

AHRQ Comparative Effectiveness Review Surveillance Program

CER #60:

Treatment for Glaucoma: Comparative Effectiveness

Original release date:

April, 2012

Surveillance Report:

May, 2013

Key Findings:

- A large number of relatively small new studies were identified that compared the effectiveness and safety of existing treatments but none sufficiently challenged the conclusions of the original report to suggest the need for an update.
- A number of US Food and Drug Administration safety label changes have been issued for the medications included in the report but most reflect warnings released prior to the release of the original report.
- A new area of research that may warrant a review is that of measuring progression in visual field loss and its effect on quality of life.

Summary Decision

This CER's priority for updating is **Low**

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Treatment for Glaucoma: Comparative Effectiveness

1. Introduction

Comparative Effectiveness Review (CER) #60, Screening for Glaucoma: Comparative Effectiveness, was released in April 2012.¹ It was therefore due for a surveillance assessment in October, 2012. At that time, we contacted experts involved in the original CER and subject experts to get their opinions as to whether the conclusions had changed and need to be updated. We also conducted an update electronic literature search. Every month since the CER's original release, we received any FDA updates on the included treatments and tests.

2. Methods

2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search of Medline for the years August 2011-December 26, 2012. This search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and six specialty journals (Journal of Glaucoma, American Journal of Ophthalmology, Ophthalmology, Archives of Ophthalmology, and the British Journal of Ophthalmology). The specialty journals were the most highly represented among the references for the original report. Appendix A includes the search methodology for this topic.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER. Notably, only randomized controlled trials were included for Key Questions 1, 3, and 4, and only studies that included patients aged 40 and over were included.

2.3 Expert Opinion

We shared the conclusions of the original report with 8 experts in the field (including the original project leader, all original technical expert panel (TEP) members, peer reviewers, and local content experts for their assessment of the need to update the report and their recommendations of any relevant new studies; 2 subject matter experts responded, including the project lead. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.^{2,3}

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe

	use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of “opposing findings”
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?

- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 90 titles. After title and abstract review, we further reviewed the full text of 12 journal articles. The remaining titles were rejected because they clearly did not meet inclusion criteria for any of the review questions. In addition to the electronic database searches, we followed up suggestions from the topic experts for studies not already included in the original report, resulting in 36 additional articles (16 were from an update search conducted by the original research team). We also reference-mined articles that met inclusion criteria as well as systematic reviews identified by the literature searches to identify additional articles that may have been published since the publication of the report.

Thus, 48 articles went on to full text review. Of these, 18 articles were rejected because they did not meet the inclusion criteria of the original report or did not report on glaucoma treatment outcomes. The remaining 30 articles were abstracted into an evidence table (Appendix B) for this assessment.⁴⁻³³

3.2 Expert Opinion

Two experts, including the original project lead, reviewed the conclusions in the original report and provided additional studies. One of the experts also provided references for a topic not considered in the original report: the impact of glaucoma-related changes in visual field and vision loss on quality of life, apart from treatment. These studies were not abstracted and were not included in the decision regarding updating priority.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Medical Treatment of Open-Angle Glaucoma				
KQ 1: Do medical, laser, and other surgical treatments for open-angle glaucoma reduce visual impairment?				
KQ1a: Comparative Effectiveness of Medical Treatments for Reducing Visual Impairment				
<ul style="list-style-type: none"> No studies of medical therapy were identified that directly addressed outcomes related to visual impairment. The available studies addressing the secondary outcomes of change in visual acuity and change in visual field loss are of too short a duration to answer this question, given that glaucoma is typically a slowly progressive disease that may take many years to cause clinically or statistically significant changes. 	No new studies were identified.	See responses to KQ 6.	2 reviewers stated the conclusion is still supported by the evidence.	Original conclusion is still valid and this portion of the original report does not need updating.
Surgical Treatment of Open-Angle Glaucoma				
KQ1b: Comparative Effectiveness of Laser and Other Surgical Treatments for Reducing Visual Impairment				
<ul style="list-style-type: none"> No studies reported on the outcome of visual impairment after laser or other surgical treatments. Visual acuity was not assessed as a primary outcome in any identified study comparing laser with other surgical treatments for glaucoma. Visual acuity was only irregularly reported, if at all. Given the limitations above, no treatment appeared to have a greater effect on visual acuity than any other treatment. 		See responses to KQ 6.	2 reviewers stated the conclusion is still supported by the evidence.	Original conclusion is still valid and this portion of the original report does not need updating.
Medical Versus Surgical Treatment of Open-Angle Glaucoma				
KQ1c: Comparative Effectiveness of Medical Versus Surgical Treatment for Reducing Visual Impairment				
<ul style="list-style-type: none"> Although trabeculectomy may 	No new studies were	See responses to KQ 6.	2 reviewers stated the	Original conclusion is

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
after adjusting for demographic and comorbid factors, the body of evidence is limited and inconclusive (systematic review).			evidence.	report does not need updating.
KQ 2: Does treatment of open-angle glaucoma improve patient-reported outcomes?				
<ul style="list-style-type: none"> • There is no direct evidence regarding the impact of glaucoma treatment on patient-reported outcomes. • Medical and surgical treatments reduce the patient's fear of blindness. • Several studies suggest that the type of glaucoma treatment does not have an influence on quality of life. • There is some evidence that, among medical treatments, patients prefer those that are less frequently applied. • Since there are unlikely to be any future trials with a placebo arm, it will not be possible to determine definitively if treatments improve patient-reported outcomes relative to no treatment. It will still be possible to compare the effectiveness of different treatments on patient-reported outcomes, however. 	2 new studies were identified that assessed the association between specific treatment modalities and patient-reported quality of life. One study found that among patients using 1 of 3 prostaglandins, bimatoprost users had the lowest quality of life and were the most likely to be using a β -blocker in addition to the prostaglandin, compared with users of latanoprost and travoprost. ²⁸ The 2 nd study found that early OAG patients who received medical treatment had higher VFQ scores than those who underwent surgical treatment or combined surgical and medical treatment. ²⁹	See responses to KQ 6	1 reviewer stated the conclusion is still supported by the evidence. 1 reviewer cited the 2 studies described in column 2.	Original conclusion is still valid and this portion of the original report does not need updating.
KQ 3: Do medical, laser, and other surgical treatments for open-angle glaucoma lower intraocular pressure?				
KQ3a: Comparative Effectiveness of Medical Treatments for Lowering Intraocular Pressure				
<ul style="list-style-type: none"> • Prostaglandins lower IOP more than dorzolamide (carbonic anhydrase inhibitor, 2.64 mmHg, three trials), brimonidine (alpha-adrenergic agonist, 1.64 mmHg, four trials), and timolol (beta- 	1 study found that 2 different preparations of the same β blocker, timolol, had the same efficacy for lowering IOP. ¹⁷ 2 studies found that	See responses to KQ 6.	1 reviewer stated the conclusion is still supported by the evidence. 1 reviewer cited several new studies, described in column 2, that	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<p>adrenergic blocker, 5 percent lower at 6 months, four trials) (systematic review).</p> <ul style="list-style-type: none"> • The prostaglandins appear similar in the extent to which they lower IOP, but some studies have reported a greater drop in IOP with bimatoprost (prostaglandin) (systematic review). • The combination dorzolamide/timolol appears to lower IOP the same amount as prostaglandins (systematic review). 	<p>latanoprost and its generic form were identical in their ability to decrease IOP.^{14, 16}</p> <p>1 study found that preservative-free latanoprost was non-inferior to preservative-containing latanoprost in efficacy.¹¹</p> <p>1 study found that preservative-free tafluprost was non-inferior to preservative-free timolol in efficacy.⁵</p> <p>1 study found that addition of the carbonic anhydrase inhibitor brinzolamide to travoprost/timolol fixed combination (TTFC) resulted in greater IOP lowering than TTFC alone.⁶</p> <p>1 study found that brimonidine-timolol FC achieved the same mean IOP as latanoprost at 12 weeks after initiation of treatment.¹⁵</p> <p>A systematic review of 18 trials found that FC treatments were more efficacious than monotherapies for IOP reduction but less efficacious than unfixed combinations (UCs).³⁰</p>		<p>compared various treatment classes.</p>	

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<p><i>Circadian Intraocular Pressure</i></p> <ul style="list-style-type: none"> • Our conclusions regarding the effect of topical therapies in lowering IOP over the 24-hour time period were limited due to the fact that one study provided almost all of the data. • All topical medications reviewed appear to lower IOP throughout the 24-hour cycle. • Prostaglandins appear to lower IOP more over the 24-hour cycle than beta-blockers, topical carbonic anhydrase inhibitors, and alpha agonists, but the evidence for this is weak. • While the IOP-lowering effects of different prostaglandins appear to vary appreciably over the 24-hour time period, the results were inconsistent and the reported difference in the amount of IOP lowering was on the order of 1 mmHg. • Results from systematic reviews comparing one prostaglandin with another were inconsistent. 	No new studies were identified.	See responses to KQ 6.	2 reviewers stated the conclusion is still supported by the evidence.	Original conclusion is still valid and this portion of the original report does not need updating.
KQ3b: Comparative Effectiveness of Laser and Other Surgical Treatments for Lowering Intraocular Pressure				
<ul style="list-style-type: none"> • Trabeculectomy lowers IOP more than nonpenetrating surgeries (systematic review). • The use of mitomycin-C intraoperatively with trabeculectomy results in lower IOP than when it is not used (systematic review). • Other alterations in surgical 	<p>1 study found that trabeculectomy with amniotic membrane transplantation (AMT) was comparable to trabeculectomy without AMT with respect to IOP reduction.²⁰</p> <p>2 studies found that</p>	No information was found.	2 reviewers stated the conclusion is still supported by the evidence; however, 1 reviewer cited several new studies, described in column 2.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<p>technique, location of surgery on the eye, and adjuvants other than mitomycin-C have not been shown to result in an added pressure decrease (primary studies).</p> <ul style="list-style-type: none"> The IOP-lowering effect of combined cataract surgery and trabeculectomy is not affected by the location of the conjunctival incision or the presence or absence of a peripheral iridectomy but may be more in two-site (cataract and trabeculectomy performed using different incisions) than one-site (cataract and trabeculectomy performed using the same incision) surgery (systematic review). Laser trabeculoplasty effectively lowers IOP in glaucoma patients, and effectiveness does not vary with the type of laser used (primary studies). The data available on the role of aqueous drainage devices in open-angle glaucoma are inadequate to draw conclusions (primary studies, systematic review). 	<p>trabeculectomy with MMC was more effective than the same procedure with bevacizumab (not approved for this use in US)¹⁰ but equally effective with trabeculectomy with a biodegradable collagen matrix.²¹</p> <p>2 studies found that IOP reduction was comparable for selective laser trabeculoplasty and argon laser trabeculoplasty.^{23, 31}</p> <p>1 study found that trabeculectomy and the ExPRESS glaucoma filtration device reduced IOP and the need for medications to a similar degree at 30 months follow-up although overall success was greater for ExPRESS.²²</p>			
KQ3c: Comparative Effectiveness of Medical Versus Surgical Treatment for Lowering Intraocular Pressure				
<ul style="list-style-type: none"> Incisional surgery lowers IOP more than lasers or medications (systematic review). Initial treatment with lasers tends to reduce the need for medications to achieve a given IOP (systematic review). 	<p>1 study found that trabeculectomy lowered IOP significantly more than did medical treatments.³²</p> <p>1 RCT that compared selective laser trabeculoplasty (SLT) with a sequential medical therapy found no</p>	See responses to KQ 6	2 reviewers stated the conclusion is still supported by the evidence.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	significant differences in IOP reduction between the two groups at 9-12 months follow-up. More patients in the medication group required additional medications to maintain IOP than those who required additional SLT. ⁸			
KQ 4: Do medical, laser, and other surgical treatments for open-angle glaucoma prevent or slow the progression of optic nerve damage and visual field loss?				
KQ4a: Comparative Effectiveness of Medical Treatments for Preventing or Slowing the Progression of Optic Nerve Damage and Visual Field Loss				
<ul style="list-style-type: none"> • A systematic review of medical treatment for glaucoma determined treatment to be protective against progressive visual field loss. This review included the results of both the Early Manifest Glaucoma Trial and the Ocular Hypertension Treatment Study. • Other included primary studies were of insufficient size or duration to detect differences in the rates of optic nerve damage or visual field loss. Given the slowly progressive nature of glaucoma, the large trials of glaucoma therapy have demonstrated the need to follow hundreds of participants for 5 or more years to detect change. • A single study addressed the comparative effectiveness of glaucoma medications with respect to their ability to prevent optic nerve damage or visual field loss and found brimonidine superior to timolol. 	1 retrospective record review found that IOP reduction was related to a decreased risk for progression of glaucoma. ³³	See responses to KQ 6.	1 reviewer stated the conclusion is still supported by the evidence. The other reviewer cited 2 studies, 1 of which was excluded for being a cohort study; the other is summarized in column 2.	Original conclusion is still valid and this portion of the original report does not need updating.
KQ4b: Comparative Effectiveness of Laser and Other Surgical Treatments for Preventing or Slowing the Progression of				

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Optic Nerve Damage and Visual Field Loss				
<ul style="list-style-type: none"> No studies comparing laser and surgical treatments were found that reported data on whether these procedures slow the progression of optic nerve damage and visual field loss. 	No new studies were identified.	No information was found.	2 reviewers stated the conclusion is still supported by the evidence.	Original conclusion is still valid and this portion of the original report does not need updating.
KQ4c: Comparative Effectiveness of Medical Versus Surgical Treatment for Preventing or Slowing the Progression of Optic Nerve Damage and Visual Field Loss				
<ul style="list-style-type: none"> Trabeculectomy may prevent more visual field loss than medicines when used as initial therapy in advanced glaucoma (systematic review). The Collaborative Initial Glaucoma Treatment Study (CIGTS) included current surgical techniques and medications, and found no difference in change in visual field (but did not report on change in the optic nerve). Treatment of ocular hypertension with medicines preserves visual fields better than no treatment (systematic review). 	No new studies were identified.	No information was found	2 reviewers stated the conclusion is still supported by the evidence.	Original conclusion is still valid and this portion of the original report does not need updating.
KQ 5: Does lowering intraocular pressure or preventing or slowing the progression of optic nerve damage and visual field loss reduce visual impairment and change vision-related quality of life?				
<ul style="list-style-type: none"> We found no good-quality studies addressing the relationship between the intermediate outcomes of IOP reduction, prevention of optic nerve damage, or prevention of visual field loss and the outcomes of visual impairment and vision-related quality of life. 	No new studies were identified.	No information was found.	2 reviewers stated the conclusion is still supported by the evidence.	Original conclusion is still valid and this portion of the original report does not need updating.
KQ 6: What are the harms associated with medical, laser, and other surgical treatments for open-angle glaucoma?				
KQ6a: Harms Associated With Medical Treatments for Open-Angle Glaucoma				
<ul style="list-style-type: none"> The prostaglandin agents produce more ocular redness than does 	Prostaglandin agents vs. beta-blocker:	FDA Medwatch Alert Drug Safety Labeling Change (4/12) for Latisse	2 reviewers stated the conclusion is still	Original conclusion is still valid and this

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<p>timolol (beta-adrenergic blocker) (systematic review).</p> <ul style="list-style-type: none"> • Within the prostaglandins, latanoprost is least likely to cause redness (systematic review). • Subjects on timolol (beta-blocker) were less likely to drop out of studies due to side effects than those on brimonidine (alpha-adrenergic agonist), latanoprost (prostaglandin analog), travoprost (prostaglandin analog), or betaxolol (beta-blocker) (systematic review). 	<p>Tafluprost was associated with significantly higher hyperemia than was timolol in a RCT.⁵</p> <p>Beta blocker prep comparisons One crossover study showed no difference in harms between timolol drops and hydrogel.¹⁷</p> <p>Prostaglandin generic vs. name brand comparison: One double blind RCT showed no difference between latanoprost and Xalatan® in safety. The most commonly reported adverse events (AEs) were ocular hyperemia and eyelash growth.¹⁴</p> <p>Among 12,880 latanoprost treated subjects, no reports of ocular melanoma and 3 reports of cutaneous melanoma were identified. Of 19,940 cases in the global safety database, 22 reports of ocular/cutaneous neoplasms were obtained, of which 11 were ocular and 6 were cutaneous melanomas. Possible association with latanoprost could not be ruled out in 4 cases, but no evidence establishes a link between latanoprost use and melanoma.¹²</p>	<p>(bimatoprost) showed burning, periorbital erythema, eye swelling , eyelid irritation, eyelid edema, eyelid pruritis, iris hyperpigmentation, lacrimation, loss of lashes, deepening of the eyelid sulcus, rash, skin discoloration, and blurred vision. www.fda.gov/Safety/MedWatch/SafetyInformation/ucm275785.htm</p> <p>FDA Medwatch Alert for Lumigan (4/12) showed dizziness, hypertension, eyelid edema, nausea, and periorbital and lid changes associated with deepening of the sulcus. www.fda.gov/Safety/MedWatch/SafetyInformation/ucm299313.htm</p> <p>FDA Medwatch Alert for Xalatan (Latanoprost) (4/12) described periorbital and lid changes resulting in deepening of the eyelid sulcus; dizziness, and headache. www.fda.gov/Safety/MedWatch/SafetyInformation/ucm226003.htm</p> <p>FDA Medwatch Alert for Zioptan (Tafluprost) (2/13) reported uveitis and iritis in postmarketing use. www.fda.gov/Safety/MedWatch/SafetyInformation/ucm342965.htm Uveitis and iritis reported postmarketing</p> <p>FDA Medwatch Alert for Travatan (Travoprost) (9/11) included additional safety information based on reports for other prostaglandin analogs. www.fda.gov/Safety/MedWatch/SafetyInformation/ucm275</p>	<p>supported by the evidence.</p>	<p>portion of the original report does not need updating.</p>

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	<p>A prospective open-label study of bimatoprost users showed that tolerance was high, AEs were reported by 6%, and eye irritation and hyperemia were the most commonly reported AEs.¹⁹</p> <p>Prostaglandin intraclass or prep comparison: Preservative-free latanoprost eye drops showed less local intolerance than latanoprost preserved with BAK.¹¹</p> <p>In a prospective open-label study, transition from latanoprost to BAK-free travoprost was associated with a decrease in superficial punctate keratopathy and hyperemia.⁴</p> <p>x-class comparisons A retrospective case-control study showed that bimatoprost but not the other prostaglandin analogs was associated with deepening of the upper eyelid sulcus among Asian patients.⁷</p> <p>Alpha adrenergic agonist/beta agonist FC compared with prostaglandin and alpha</p>	<p>159.htm</p> <p>FDA Medwatch Alert for Cosopt (dorzolamine hydrochloride/timolol maleate) (6/10) reported Stevens-Johnson Syndrome and toxic epidermal necrolysis in low numbers during clinical trials or in clinical practice. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm218879.htm</p> <p>FDA Medwatch Alert for Cosopt reported the following text added: "...increased potential for developing corneal edema in patients with low endothelial cell counts. Precaution should be used when prescribing Cosopt to this group of patients."</p> <p>FDA Medwatch Alert for Trusopt (6/10) reported Stevens-Johnson Syndrome and toxic epidermal necrolysis in low numbers during clinical trials or in clinical practice. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm218879.htm</p> <p>FDA Medwatch Alert for Brimonidine/timolol (Combigan) (10/12) reported ocular hypersensitivity, increased IOP, and in children, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in postmarketing. www.fda.gov/Safety/MedWatch/SafetyInformation/ucm327514.htm</p>		

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	<p>agonist/prostaglandin/beta agonist compared with prostaglandin/alpha agonist FC alone showed no difference in AEs^{6, 15}</p> <p>A prospective single-blind crossover comparison of 2 FC preps of alpha agonist and beta agonist showed that dorzolamide/timolol was associated with more bitter taste and stinging than was brimonidine/timolol, but the latter was associated with more conjunctival hyperemia.¹⁸</p> <p>FCs led to a lower risk for hyperemia than UCs or their respective PG analog monotherapies (systematic review)³⁰</p>			
KQ6b: Harms Associated With Laser and Other Surgical Treatments for Open-Angle Glaucoma				
<ul style="list-style-type: none"> • Trabeculectomy results in more complications than nonpenetrating surgeries (systematic review). • The profile of harms does not differ between one- and two-site combined cataract and glaucoma surgery (systematic review). 	<p>AMT had no major complications compared with trabeculectomy with no anti-metabolites in a prospective RCT.²⁰</p> <p>Trabeculectomy with OLO compared with MMC showed no adverse reactions and similar complication rates in a RCT.²¹</p> <p>Ex-PRESS showed fewer postop complications and</p>		<p>1reviewer stated the conclusion is still supported by the evidence. The other reviewer cited 1 new study showing that 25% of patients followed for at least 5 years post-op had complications or needed further treatment.¹³</p>	<p>Original conclusion is still valid and this portion of the original report does not need updating.</p>

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	<p>need for interventions than trabeculectomy in a prospective randomized study.²²</p> <p>SLT and ALT showed similar incidence of complications in a prospective RCT²³ but in a follow-up of a prospective RCT by another group, ALT was associated with a higher rate of AEs, namely poorer IOP reduction (really lower efficacy).³¹</p> <p>In a retrospective case series of 262 cases of Ab interno trabeculotomy surgery with trabectome, 12 showed delayed onset hyphemia that seemed to be associated with exertion or ocular compression.²⁷</p> <p>A prospective non-randomized cohort study comparing ab interno trabeculectomy alone with the procedure followed by IOL implant in POAG and exfoliative glaucoma (XFG) patients, late complications were more prevalent in XFG patients who underwent trabeculectomy along, whereas for trabeculectomy plus IOL, hypotony was seen in 1</p>			

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	<p>XFG patient but not in the POAG group.²⁵</p> <p>A retrospective chart review of 132 eyes comparing trabeculectomy with MMC vs. 5FU showed 1 case each of blebitis and endophthalmitis in in both groups and 4 cases of persistent hypotony in 4 of the MMC treated eyes.²⁴</p> <p>A comparative case series of trabeculectomy and IOL implantation vs. IOL alone showed fewer postop IOP spikes in the combined group but greater requirement for postop corrective measures in this group as well.²⁶</p> <p>A prospective nonrandomized trial of SLT showed that nearly 25% of patients experienced mild postop pain and nearly 43% of patients experienced inflammation. Rates of postop AEs varied with the type of glaucoma. Patients with pigmentary glaucoma experienced significantly more AEs (including IOP spiking) and had greater need for additional SLT procedures.⁹</p>			

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	A longitudinal cohort study based on a RCT (the CIGTS) reported that 3 of 247 patients who were followed for at least 5 years after trabeculectomy had endophthalmitis and 4 had hypotony; a large number of others required further surgery or surgical revision. ¹³			
KQ6c: Harms Reported in Studies of Medical Versus Surgical Treatments for Open-Angle Glaucoma				
<ul style="list-style-type: none"> • Trabeculectomy is associated with cataract worsening and an increased need for cataract surgery over time when compared to medical treatments for glaucoma (systematic review). • Intraocular surgery rarely results in severe vision loss due to infection and/or bleeding. These risks are not associated with medical or laser treatments. • Laser trabeculoplasty can produce peripheral anterior synechiae, whereas medical treatment does not (systematic review). 	No new studies were identified	No information was found.	2 reviewers stated the conclusion is still supported by the evidence.	Original conclusion is still valid and this portion of the original report does not need updating.

Legend: 5FU 5-fluorouracil; ALT argon laser trabeculoplasty; BAK benzalkonium; bid: twice daily; BP blood pressure; BUN blood urea nitrogen; FC fixed combination; hx history; IOL intraocular lens (implant); IOP intraocular pressure; MMC mitomycin; MT monotherapy; NEI-VFQ National Eye Institute Visual Function Questionnaire; OHT ocular hypertension; PEX pseudoexfoliative glaucoma; PG pigmentary glaucoma; POAG primary open-angle glaucoma; qd: once daily; QoL quality of life; SLT Selective laser trabeculoplasty; tx treatment; SCEPC: Southern California Evidence-based Practice Center; UC unfixed combination

References

1. Boland MV, Ervin AM, Friedman D, et al. Treatment for Glaucoma: Comparative Effectiveness. Comparative Effectiveness Review No. 60. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHS 290-2007-10061-I.) AHRQ Publication No. 12-EHC038-EF. Rockville, MD: Agency for Healthcare Research and Quality. www.effectivehealthcare.ahrq.gov/reports/final.cfm. April 2012 Apr PMID 22649800.
2. Shekelle PG, Newberry SJ, Maglione M, et al. Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009) (Prepared by the Southern California Evidence-based Practice Center). Rockville, MD: Agency for Healthcare Research and Quality; October 2009.
3. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med*. 2007 Aug 21;147(4):224-33. PMID 17638714.
4. Aihara M, Otani S, Kozaki J, et al. Long-term effect of BAK-free travoprost on ocular surface and intraocular pressure in glaucoma patients after transition from latanoprost. *J Glaucoma*. 2012 Jan;21(1):60-4. PMID 21278589.
5. Chabi A, Varma R, Tsai JC, et al. 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 Jun;153(6):1187-96. PMID 22310086.
6. Goldberg I, Crowston JG, Jasek MC, et al. Intraocular pressure-lowering efficacy of brinzolamide when added to travoprost/timolol fixed combination as adjunctive therapy. *J Glaucoma*. 2012 Jan;21(1):55-9. PMID 21048504.
7. Inoue K, Shiokawa M, Wakakura M, et al. Deepening of the Upper Eyelid Sulcus Caused by 5 Types of Prostaglandin Analogs. *J Glaucoma*. 2012 Aug 29 PMID 22936280.
8. Katz LJ, Steinmann WC, Kabir A, et al. Selective laser trabeculoplasty versus medical therapy as initial treatment of glaucoma: a prospective, randomized trial. *J Glaucoma*. 2012 Sep;21(7):460-8. PMID 21543992.
9. Koucheiki B, Hashemi H. Selective laser trabeculoplasty in the treatment of open-angle glaucoma. *J Glaucoma*. 2012 Jan;21(1):65-70. PMID 21278588.
10. Nilforushan N, Yadgari M, Kish SK, et al. Subconjunctival bevacizumab versus mitomycin C adjunctive to trabeculectomy. *Am J Ophthalmol*. 2012 Feb;153(2):352-7 e1. PMID 21982106.
11. Rouland JF, Traverso CE, Stalmans I, et al. Efficacy and safety of preservative-free latanoprost eyedrops, compared with BAK-preserved latanoprost in patients with ocular hypertension or glaucoma. *Br J Ophthalmol*. 2012 Nov 30 PMID 23203707.

12. Tressler CS, Wiseman RL, Dombi TM, et al. Lack of evidence for a link between latanoprost use and malignant melanoma: an analysis of safety databases and a review of the literature. *Br J Ophthalmol*. 2011 Nov;95(11):1490-5. PMID 21515566.
13. Zahid S, Musch DC, Niziol LM, et al. Risk of Endophthalmitis and Other Long-Term Complications of Trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS). *Am J Ophthalmol*. 2012 Dec 12PMID 23246272.
14. Digiuni M, Manni G, Vetrugno M, et al. An Evaluation of Therapeutic Noninferiority of 0.005% Latanoprost Ophthalmic Solution and Xalatan in Patients With Glaucoma or Ocular Hypertension. *J Glaucoma*. 2012 May 16PMID 22595934.
15. Katz LJ, Rauchman SH, Cottingham AJ, Jr., et al. Fixed-combination brimonidine-timolol versus latanoprost in glaucoma and ocular hypertension: a 12-week, randomized, comparison study. *Curr Med Res Opin*. 2012 May;28(5):781-8. PMID 22458918.
16. Allaire C, Dietrich A, Allmeier H, et al. Latanoprost 0.005% test formulation is as effective as Xalatan(R) in patients with ocular hypertension and primary open-angle glaucoma. *Eur J Ophthalmol*. 2012 Jan-Feb;22(1):19-27. PMID 22167539.
17. Quaranta L, Katsanos A, Floriani I, et al. Circadian intraocular pressure and blood pressure reduction with timolol 0.5% solution and timogel 0.1% in patients with primary open-angle glaucoma. *J Clin Pharmacol*. 2012 Oct;52(10):1552-7. PMID 22110164.
18. Konstas AG, Quaranta L, Yan DB, et al. Twenty-four hour efficacy with the dorzolamide/timolol-fixed combination compared with the brimonidine/timolol-fixed combination in primary open-angle glaucoma. *Eye (Lond)*. 2012 Jan;26(1):80-7. PMID 21960068.
19. Pfennigsdorf S, Ramez O, von Kistowski G, et al. Multicenter, prospective, open-label, observational study of bimatoprost 0.01% in patients with primary open-angle glaucoma or ocular hypertension. *Clin Ophthalmol*. 2012;6:739-46. PMID 22654501.
20. Stavarakas P, Georgopoulos G, Milia M, et al. The use of amniotic membrane in trabeculectomy for the treatment of primary open-angle glaucoma: a prospective study. *Clin Ophthalmol*. 2012;6:205-12. PMID 22347791.
21. Cillino S, Di Pace F, Cillino G, et al. Biodegradable collagen matrix implant vs mitomycin-C as an adjuvant in trabeculectomy: a 24-month, randomized clinical trial. *Eye (Lond)*. 2011 Dec;25(12):1598-606. PMID 21921953.
22. Dahan E, Ben Simon GJ, Lafuma A. Comparison of trabeculectomy and Ex-PRESS implantation in fellow eyes of the same patient: a prospective, randomised study. *Eye (Lond)*. 2012 May;26(5):703-10. PMID 22344189.

23. Bovell AM, Damji KF, Hodge WG, et al. Long term effects on the lowering of intraocular pressure: selective laser or argon laser trabeculoplasty? *Can J Ophthalmol*. 2011 Oct;46(5):408-13. PMID 21995983.
24. Anand N, Dawda VK. A comparative study of mitomycin C and 5-Fluorouracil trabeculectomy in west Africa. *Middle East Afr J Ophthalmol*. 2012 Jan;19(1):147-52. PMID 22346131.
25. Ting JL, Damji KF, Stiles MC, et al. Ab interno trabeculectomy: outcomes in exfoliation versus primary open-angle glaucoma. *J Cataract Refract Surg*. 2012 Feb;38(2):315-23. PMID 22322166.
26. Shingleton BJ, Wooler KB, Bourne CI, et al. Combined cataract and trabeculectomy surgery in eyes with pseudoexfoliation glaucoma. *J Cataract Refract Surg*. 2011 Nov;37(11):1961-70. PMID 21907537.
27. Ahuja Y, Malihi M, Sit AJ. Delayed-onset symptomatic hyphema after ab interno trabeculotomy surgery. *Am J Ophthalmol*. 2012 Sep;154(3):476-80 e2. PMID 22789561.
28. Guedes RA, Guedes VM, Freitas SM, et al. Quality of life of glaucoma patients under medical therapy with different prostaglandins. *Clin Ophthalmol*. 2012;6:1749-53. PMID 23152652.
29. Paletta Guedes RA, Paletta Guedes VM, Freitas SM, et al. Quality of Life of Medically Versus Surgically Treated Glaucoma Patients. *J Glaucoma*. 2012 Mar 7PMID 22407390.
30. Quaranta L, Biagioli E, Riva I, et al. Prostaglandin Analogs and Timolol-Fixed Versus Unfixed Combinations or Monotherapy for Open-Angle Glaucoma: A Systematic Review and Meta-Analysis. *J Ocul Pharmacol Ther*. 2012 Dec 11PMID 23231442.
31. Rosenfeld E, Shemesh G, Kurtz S. The efficacy of selective laser trabeculoplasty versus argon laser trabeculoplasty in pseudophakic glaucoma patients. *Clin Ophthalmol*. 2012;6:1935-40. PMID 23225995.
32. Congdon NG, Krishnadas R, Friedman DS, et al. A study of initial therapy for glaucoma in southern India: India Glaucoma Outcomes and Treatment (INGOT) Study. *Ophthalmic Epidemiol*. 2012 Jun;19(3):149-58. PMID 22568428.
33. Kim M, Kim DM, Park KH, et al. Intraocular pressure reduction with topical medications and progression of normal-tension glaucoma: a 12-year mean follow-up study. *Acta Ophthalmol*. 2013 Feb 14PMID 23406253.

Appendices

Appendix A: Search Methodology

Appendix B: Evidence Tables

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

Searched 12/26/2012

Update search covering 8/01/2011 – present

("Ocular Hypertension"[mh] OR "ocular hypertension"[tiab] OR "Intraocular Pressure"[mh] OR "intraocular pressure"[tiab] OR "glaucoma, open-angle" [mh] OR "Open angle glaucoma" [tiab] OR "low tension glaucoma" [tiab] OR "normal tension glaucoma" [tiab] OR "pseudoexfoliative glaucoma" [tiab] OR "pseudoexfoliative syndrome" [tiab]) AND ("Trabeculectomy"[mh] OR trabeculectomy[tiab] OR "Laser Coagulation"[mh] OR "laser coagulation"[tiab] OR photocoagulation[tiab] OR "sclerostomy"[mh] OR sclerostomy[tiab] OR canaloplasty [tiab] OR viscocanalostomy[tiab] OR "glaucoma drainage implants"[mh] OR "glaucoma drainage implants"[tiab] OR shunt[tiab] OR "laser therapy"[tiab] OR "laser surgery"[tiab] OR apraclonidine[tiab] OR "brimonidine"[Substance Name] OR brimonidine[tiab] OR "Timolol"[mh] OR Timolol[tiab] OR "Betaxolol"[Mesh] OR Betaxolol [tiab] OR "Levobunolol"[mh] OR "Metipranolol"[mh] OR "Carbonic Anhydrase Inhibitors"[mh] OR "Carbonic Anhydrase Inhibitors"[tiab] OR "dorzolamide"[Substance Name] OR dorzolamide[tiab] OR "Acetazolamide"[mh] OR Acetazolamide[tiab] OR "Cholinergic Agents"[mh] OR "Pilocarpine"[mh] OR Pilocarpine[tiab] OR "Carbachol"[mh] OR "Prostaglandins, Synthetic"[mh] OR Prostaglandins[tiab] OR travoprost[tiab] OR bimatoprost[tiab] OR latanoprost[tiab] OR "isopropyl unoprostone"[Substance Name] OR "Antihypertensive Agents"[mh] OR "Epinephrine"[mh] OR Epinephrine[tiab]) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]) AND Journal of Glaucoma[journal] OR American Journal of Ophthalmology[journal] OR ophthalmology[journal] OR archives of ophthalmology[journal] OR "the British Journal of Ophthalmology"[journal] AND ("Annals of internal medicine"[Journal] OR "bmj"[Journal] OR "jama"[Journal] OR "lancet"[Journal] OR "The New England journal of medicine"[Journal])

Results: 90

Appendix B. Evidence Table

Author, Year Study Design	Population (number, age, condition, relevant comorbidities, exclusion criteria)	Intervention/comparison Outcomes	Findings and conclusions
Patient reported Outcomes (KQ2)			
Guedes 2012a ²⁸ Cross-sectional	117 adult glaucoma patients under prostaglandin treatment for ≥3 months with no Hx of ocular surgery (92/117 with OAG)	Prostaglandin treatments (Bimatoprost 18.8%; latanoprost 35.9%; travoprost 45.3%) NEI-VFQ	Bimatoprost users had the lowest QoL scores and were the most likely to be using a β-blocker in addition to the prostaglandin.
Guedes 2012b ²⁹ Cross-sectional	225 adult glaucoma patients	1) only medical tx or 2) surgery or 3) both medical and surgical tx for glaucoma NEI-VFQ and potential influencing factors from medical records (stage and type of disease, visual acuity, comorbidity)	Medical tx was associated with a higher VFQ score than surgical tx or surgical tx combined with medical tx. Surgery significantly lowered VFQ scores among patients with early glaucoma. Type of surgery did not affect score. Rx type did not affect score, except that bimatoprost lowered score and latanoprost increased it. Education and comorbidities but not sex race or type of glaucoma affected score (education and comorbidities were associated with an increased and decreased score, respectively).
Comparative Effectiveness of medical treatments on IOP (and AEs)			
Quaranta 2012 ¹⁷ Single-blind crossover	28 treatment naïve POAG patients ≥45 yoa	Timolol 0.5% x2 months followed by timolol 0.1% hydrogel or the reverse IOP (sitting Goldmann or supine Perkins every 4 hours for 24 hours and BP) at baseline and after 2 months	Efficacy: Both preparations showed similar significant efficacy (decrease from 23.1 to 18.9) Safety: AEs: BP was unaffected. Effects on ocular perfusion pressure were minimal
Allaire 2012 ¹⁶ Single-blind parallel RCT	266 POAG or OHT patients, mean age 61.8	Latanoprost (generic) or Xalatan® qdx6 weeks Mean change in 8AM IOP from baseline to week 6 Secondary endpoints: mean change at week 2 and in noon and 4PM IOP, safety, tolerability	Efficacy: Mean change in IOP was the same for both drugs -7.29 vs. -7.52); Latanoprost was noninferior to Xalatan. Safety: Both demonstrated comparable safety and tolerability
Digiuni 2012 ¹⁴ Double-blind RCT	184 POAG or OHT patients Age ≥18 (mean age 65.3)	Latanoprost (generic) or Xalatan® qdx12 weeks Mean change in IOP from baseline to week 12	Efficacy: Both demonstrated comparably efficacy Safety: No significant differences were seen between the two preparations. The

Author, Year Study Design	Population (number, age, condition, relevant comorbidities, exclusion criteria)	Intervention/comparison Outcomes	Findings and conclusions
			most commonly reported local AEs were ocular hyperemia and eyelash growth; systemically, a slight increase was seen in SBP for latanoprost, glucose(latanoprost), BUN (Xalatan), and uric acid (both groups)
Rouland 2012 ¹¹ Prospective single-blind RCT	402 POAG or OHT patients Age≥18(mean 64.8, range 24-93), managed with benzalkonium chloride (BAK)-preserved latanoprost (BPL) with stable IOP with washout	Preservative-free latanoprost eye drops (T235) vs. BPLx12 weeks Mean change in IOP	Efficacy: T2345 showed non-inferiority to BPL from day 15. Safety: Local intolerance was lower in T2345.
Chabi 2012 ⁵ Double-blind RCT	643 POAG or OHT patients Age≥18(mean 63.3) managed with other Rx, after washout	Preservative-free(PF) tafluprost vs. PF timololx12 weeks Mean change in IOP at 3 daily time points at weeks 2, 6, and 12	Efficacy: Tafluprost was noninferior to timolol Safety: Hyperemia was slightly but significantly higher in the tafluprost group. No other differences were seen.
Goldberg 2012 ⁶ Double-blind RTC	153 POAG or OHT patients Age≥18	Brinzolamide added to travoprost/timolol Fixed Combination (FC) (TTFC) vs. TTFC alone	Efficacy: Addition of brinzolamide led to a greater decrease in IOP than TTFC alone Safety: No statistical differences were seen in AEs
Katz 2012 ¹⁵ Single-blind RCT	148 POAG or OHT or CAG with iridotomy patients, IOP≥24 Age≥18	FC brimonidine-timolol vs. latanoprost x12 weeks Difference in diurnal IOP at week 12	Efficacy: No differences were seen in mean IOP at week 12 between groups. Brimonidine-timolol resulted in more patients achieving at least a 20% decrease in IOP but the difference was not significant Safety: Both treatments had favorable tolerability
Quaranta 2012 ³⁰ Systematic review	Patients with POAG or OHT	Fixed (FC) vs. unfixed combinations (UC) vs. monotherapies (Mt) of PG analogs and β blockers Efficacy (IOP reductions) and tolerability	Efficacy: 18 eligible trials had 23 comparisons of FC vs. Mt and 5 of FC vs. UC showed that FCs were more efficacious than Mt but were less efficacious than UC. Compared with timolol Mt, latanoprost/timolol FC led to a greater IOP reduction than bimatoprost/timolol or travoprost/timolol

Author, Year Study Design	Population (number, age, condition, relevant comorbidities, exclusion criteria)	Intervention/comparison Outcomes	Findings and conclusions
Comparative effectiveness of surgical tx on IOP			Safety: FCs led to a lower hyperemia risk than UCs or their respective PG analog (PGA) Mts
Stavrakas 2012 ²⁰ Prospective RCT	59 POAG eyes, median age 71 (IQR 67, 76 and 63, 80 for two groups)	32 eyes: amnion shielded trabeculectomy (amniotic membrane transplantation, AMT) 27 eyes : trabeculectomy without antimetabolites Postop IOP and IOP at 24 months	Efficacy: Trabeculectomy with AMT to prevent fibrosis and scarring showed favorable effects on bleb survival cf. the control procedure however differences in IOP and IOP reduction were non-significant immediately postop and at 24 months. Safety: no major complications were observed. Given the risks and absence of major benefit, AMT does not yet seem to be useful as a routine procedure
Nilforushan 2012 ¹⁰ RCT	36 eyes from 34 patients with glaucoma, IOP>21 Age≥18(mean 59.6)	Trabeculectomy with subconjunctival injection of bevacizumab vs. mitomycin C(MMC) Best corrected IOP, visual acuity, number of IOP medications, complications, and bleb morphology at approx. 7.5 months	Both treatments were effective in lowering IOP and reducing need for medication but MMC was more effective than bevacizumab.
Cillino 2011 ²¹ RCT	40 eyes of 40 POAG patients Age≥18 (mean 64.5), IOP>21 or progressive visual field deterioration on MTMT	Trabeculectomy with biodegradable collagen (ologen, OLO) matrix implant vs. MMC IOP≤21, 17, 15; SD-OCT, bleb evaluation, number of medications, and frequency of postop procedures and complications at 24 months	OLO and MMC had similar long term rates of success. No adverse reactions were noted. Frequency of postop complications was similar between groups
Dahan 2012 ²² Prospective randomized study	30 eyes of 15 patients with bilateral POAG not controlled by medications Age≥18	Trabeculectomy vs. Ex-PRESS glaucoma filtration device implantation IOP or need for medications over 30 months postop	Efficacy: IOP reduction and need for medications were comparable for both procedures at 30 months. Complete success rates were higher for Ex-PRESS Safety: Postop complications and need for interventions were fewer in the ExPRESS group than the trabeculectomy group
Bovell 2011 ²³	176 eyes of 152 OAG patients with	Selective laser trabeculoplasty (SLT)	Efficacy:

Author, Year Study Design	Population (number, age, condition, relevant comorbidities, exclusion criteria)	Intervention/comparison Outcomes	Findings and conclusions
Prospective RCT	uncontrolled IOP on maximal tolerated medical therapy, with or without previous argon laser trabeculoplasty (ALT); mean age 69.6±~10	vs. ALT Outcomes: change in IOP from baseline at 3, 4, and 5 years	IOP lowering was similar for each procedure at 3, 4, and 5 years; medication changes were similar in both groups; survival analysis indicated time to 50% failure was similar in both groups. Safety: Incidence of complications (e.g., IOP spikes) was the same for both treatments (as reported previously)
Rosenfeld 2012 ³¹ Follow-up of a prospective RCT	37 eyes of 37 patients with POAG, PEG, pigmentary glaucoma, or OHT and who had previously undergone phacoemulsification-assisted cataract excision surgery with lens implantation; mean age 71.92	18 patients who received ALT vs. 19 patients who received SLT Outcomes: IOP measurement at regular intervals to 12 months postop	Efficacy: SLT and ALT were equally effective Safety: 15 patients excluded for AEs, 12 ALT and 3 SLT, but the AE was unsatisfactory IOP reduction, resulting in medication change, trabeculectomy or repeat ALT
Congdon 2011 ³² RCT open label	298 patients with glaucoma, some with and some without cataract Age≥30	Trabeculectomy plus 5 fluorouracil vs. latanoprost qd or switch to latanoprost+dorzolamide/timolol FC bid at 4 weeks if IOP still>20, with switch to brimonidine at 8 weeks if IO<20 still not achieved IOP and visual function at 12 months	Trabeculectomy lowered IOP significantly more than medical tx but loss of visual acuity was greater with surgery. Combining phacoemulsification and intraocular lens insertion improved visual acuity with significant IOP lowering
Comparative effectiveness of medical vs. surgical treatment			
Katz 2012 ⁸ RCT	69 patients (127 eyes) with OAG or OHT, age 25-82, IOP≥24 (20 in the lower eye) and ≤31	Selective laser trabeculectomy (SLT) vs. medical tx (prostaglandin→+β blocker→brimonidine→dorzolamide, brinzolamide, or FC dorzolamide-timolol 12 month follow-up; IOP or number of steps required to achieve target range	No difference was seen in IOP reduction after 9-12 months, More tx steps were needed to maintain target IOP in the medication group but the difference was not statistically significant.
Effectiveness of treatments in reduction of progression			
Kim 2013 ³³ Retrospective record review	121 eyes of 121 normal-tension glaucoma patients at least 7 years after initial medical tx (mean age 50.5)	Medical treatment; patients divided into 3 groups based on % IOP reduction from baseline Mean follow-up 12 years Progression as measured by structural (RNFL) or functional (visual field) loss	The greater the reduction in IOP, the less cumulative risk for progression; lower percentage reduction in IOP was a consistent risk factor for progression
Harms associated with medical treatments in RCTs with no efficacy outcomes or non-RCTs			
Tressler 2011 ¹² Epidemiological study and	2 safety databases (postmarket reporting) representing 40 trials	(24 latanoprost and 16 FC latanoprost/timolol trials)	Among 12,880 latanoprost treated subjects, no reports of ocular melanoma

Author, Year Study Design	Population (number, age, condition, relevant comorbidities, exclusion criteria)	Intervention/comparison Outcomes	Findings and conclusions
systematic review of potential mechanisms		Outcome: malignant melanoma	and 3 reports of cutaneous melanoma were identified. Of 19,940 cases in the global safety database, 22 reports of ocular/cutaneous neoplasms were obtained, of which 11 were ocular and 6 were cutaneous melanomas. Possible association with latanoprost could not be ruled out in 4 cases, but no evidence establishes a link between latanoprost use and melanoma
Inoue 2012 ⁷ Retrospective case control study	250 POAG or OHT patients, age 28-86	5 groups of 50 patients, each group treated with 1 of 5 types prostaglandin: latanoprost, travoprost, tafluprost, bimatoprost, unoprostone >3 months Deepening of upper eyelid sulcus as determined by photography and self-report questionnaire	Bimatoprost was significantly associated with the AE, whereas the others were not
Aihara 2012 ⁴ Prospective open-label trial	114 patients (67 completed) age not specified	Transition from Latanoprost to BAK-free travoprost 12 month follow-up	BAK-free travoprost was associated with reductions in superficial punctate keratopathy and hyperemia at 12 months
Pfennigsdorf 2012 ¹⁹ Prospective open label study	10,337 POAG or OHT patients	0.01% bimatoprost , 10-14 weeks Change in IOP, AEs	6.1% of patients reported AEs. Eye irritation and hyperemia were the most commonly reported AEs. Tolerability and adherence were high.
Konstas 2012 ¹⁸ Prospective, single-blind crossover study	77 eyes of 77 POAG patients Mean age 65.3 (range31-81)	Dorzolamide/timolol FC(DTFC) vs. brimonidine/timolol FC 2-month timolol run in 3 months tx w/ each therapy	No SAEs were reported, DTFC was associated with more bitter taste and stinging than BTFC, and BTFC was associated with more conjunctival hyperemia
Ahuja 2012 ²⁷ Retrospective case series	262 cases of OAG	Ab interno trabeculotomy surgery with trabectome Hyphema 2 months postop	Of 262 surgery cases, 12 cases of delayed onset symptomatic hyphema were reported among patients; age range 66-82 years). Triggers suspected to be exertion related increase in pressure or ocular compression
Ting 2012 ²⁵ Prospective non-randomized cohort study	Patients with POAG (713) or exfoliative glaucoma (112) mean age ~70	Ab interno trabeculotomy alone vs. with IOL implant Efficacy and safety at 1 year follow-up	Late complications were more prevalent in POAG patients than in XFG patients who underwent trabeculectomy alone. Among those who underwent trabeculectomy plus IOL, hypotony was

Author, Year Study Design	Population (number, age, condition, relevant comorbidities, exclusion criteria)	Intervention/comparison Outcomes	Findings and conclusions
			seen in 1 XFG patient at 1 day postop but none in the POAG group. No other differences were seen.
Anand 2012 ²⁴ Retrospective chart review	132 eyes, mean age 58.5	Trabeculectomy with MMC vs. 5FU Follow-up 12 months or more	Blebitis and endophthalmitis were reported in 1 eye each in both groups. Persistent hypotony was observed in 4 eyes (6.8%) in the MMC group only
Shingleton 2011 ²⁶ Comparative case series	378 patients with pseudoexfoliation glaucoma Mean age ~77	Trabeculectomy plus IOL implantation vs. IOL alone Up to 10 years follow-up	Combined procedures were associated with fewer 1-day postop IOP spikes; eyes undergoing combined procedures required a range of postop corrections but no way to compare this to those who underwent IOL alone
Koucheiki 2012 ⁹ Prospective, nonrandomized trial	136 eyes, no age specified	SLT Mean follow-up 16.6±4.3 months	23.5% of patients reported mild pain” Pigmentary glaucoma(PG) patients reported significantly more mild pain than POAG or pseudoexfoliative (PEX) glaucoma patients Postop inflammation was reported in 42.6% of patients: PG patients had significantly more inflammation than POAG or PEX. PG patients also had significantly increased need for additional SLT procedure and IOP spiking.
Zahid 2012 ¹³ Longitudinal cohort study based on RCT	285 patients in the Collaborative Initial Glaucoma Treatment Study, age not specified, randomized to trabeculectomy	Trabeculectomy patients followed for an average of 7.2 years 163 patients received 5FU during surgery	Of 247 patients with at least 5 years follow-up, 50 required further surgery: 40 required at least 1 bleb revision; 15 had bleb leak; 8 had blebitis, and 4 had hypotony; also 3 patients developed endophthalmitis (5-year risk 1/1%)

Table notes: 5FU 5-fluorouracil; ALT argon laser trabeculoplasty; BAK benzalkonium; bid: twice daily; BP blood pressure; BUN blood urea nitrogen; FC fixed combination; hx history; IOL intraocular lens (implant); IOP intraocular pressure; MMC mitomycin; MT monotherapy; NEI-VFQ National Eye Institute Visual Function Questionnaire; OHT ocular hypertension; PEX pseudoexfoliative glaucoma; PG pigmentary glaucoma; POAG primary open-angle glaucoma; qd: once daily; QoL quality of life; SLT Selective laser trabeculoplasty; tx treatment; UC unfixated combination

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: Treatment for Glaucoma: Comparative Effectiveness

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Medical Treatment of Open-Angle Glaucoma			
KQ 1: Do medical, laser, and other surgical treatments for open-angle glaucoma reduce visual impairment?			
KQ1a: Comparative Effectiveness of Medical Treatments for Reducing Visual Impairment			
<ul style="list-style-type: none"> • No studies of medical therapy were identified that directly addressed outcomes related to visual impairment. • The available studies addressing the secondary outcomes of change in visual acuity and change in visual field loss are of too short a duration to answer this question, given that glaucoma is typically a slowly progressive disease that may take many years to cause clinically or statistically significant changes. 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
Surgical Treatment of Open-Angle Glaucoma			
KQ1b: Comparative Effectiveness of Laser and Other Surgical Treatments for Reducing Visual Impairment			
<ul style="list-style-type: none"> • No studies reported on the outcome of visual impairment after laser or other surgical treatments. • Visual acuity was not assessed as a primary outcome in any identified study 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>comparing laser with other surgical treatments for glaucoma. Visual acuity was only irregularly reported, if at all.</p> <ul style="list-style-type: none"> Given the limitations above, no treatment appeared to have a greater effect on visual acuity than any other treatment. 			
Medical Versus Surgical Treatment of Open-Angle Glaucoma			
KQ1c: Comparative Effectiveness of Medical Versus Surgical Treatment for Reducing Visual Impairment			
<ul style="list-style-type: none"> Although trabeculectomy may reduce the risk of vision loss compared to medical treatment after adjusting for demographic and comorbid factors, the body of evidence is limited and inconclusive (systematic review). 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
KQ 2: Does treatment of open-angle glaucoma improve patient-reported outcomes?			
<ul style="list-style-type: none"> There is no direct evidence regarding the impact of glaucoma treatment on patient-reported outcomes. Medical and surgical treatments reduce the patient's fear of blindness. Several studies suggest that the type of glaucoma treatment does not have an influence on quality of life. There is some evidence that, among medical treatments, patients prefer those that are less frequently applied. Since there are unlikely to be any future trials with a placebo arm, it will not be possible to determine definitively if treatments improve patient-reported outcomes relative to no treatment. It will 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
still be possible to compare the effectiveness of different treatments on patient-reported outcomes, however.			
KQ 3: Do medical, laser, and other surgical treatments for open-angle glaucoma lower intraocular pressure?			
KQ3a: Comparative Effectiveness of Medical Treatments for Lowering Intraocular Pressure			
<ul style="list-style-type: none"> • Prostaglandins lower IOP more than dorzolamide (carbonic anhydrase inhibitor, 2.64 mmHg, three trials), brimonidine (alpha-adrenergic agonist, 1.64 mmHg, four trials), and timolol (beta-adrenergic blocker, 5 percent lower at 6 months, four trials) (systematic review). • The prostaglandins appear similar in the extent to which they lower IOP, but some studies have reported a greater drop in IOP with bimatoprost (prostaglandin) (systematic review). • The combination dorzolamide/timolol appears to lower IOP the same amount as prostaglandins (systematic review). 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<p><i>Circadian Intraocular Pressure</i></p> <ul style="list-style-type: none"> • Our conclusions regarding the effect of topical therapies in lowering IOP over the 24-hour time period were limited due to the fact that one study provided almost all of the data. • All topical medications reviewed appear to lower IOP throughout the 24-hour cycle. • Prostaglandins appear to lower IOP more over the 24-hour cycle than beta- 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>blockers, topical carbonic anhydrase inhibitors, and alpha agonists, but the evidence for this is weak.</p> <ul style="list-style-type: none"> • While the IOP-lowering effects of different prostaglandins appear to vary appreciably over the 24-hour time period, the results were inconsistent and the reported difference in the amount of IOP lowering was on the order of 1 mmHg. • Results from systematic reviews comparing one prostaglandin with another were inconsistent. 			
KQ3b: Comparative Effectiveness of Laser and Other Surgical Treatments for Lowering Intraocular Pressure			
<ul style="list-style-type: none"> • Trabeculectomy lowers IOP more than nonpenetrating surgeries (systematic review). • The use of mitomycin-C intraoperatively with trabeculectomy results in lower IOP than when it is not used (systematic review). • Other alterations in surgical technique, location of surgery on the eye, and adjuvants other than mitomycin-C have not been shown to result in an added pressure decrease (primary studies). • The IOP-lowering effect of combined cataract surgery and trabeculectomy is not affected by the location of the conjunctival incision or the presence or absence of a peripheral iridectomy but may be more in two-site (cataract and trabeculectomy performed using different 	<input type="checkbox"/>	<p>New Evidence:</p>	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>incisions) than one-site (cataract and trabeculectomy performed using the same incision) surgery (systematic review).</p> <ul style="list-style-type: none"> • Laser trabeculoplasty effectively lowers IOP in glaucoma patients, and effectiveness does not vary with the type of laser used (primary studies). • The data available on the role of aqueous drainage devices in open-angle glaucoma are inadequate to draw conclusions (primary studies, systematic review). 			
KQ3c: Comparative Effectiveness of Medical Versus Surgical Treatment for Lowering Intraocular Pressure			
<ul style="list-style-type: none"> • Incisional surgery lowers IOP more than lasers or medications (systematic review). • Initial treatment with lasers tends to reduce the need for medications to achieve a given IOP (systematic review). 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
KQ 4: Do medical, laser, and other surgical treatments for open-angle glaucoma prevent or slow the progression of optic nerve damage and visual field loss?			
KQ4a: Comparative Effectiveness of Medical Treatments for Preventing or Slowing the Progression of Optic Nerve Damage and Visual Field Loss			
<ul style="list-style-type: none"> • A systematic review of medical treatment for glaucoma determined treatment to be protective against progressive visual field loss. This review included the results of both the Early Manifest Glaucoma Trial and the Ocular Hypertension Treatment Study. • Other included primary studies were of insufficient size or duration to detect differences in the rates of optic nerve damage or visual field loss. Given the 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>slowly progressive nature of glaucoma, the large trials of glaucoma therapy have demonstrated the need to follow hundreds of participants for 5 or more years to detect change.</p> <ul style="list-style-type: none"> • A single study addressed the comparative effectiveness of glaucoma medications with respect to their ability to prevent optic nerve damage or visual field loss and found brimonidine superior to timolol. 			
KQ4b: Comparative Effectiveness of Laser and Other Surgical Treatments for Preventing or Slowing the Progression of Optic Nerve Damage and Visual Field Loss			
<ul style="list-style-type: none"> • No studies comparing laser and surgical treatments were found that reported data on whether these procedures slow the progression of optic nerve damage and visual field loss. 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
KQ4c: Comparative Effectiveness of Medical Versus Surgical Treatment for Preventing or Slowing the Progression of Optic Nerve Damage and Visual Field Loss			
<ul style="list-style-type: none"> • Trabeculectomy may prevent more visual field loss than medicines when used as initial therapy in advanced glaucoma (systematic review). • The Collaborative Initial Glaucoma Treatment Study (CIGTS) included current surgical techniques and medications, and found no difference in change in visual field (but did not report on change in the optic nerve). • Treatment of ocular hypertension with medicines preserves visual fields better 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
than no treatment (systematic review).			
KQ 5: Does lowering intraocular pressure or preventing or slowing the progression of optic nerve damage and visual field loss reduce visual impairment and change vision-related quality of life?			
<ul style="list-style-type: none"> • We found no good-quality studies addressing the relationship between the intermediate outcomes of IOP reduction, prevention of optic nerve damage, or prevention of visual field loss and the outcomes of visual impairment and vision-related quality of life. 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
KQ 6: What are the harms associated with medical, laser, and other surgical treatments for open-angle glaucoma?			
KQ6a: Harms Associated With Medical Treatments for Open-Angle Glaucoma			
<ul style="list-style-type: none"> • The prostaglandin agents produce more ocular redness than does timolol (beta-adrenergic blocker) (systematic review). • Within the prostaglandins, latanoprost is least likely to cause redness (systematic review). • Subjects on timolol (beta-blocker) were less likely to drop out of studies due to side effects than those on brimonidine (alpha-adrenergic agonist), latanoprost (prostaglandin analog), travoprost (prostaglandin analog), or betaxolol (beta-blocker) (systematic review). 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
KQ6b: Harms Associated With Laser and Other Surgical Treatments for Open-Angle Glaucoma			
<ul style="list-style-type: none"> • Trabeculectomy results in more complications than nonpenetrating surgeries (systematic review). • The profile of harms does not differ between one- and two-site combined 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
cataract and glaucoma surgery (systematic review).			
KQ6c: Harms Reported in Studies of Medical Versus Surgical Treatments for Open-Angle Glaucoma			
<ul style="list-style-type: none"> • Trabeculectomy is associated with cataract worsening and an increased need for cataract surgery over time when compared to medical treatments for glaucoma (systematic review). • Intraocular surgery rarely results in severe vision loss due to infection and/or bleeding. These risks are not associated with medical or laser treatments. • Laser trabeculoplasty can produce peripheral anterior synechiae, whereas medical treatment does not (systematic review). 	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<p>Are there new data that could inform the key questions that might not be addressed in the conclusions?</p>			