoma services. *Med Decis Making* 2013;33:986-97; PMID: 23515216

RCT on shared care (Holland)

The study was an economic evaluation conducted alongside a large randomised controlled trial. Four analytic perspectives were analyzed: the hospital, the patient, health care, and society in Holland. The time horizon was 30 months.

- 866 patients were randomised to usual care (glaucoma specialist) or a glaucoma follow-up unit (care from optometrists and ophthalmic technicians).
- For quality of care, the authors found no outcomes with statistically significant differences between the interventions. For all perspectives, the costs were reduced with the glaucoma follow-up unit.

From a societal perspective the incremental cost-effectiveness ratio with the glaucoma follow-up unit, compared with usual care, was a saving of EUR 27 per 0.1 increase in overall patient satisfaction, per year.



- The cost-effectiveness plane indicated that in 70% of simulations the glaucoma follow-up unit was more effective and less costly than usual care.

References

Holtzer-Goor KM, van Sprundel E, Lemij HG, Plochg T, Klazinga NS, Koopmanschap MA. Cost-effectiveness of monitoring glaucoma patients in shared care: an economic evaluation alongside a randomized controlled trial. *BMC Health Serv Res* 2010;10:312; PMID: 21083880

[E90]

Level of evidence = B

Glaucoma is usually a slowly progressive disease in which, however, the rate of change of the nerve fiber layer, optic disc and visual field abnormalities may vary greatly from patient to patient and it may take several years to detect progression of abnormalities.

References

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Pohjanpelto P. Long-term prognosis of visual field in glaucoma simplex and glaucoma capsulare. *Acta Ophthalmol* 1985;63:418-23; PMID: 4050362



[E91]

Level of evidence = D

It has been estimated that in patients under treatment the time from the appearance of the first visual field changes to blindness may vary from 30 to 40 years.

References

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[E92]

Level of evidence = B

The abnormalities progress in a considerable number of treated patients with glaucoma.

References

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[E93]

Level of evidence = B

Age, disc hemorrhages (for normal tension glaucoma), baseline visual field loss, baseline intraocular pressure, and exfoliation syndrome seem to be associated with glaucomatous visual field progression.

Evidence-Based Review

To examine which prognostic factors are associated with glaucomatous visual field progression, by consulting relevant databases, 2733 articles were published up to September 2010, of which 85 articles investigating prognostic factors for visual field progression in patients with open-angle glaucoma (OAG) were eligible. Results for each factor in tables, noting the direction of the association between the prognostic factor and progression, and the accompanying P value. Four authors, working blind to the factors, independently judged the extent to which a prognostic factor was associated with glaucomatous visual field progression. If there were different associations for normal-tension glaucoma (NTG) studies, they were judged separately. Consensus was reached during group meetings.

A total of 103 different prognostic factors were investigated in 85 articles. The following factors were clearly associated with glaucomatous visual field progression: age, disc hemorrhages (for NTG), baseline visual field loss, baseline intraocular pressure (IOP), and exfoliation syndrome. An association was unlikely for family history of glaucoma, atherosclerosis, systemic hypertension, visual acuity, sex (for NTG), systolic blood pressure, myopic refractive error (for NTG), and Raynaud's phenomenon.

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[E94]

Level of evidence = B

Glaucoma seems to worsen the patient's quality of life: the degree of deterioration correlates with the severity of the visual field damage.

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[E95]

Level of evidence = B

Glaucoma does not seem to influence mortality.

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