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Ab interno supraciliary microstent surgery for open-angle glaucoma (Review)

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TABLE OF CONTENTS

[Intervention Review]

Ab interno supraciliary microstent surgery for open-angle glaucoma

Amanjeet Sandhu[1], Hari Jayaram[1,2], Kuang Hu[1], Catey Bunce[3], Gus Gazzard[1,2]

[1]Glaucoma Service, Moorfields Eye Hospital NHS Foundation Trust, London, UK. [2]Institute of Ophthalmology UCL & NIHR Biomedical Research Centre, London, UK. [3]London, UK

Contact address: Amanjeet Sandhu, amanjeet.sandhu1@nhs.net.

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ABSTRACT

Background

Glaucoma is the leading cause of global irreversible blindness, often associated with raised intraocular pressure (IOP). Where medical or laser treatment has failed or is not tolerated, surgery is often required. Minimally-invasive surgical approaches have been developed in recent years to reduce IOP with lower surgical risks. Supraciliary microstent surgery for the treatment of open-angle glaucoma (OAG) is one such approach.

Objectives

To evaluate the efficacy and safety of supraciliary microstent surgery for the treatment of OAG, and to compare with standard medical, laser or surgical treatments.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; which contains the Cochrane Eyes and Vision Trials Register; 2020, Issue 8); Ovid MEDLINE; Ovid Embase; the ISRCTN registry; ClinicalTrials.gov and the WHO ICTRP. The date of the search was 27 August 2020.

Selection criteria

We searched for randomised controlled trials (RCTs) of supraciliary microstent surgery, alone or with cataract surgery, compared to other surgical treatments (cataract surgery alone, other minimally invasive glaucoma device techniques, trabeculectomy), laser treatment or medical treatment.

Data collection and analysis

Two review authors independently screened titles and abstracts from the database search to identify studies that met the selection criteria. Data extraction, analysis, and evaluation of risk of bias from selected studies was performed independently and according to standard Cochrane methodology.

Main results

One study met the inclusion criteria of this review, evaluating the efficacy and safety of the Cypass supraciliary microstent surgery for the treatment of OAG, comparing phacoemulsification + supraciliary microstent surgery with phacoemulsification alone over 24 months. This study comprised 505 eyes of 505 participants with both OAG and cataract, 374 randomised to the phacoemulsification + microstent group.

In this study, the perceived risk of bias from random sequence generation, allocation concealment and selective reporting was low. However, we considered the study to be at high risk of performance bias as surgeons/investigators were unmasked. Attrition bias was unclear, with 448/505 participants contributing to per protocol analysis.

Insertion of a Cypass supraciliary microstent combined with phacoemulsification probably increases the proportion of participants who are medication-free (not using eye-drops) at 24 months compared with phacoemulsification alone (85% versus 59%, risk ratio (RR) 1.27, 95% confidence interval (CI) 1.09 to 1.49, moderate-certainty evidence).

There is high-certainty evidence that a greater improvement in mean IOP occurs in the phacoemulsification + microstent group - mean (SD) change in IOP from baseline of -5.4 (3.9) mmHg in the phacoemulsification group, compared to -7.4 (4.4) mmHg in the phacoemulsification + microstent group at 24 months (mean difference -2.0 mmHg, 95% CI -2.85 to -1.15).

There is moderate-certainty evidence that insertion of a microstent is probably associated with a greater reduction in use of IOP-lowering drops (mean reduction of 0.7 medications in the phacoemulsification group, compared to a mean reduction of 1.2 medications in the phacoemulsification + microstent group).

Insertion of a microstent during phacoemulsification may reduce the requirement for further glaucoma intervention to control IOP at a later stage compared to phacoemulsification alone (RR 0.26, 95% CI 0.07 to 1.04, low-certainty evidence).

There is no evidence relating to the rate of visual field progression, or proportion of participants whose visual field loss progressed in this study.

There is moderate-certainty evidence showing little or no difference in the proportion of participants experiencing postoperative complications over 24 months between participants in the microstent group compared to those who received phacoemulsification alone (RR 1.1, 95% CI 0.8 to 1.4).

Five year post-approval data regarding the safety of the Cypass supraciliary microstent showed increased endothelial cell loss, associated with the position of the microstent in the anterior chamber.

There were no reported health-related quality of life (HRQoL) outcomes in the included study.

Authors' conclusions

Data from this single RCT show superiority of supraciliary microstent surgery when combined with phacoemulsification compared to phacoemulsification alone in achieving medication-free control of OAG. However, there are long-term safety concerns with the device used in this trial, relating to the observed significant loss of corneal endothelial cells at five years following device implantation. At the time of this review, this device has been withdrawn from the market.

This review has found that few high-quality studies exist comparing supraciliary microstent surgery to standard medical, laser or surgical glaucoma treatments. This should be addressed by further appropriately designed RCTs with sufficient long-term follow-up to ensure robust safety data are obtained. Consideration of health-related quality of life outcomes should also feature in trial design.

PLAIN LANGUAGE SUMMARY

Does placing a tiny tube (microstent) under the surface of the eye relieve long-lasting high pressure inside the eye (glaucoma)?

What is open-angle glaucoma?
Glaucoma is a common eye condition caused by fluid building up in the front part of the eye, which increases pressure inside the eye. The increased pressure damages the nerve that connects the eye to the brain (optic nerve), causing loss of sight. Glaucoma can lead to permanent loss of sight (blindness) if it is not diagnosed and treated early.

Open-angle glaucoma is the most common type of glaucoma and tends to develop slowly over many years. It is caused by drainage channels in the eye gradually becoming blocked over time.

Treatments for glaucoma
Treatment cannot reverse any loss of sight that happened before glaucoma was diagnosed but can slow or stop loss of sight. All treatments for glaucoma aim to reduce the pressure in the eye. These include:

- medicines, given as eye-drops;
- laser treatment to reduce the production of fluid and open up blocked drainage channels; or
- surgery to drain fluid from the eye.

One treatment involves placing a tiny tube (called a microstent) under the surface of the eye to create a drainage channel for excess fluid. Microstents can often be placed during surgery to treat cataracts: cloudy patches that develop on the lens inside the eye and make sight misty and blurred.

Why we did this Cochrane Review
Placing a microstent may lower pressure inside the eye and reduce the need for eye-drop medicines or for other types of surgery that may have greater risks. We wanted to find out if placing a microstent during cataract surgery would lower pressure inside the eye in people with open-angle glaucoma.

We were also interested in how the microstent affected:

- the need for medicines to reduce pressure in the eye; and
- people's well-being.

What did we do?
We searched for studies that tested the effect of placing a microstent during cataract surgery in people with open-angle glaucoma. We looked for randomised controlled studies, in which those people who received a microstent and those who did not, was decided by chance. This type of study usually gives the most reliable evidence about the effects of a treatment.

Search date: we included evidence published up to August 2020.

What we found
We found one study that took place in the USA and involved 505 people (aged 45 years and older) with open angle glaucoma and a cataract.

The study divided patients into two groups. One group had a microstent placed during surgery to treat their cataract; the other group received surgery to treat their cataract only. Patients in the study were assessed for two years.

The study was funded by a company that makes microstents for use in treating glaucoma.

What are the main results of our review?
Two years after having cataract surgery, in people who also had a microstent placed:

- more of them (85% in this group compared to 59% in the other) did not need eye-drop medicines to treat glaucoma (evidence from 448 people);
- they had greater reductions in pressure inside the affected eye, than people not given a microstent (448 people);
- they had greater reductions, on average, in the use of eye-drop medicines, than people not given a microstent (448 people); and
- fewer people needed further surgery to treat glaucoma (505 people).

However, placing the microstent caused a higher number of unwanted effects (complications) reported in the two years after surgery, compared with cataract surgery alone (evidence from 505 people). On average, for every 1000 people, 390 people given the microstent would have complications, compared with 360 people not given the microstent. There are safety concerns about the microstent used in this study causing long-lasting damage to the clear layer at the front of the eye (cornea).

The study did not measure people's well-being (quality of life) or measure how people's sight was affected over the two years after surgery.

Our confidence in these results
We are confident about the reductions in pressure inside the eye, and about complications after surgery. We do not expect that further evidence will change these results.

We are moderately confident about the reductions in the need for eye-drop medicines to lower pressure inside the eye. Although the patients in the study did not know which treatment group they were in, the people delivering the treatments did know, and this may have affected the results. These results may change if further evidence becomes available.

We are less confident about how many people needed further surgery to treat glaucoma; further evidence is likely to change these results.

Key messages
Placing a microstent in the eye during cataract surgery lowers pressure inside the eye in people with open angle glaucoma, and reduces their need for pressure-lowering medicines, more than cataract surgery alone. But placing of the microstent was linked with an increase in complications after surgery.

SUMMARY OF FINDINGS

Summary of findings 1. Phacoemulsification + supraciliary microstent surgery versus phacoemulsification alone for open-angle glaucoma, at 24 months

Phacoemulsification + supraciliary microstent surgery versus phacoemulsification alone for open-angle glaucoma

Patient or population: people with open-angle glaucoma
Setting: hospital or outpatient clinic
Intervention: phacoemulsification + supraciliary microstent surgery
Comparison: phacoemulsification alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with phacoemulsification alone	Risk with phacoemulsification + supraciliary microstent surgery				
Proportion of participants who were medication-free (not using eye-drops) at 24 months (medium-term)	Study population		RR 1.27 (1.09 to 1.49)	448 (1 RCT)	⊕⊕⊕⊖ MODERATE[1]	
	595 per 1000 (500 to 685)	849 per 1000 (806 to 886)				
Mean change in unmedicated IOP 24 months (medium-term)	Study population		MD -2.0 mmHg (-2.85 to -1.15)	448 (1 RCT)	⊕⊕⊕⊕ HIGH[2]	
	The mean change (reduction) in IOP in the control group at 24 months was 5.4 (SD 3.9) mmHg	The mean change (reduction) in IOP in the intervention group at 24 months was 7.4 (SD 4.4) mmHg				
Mean change in daily IOP-lowering medications at 24 months (medium-term)	Study population		MD -0.5 medications (-0.68 to -0.32)	448 (1 RCT)	⊕⊕⊕⊖ MODERATE[1]	
	The mean reduction in number of IOP-lowering drops was 0.7 medications	The mean reduction in number of IOP-lowering drops was 1.2 medications				
Proportion of participants who required further glaucoma surgery at 24 months (medium-term)	Study population		RR 0.26 (0.07 to 1.04)	505 (1 RCT)	⊕⊕⊖⊖ LOW[3]	
	31 per 1,000	8 per 1,000 (2 to 32)				

Mean change in health-related quality of life	The included study did not report this outcome.					
Rate of visual field progression or proportion of participants whose field loss progressed	The included study did not report this outcome.					
Proportion of participants experiencing postoperative complications over 24 months (medium-term)	Study population		RR 1.1 (0.8 to 1.4)	505 (1 RCT)	⊕⊕⊕⊕ MODERATE[4]	Five year post-approval data regarding the safety of the Cypass supraciliary microstent showed increased endothelial cell loss, associated with the position of the microstent in the anterior chamber.
	360 per 1,000	390 per 1,000				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **IOP:** intraocular pressure; **MD:** mean difference**OR:** odds ratio; **RR:** risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level for study limitations: although participants were masked to their treatment group throughout the study period, as were IOP reading technicians, surgeons/Investigators were not.
[2]Not downgraded for study limitations as IOP assessment was masked.
[3]Downgraded two levels: one for imprecision - confidence intervals included 1, no effect, and one level for risk of bias.
[4]Downgraded one level for imprecision: confidence intervals included 1, no effect.

BACKGROUND

Description of the condition

Glaucoma is a chronic progressive optic neuropathy, affecting up to 4% of people by the age of 80 years (Burr 2007). It is the leading cause of irreversible blindness, affecting 60 million people globally (Quigley 2006). This figure is expected to increase to 80 million people by 2020. Open-angle glaucoma (OAG) is the commonest type, accounting for three-quarters of cases (Quigley 2006). In one large population cohort, one in six patients with OAG became bilaterally blind (Peters 2013). The only proven way to prevent vision loss is to reduce the pressure inside the eye (intraocular pressure) over the long term (AGIS 2000; CNTG Study Group 1998; Heijl 2002; Kass 2002). Approaches to reducing intraocular pressure (IOP) include medical therapy, laser treatments, and surgery. Commercially available eye-drop preparations have a short-lasting effect; medical therapy requires eye-drops to be instilled one or more times daily for life. Adherence is very poor, even if use is monitored (Friedman 2009; Okeke 2009). Conventional surgical techniques such as trabeculectomy are associated with significant risks, with more than 40% of patients developing perioperative complications (Kirwan 2013; Lichter 2001) and re-operation being needed in 7% to 18% (Gedde 2012; Kirwan 2013). Therefore, they are often reserved for disease that is progressing despite other treatments (King 2013).

Description of the intervention

Recently, a number of minimally-invasive surgical techniques have been developed with the aim of achieving long-term reduction of IOP with a better safety profile than conventional surgery (Francis 2011). Among them is ab interno supraciliary microstent surgery - the Cypass Microstent (Alcon Laboratories, a division of Novartis, Basel, Switzerland) and the iStent Supra (Glaukos Corporation, Laguna Hills, CA, USA) are examples of these devices. The former is FDA approved and also CE (European Conformity) marked in Europe. The latter is undergoing a phase 3 clinical trial with a view to obtaining FDA approval, but is CE marked in Europe.

How the intervention might work

In cases of open-angle glaucoma, an increased resistance to outflow is thought to exist not only at the level of the trabecular meshwork but also within the ciliary body part of the uveoscleral pathway.

With the uveoscleral pathway thought to contribute up to half of physiological aqueous outflow (Toris 1999), supraciliary microstents such as the Cypass and iStent Supra have been developed to bypass this, leading to an increase in aqueous outflow and a reduction in intraocular pressure.

Why it is important to do this review

Consultation with patients and healthcare professionals has identified a need for better treatments for glaucoma (James Lind Alliance 2013). Minimally-invasive glaucoma procedures allow the possibility of safe and effective long-term reduction of IOP, removing concerns about permanent vision loss due to non-adherence to eye-drops. A single treatment may also be more acceptable to patients than lifelong daily administration of eye-drops.

The evidence base intended to support the use of supraciliary microstents in practice continues to grow. Randomised controlled clinical studies to assess the safety and efficacy of the Cypass and iStent Supra alone have recruited in excess of 1000 participants. However, what is less clear is where this evidence lies in the current landscape of existing interventional options to manage open-angle glaucoma, presently including medical, laser, trabeculectomy and other minimally-invasive glaucoma procedures. Since phacoemulsification alone has been shown to reduce IOP (Mansberger 2012), we specifically examined the evidence for the efficacy of supraciliary drainage devices when combined with phacoemulsification in comparison to phacoemulsification alone.

With both the Cypass and iStent Supra devices holding a CE mark for use in Europe and the Cypass already FDA approved, the user availability of such supraciliary microstents is expected to grow in the coming years, increasing the importance of a review that will critically evaluate the current evidence relating to this group of devices.

This Cochrane review was conducted in parallel with other reviews currently undertaken by the Cochrane Eyes and Vision MIGS Consortium, which includes minimally-invasive glaucoma surgery (MIGS) techniques and devices such as the Trabectome (NeoMedix, Tustin, California) (Hu 2021), Hydrus Schlemm's canal Microstent (Ivantis Inc., Irvine, California) (Otarola 2020), endoscopic cytophotocoagulation (ECP) (Endo Optiks, Waltham, Massachusetts) (Tóth 2019), XEN Glaucoma Implant (Allergan, Dublin, Ireland) (King 2018) and IStent or IStent inject (Glaukos Corporation, Laguna Hills, California) (Le 2019).

OBJECTIVES

To evaluate the efficacy and safety of supraciliary microstent surgery for the treatment of OAG, and to compare with standard medical, laser or surgical treatments.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) reported in any language irrespective of their publication status.

Types of participants

Study participants had OAG of any type, including primary and secondary OAG. Closed angle glaucoma was excluded. As there are no universally-accepted criteria by which glaucoma may be defined, we permitted studies to use their own definitions of glaucoma (provided these were clearly stated). In addition, participants with ocular hypertension, normal tension glaucoma, or possible glaucoma (suspects for glaucoma) were included. We did not apply any restrictions regarding location, setting, or demographic factors.

Types of interventions

We compared ab interno supraciliary microstent surgery with the Cypass (Alcon Laboratories, a division of Novartis, Basel, Switzerland), iStent Supra (Glaukos Corporation, Laguna Hills, CA,

USA) or other supraciliary microstents that were identified during this review to:

- laser treatment (selective laser trabeculoplasty or argon laser trabeculoplasty);
- other minimally-invasive glaucoma surgery (MIGS) techniques;
- conventional glaucoma surgery (trabeculectomy);
- medical therapy.

RCTs were considered where supraciliary microstent devices were used in combination with phacoemulsification, as well as RCTs where these devices were used in isolation.

Types of outcome measures

We did not use the reporting of particular outcomes as a criterion for eligibility for review. We did not exclude studies from review solely on the grounds of an outcome of interest not being reported.

We planned to report outcomes in the short-term (six to 18 months), medium-term (18 to 36 months), and long-term (36 months onwards).

Primary outcomes

- Proportion of participants who were medication-free (not using eye-drops).

Several different glaucoma outcome measures have been specified as primary outcomes in other Cochrane Reviews and protocols (Ismail 2015). A recent study classified IOP, visual field, safety, and anatomic outcomes as being highly important to glaucoma experts (Ismail 2016). A panel of patients from the Patient and Public Involvement Group of the National Institute for Health Research (NIHR) Biomedical Research Centre for Ophthalmology identified drop-free disease control as a highly valued outcome (unpublished). We chose a participant-centred primary outcome.

Secondary outcomes

- Mean change in IOP, measured using Goldmann applanation tonometry;
- Mean change in number of IOP-lowering drops taken per day;
- Proportion of participants who achieved an IOP 21 mmHg or less;
- Proportion of participants who achieved an IOP 17 mmHg or less;
- Proportion of participants who achieved an IOP 14 mmHg or less;
- Proportion of participants who required further glaucoma surgery, including laser, as recorded by the investigators of the included trial;
- Rate of visual field progression (decibels (dB)/time) or proportion of participants whose field loss progressed in the follow-up period;
- Mean change in health-related quality of life (HRQoL).

Adverse effects

- Proportion of participants experiencing intraoperative and postoperative complications, including, but not restricted to, the following:
  * loss of visual acuity (more than 2 Snellen lines or more than 0.3 logMAR, according to the method of recording visual acuity; or loss of light perception);
  * bleeding, as recorded by the investigators;
  * endophthalmitis, as recorded by the investigators;
  * IOP spikes (postoperative rise in IOP, measured using Goldmann applanation tonometry, of more than 10 mmHg compared to the previous assessment, including measurements taken during the first postoperative month).

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following databases for randomised controlled trials and controlled clinical trials. There were no restrictions to language or year of publication. The date of the search was 27 August 2020.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 8) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 27 August 2020) (Appendix 1);
- MEDLINE Ovid (1946 to 27 August 2020) (Appendix 2);
- Embase Ovid (1980 to 27 August 2020) (Appendix 3);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 27 August 2020) (Appendix 4);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 27 August 2020) (Appendix 5);
- World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 27 August 2020) (Appendix 6).

Searching other resources

We searched the reference lists of included studies for other possible studies. We also searched the websites of the manufacturers of current ab interno supraciliary microstents (Alcon.com, Alcon Laboratories, a division of Novartis, Basel, Switzerland; Glaukos.com, Glaukos Corporation, Laguna Hills, CA, USA) for any information on forthcoming trials.

Data collection and analysis

Selection of studies

Two review authors working independently (AS, HJ) screened titles and abstracts of all articles identified by the search using web-based online review management software (Covidence). If abstracts were not available, full-text articles were screened. Two review authors (AS, HJ) independently assessed full-text reports of all potentially eligible studies. If there was disagreement regarding eligibility, a third review author arbitrated. If any full-text reports were rejected, the reasons for this were recorded in the Characteristics of excluded studies table.

Data extraction and management

We extracted data from reports of included studies using a data collection form. Two review authors (AS, HJ) worked independently

to extract study characteristics from reports and entered the data into Review Manager 5 (RevMan 5) (Review Manager 2020). The same authors extracted the data for analyses, and one review author (AS) checked the data before entering it into Review Manager (RevMan 5). If there was disagreement, a third review author arbitrated.

The process included cross-checking data entry independently using Covidence to support this. If there was disagreement, a third independent review author would arbitrate.

We presented the data collected in Appendix 7 in the Characteristics of included studies table. Where data on included studies were missing or unclear, we planned to contact the individuals or organisations involved to obtain clarification. We collected and used the most detailed numerical data available to facilitate analyses of included studies. We attempted to obtain these data from individuals or organisations in preference to less precise methods such as extracting numeric data from graphs. If this was necessary, two independent review authors extracted the data and a third review author arbitrated, in case of disagreement.

Assessment of risk of bias in included studies

We used the Cochrane 'Risk of bias' tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017) to assess the risk of bias and assign judgements of this for included studies. Two review authors (AS, HJ) performed this 'Risk of bias' assessment independently. In the event of a disagreement, a third review author was available to arbitrate.

Measures of treatment effect

The primary outcome was the proportion of participants who were medication-free at the studies' end. We used a risk ratio as the treatment effect measure. In assessing this effect measure, we have reported how prescribing of IOP-lowering eye-drops was determined during follow-up, where this information was available. We examined whether the people measuring IOP and those deciding upon the prescribing of IOP-lowering eye-drops were masked to treatment group.

We have also reported mean change in IOP from randomisation to the studies' end. Secondary safety outcomes were to be reported as risk ratios. Health-related quality of life outcomes were to be reported as differences in means or risk ratios for continuous and binary data, respectively.

Unit of analysis issues

We assessed whether included studies had included one or two eyes from each participant and whether or not randomisation has been conducted at the level of the participant or the eye. There is a potential for medical treatments, such as topical beta blockers used for one eye, to influence the outcome in the other eye (Piltz 2000). Surgery to lower IOP in one eye may also affect the IOP of the fellow eye (Radcliffe 2010). Therefore, we have excluded studies that had adopted a paired eye design. In the event of a multiple arm study being identified, this could be included providing the respective study design was adequate to ensure independent analysis of each treatment group occurred.

Dealing with missing data

We endeavoured to minimise missing outcome data by contacting individuals and organisations to obtain them. If the data were unavailable but the level of missing data in each group and reasons for missing data in each group were similar, we simply analysed available-case data if an intention-to-treat (ITT) analysis had not been performed. We reported if authors had conducted their own ITT analysis despite missing data, but intended to document whether they provided any justification for the method they had used to deal with missing data and whether they had compared their ITT result with an available-case result.

Assessment of heterogeneity

We intended to assess the heterogeneity between trials by careful examination of the study reports, assessing forest plots and an examination of the I^2 value, however, as only one RCT met the inclusion criteria of this review, this was not necessary.

Assessment of reporting biases

We planned to use a funnel plot to assess the risk of publication bias if there were more than 10 trials within our review.

Data synthesis

We planned to undertake a meta-analysis where data appeared clinically, methodologically, and statistically homogeneous. We planned to check that participants, interventions, comparators, and outcomes were sufficiently similar to give a clinically meaningful result and that our I^2 result did not indicate considerable inconsistency (i.e. I^2 less than 50%). If all estimates were in the same direction, we would meta-analyse even where heterogeneity was evident but would comment on this. We planned to use a random-effects model unless there were fewer than three eligible studies, in which case, we would use a fixed-effect model. As we found only one study, a fixed-effects model was used.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were performed in this review.

Sensitivity analysis

We planned to assess the impact of including studies at high risk of bias for an outcome in one or more key domains. However, there were too few included studies to conduct such analyses.

Summary of findings and assessment of the certainty of the evidence

We prepared a table to summarise the findings of the review, including the assessment of the certainty of evidence for all outcomes using the GRADE approach (GRADEpro).

We reported the following outcomes at medium-term follow-up (18 to 36 months) in the 'Summary of findings' table for each comparison listed in the Types of interventions: Ab interno supraciliary microstent surgery compared with laser treatment, other MIGS techniques, conventional glaucoma surgery (trabeculectomy), or medical therapy.

- Proportion of participants who were medication-free (not using eye drops);

- Mean change in IOP, measured using Goldmann applanation tonometry;
- Mean change in number of IOP-lowering drops taken per day;
- Proportion of participants who required further glaucoma surgery, including laser;
- Rate of visual field progression (decibels (dB)/time) or proportion of participants whose field loss progressed in the follow up period;
- Mean change in health-related quality of life;
- Proportion of participants experiencing intraoperative and postoperative complications (any time point).

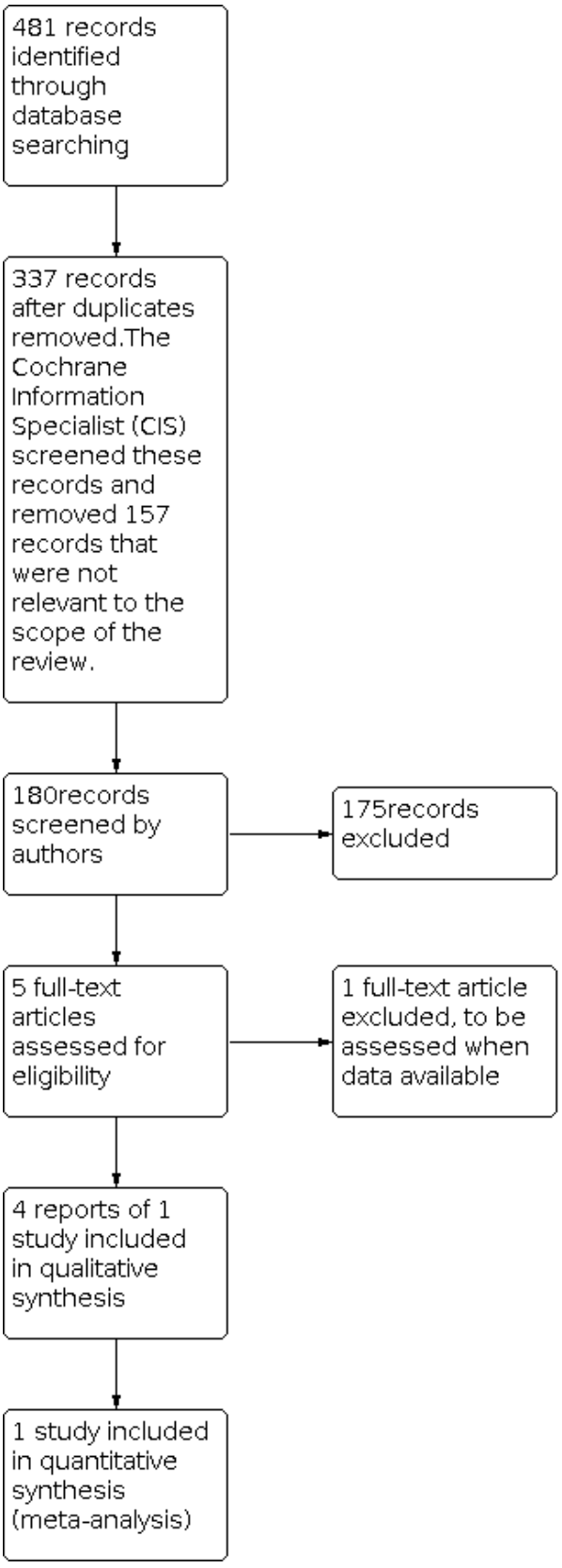
RESULTS

Description of studies

Results of the search

The electronic searches identified 481 references (Figure 1). After 144 duplicates were removed, the Cochrane Information Specialist (CIS) screened the remaining 337 records and removed 157 references that were not relevant to the scope of the review. We screened the remaining 180 references and obtained five full-text reports for further assessment. We identified four full-text reports of one study that met the inclusion criteria (COMPASS Trial), which included additional safety extension reports of the same study (Reiss 2019; Lass 2019). We identified one report of one ongoing study that potentially meets the inclusion criteria (NCT01461278). The findings of this study should be considered upon study completion (last trial update 3/2020).

Figure 1.



Included studies

We included one RCT, the COMPASS Trial, comprising 505 eyes and participants. This prospective, randomised, multicentre, controlled, interventional study reported two-year and, in a later publication, also five-year safety and efficacy results. It was conducted across 24 sites in the USA. People aged 45 years or older with mild to moderate primary open-angle glaucoma, baseline unmedicated IOP between 21 and 33 mmHg, and cataract (best corrected visual acuity of 6/12 or worse), were randomised to phacoemulsification only, or phacoemulsification combined with ab interno supraciliary microstent insertion.

The primary outcome was the percentage of participants achieving a ≥ 20% diurnal lowering of unmedicated IOP from baseline. Secondary outcomes included mean unmedicated change in IOP, percentage of eyes with unmedicated IOP ≥ 6 and ≤ 18 mmHg, and change in number of glaucoma medications required. Additionally, the incidence of ocular adverse events was also recorded, both at two years. See the Characteristics of included studies table for more information.

Ongoing studies

One ongoing study met our inclusion criteria but is yet to report its findings (NCT01461278). Information on this study was obtained from the clinicaltrials.gov registry and also the device company website. Recruitment into this phase three clinical trial has been completed (1200 participants). This is a prospective, randomised, single-masked, controlled, parallel-group, multicentre study to evaluate the safety and efficacy of the Glaukos Suprachoroidal stent model G3 (also known as the Istent Supra) in people with mild to moderate primary open-angle glaucoma. Study completion is expected to be December 2020. See the Characteristics of ongoing studies for more information.

Excluded studies

We did not exclude any studies from this review.

Risk of bias in included studies

An assessment of the risk of bias for the included study (COMPASS Trial), is shown in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

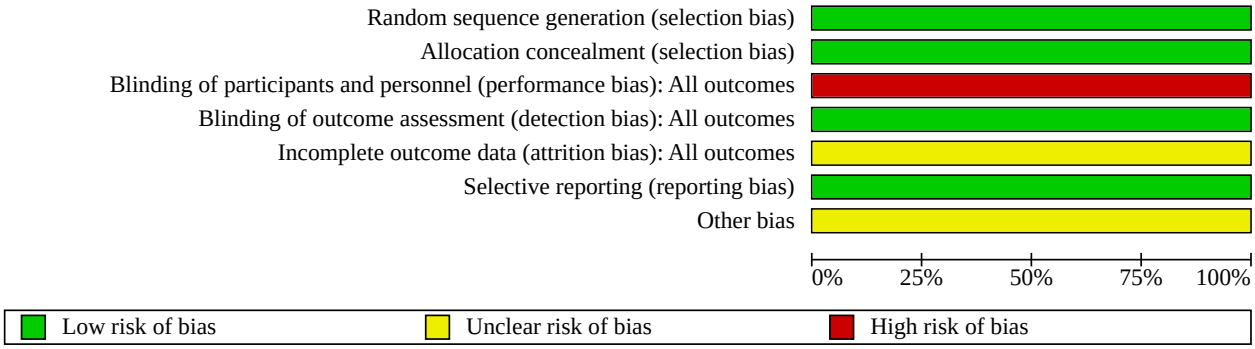
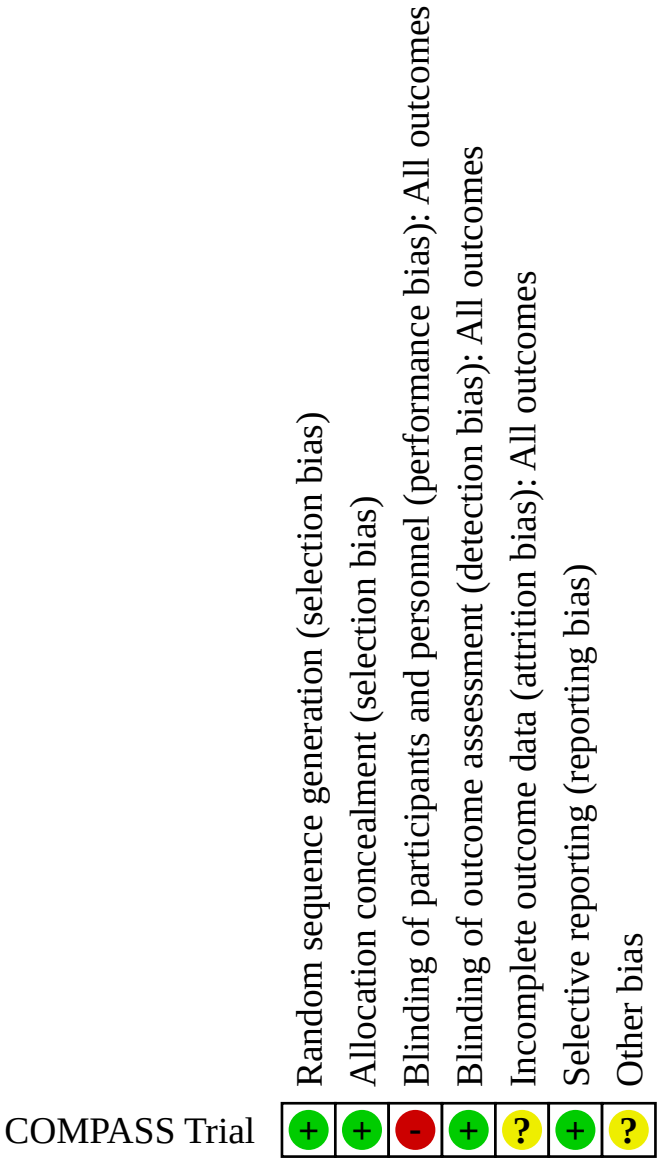


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Low risk of bias - after central randomisation, group assignment was informed only after completion of cataract surgery. Allocation concealment occurred up to this point.

The same randomisation was maintained throughout the five-year COMPASS XT safety and effectiveness study extension.

Blinding

Performance bias

We considered the study to be at high risk of performance bias because, whilst participants and IOP reading technicians were masked to their treatment group throughout the study period, surgeons and investigators were not masked.

Detection bias

We considered the study to be at low risk for detection bias as the IOP reading technicians were masked to group assignment.

The COMPASS XT study extension results were unmasked observations.

Incomplete outcome data

In the COMPASS Trial, 88.7% of recruited study participants contributed to the per protocol analysis (448/505). We assessed attrition bias as unclear as details were not provided, although the rates of attrition in the groups were similar.

In the COMPASS XT study, only 282 of the 480 cases who completed the 24-month COMPASS Trial agreed to enrol, 253 of these completing five years.

Selective reporting

We considered the study to be at low risk of bias as the results aligned accurately with the registered study design and stated outcome measures (NCT01085357, part of COMPASS Trial).

Other potential sources of bias

Although an objective and structured algorithm was described for the reintroduction of IOP-lowering medications, in participants with IOP > 18 and < 21 mmHg, decisions were made on a 'case by case basis' giving rise to potential bias given that decision-making investigators may be aware of group assignment.

Effects of interventions

See: **Summary of findings 1** Phacoemulsification + supraciliary microstent surgery versus phacoemulsification alone for open-angle glaucoma, at 24 months

Phacoemulsification + supraciliary microstent versus phacoemulsification alone

Proportion of participants who are medication-free (not using eye-drops)

In the COMPASS Trial, of the 448 participants completing 24 months follow-up per-protocol, 59.1% of the control group (phacoemulsification alone) were drop-free compared to 84.8% in the phacoemulsification combined with ab interno supraciliary microstent insertion group (risk ratio (RR) 1.27, 95% confidence interval (CI) 1.09 to 1.49) (Analysis 1.1) - there was moderate-certainty in this group of an effective intervention.

The 60-month safety and effectiveness study did not state the percentage of participants remaining medication-free to compare directly with the 24-month data.

Mean change in unmedicated IOP measured using Goldmann applanation tonometry

In the COMPASS Trial, at 24 months, a mean (SD) change in unmedicated IOP from baseline of 5.4 (3.9) mmHg in the control group (n = 116) was reported, compared to 7.4 (4.4) mmHg in the phacoemulsification + microstent group (n = 332); mean difference -2.0 (95% CI -2.85 to -1.15) (Analysis 1.2).

At 60 months, descriptive analysis showed a mean medicated/unmedicated IOP reduction of 8.0 (95% CI 6.8 to 9.2) in the control (n = 52) and 8.4 (95% CI 7.8 to 8.9) in the microstent (n = 200) groups, respectively.

Mean change in number of IOP-lowering medications taken per day

In the COMPASS Trial, at 24 months, mean (SD) IOP-lowering medication use changed from 1.3 (1.0) medications at baseline to 0.6 (0.8) in the control group (n = 116) - a mean change of 0.7 medications, and in the phacoemulsification + microstent group (n = 332), IOP medication use changed from 1.4 (0.9) at baseline to 0.2 (0.6) at 24 months - a mean change of 1.2 medications. This showed a mean difference of -0.50 medications (95% CI -0.68 to -0.32)(Analysis 1.3).

Proportion of participants who achieved an IOP ≤ 21 mmHg

This outcome was not reported in the included trial.

Proportion of participants who achieved an IOP ≤ 17 mmHg

This specific outcome measure was not reported in the included trial, however, 66.7% and 44.0% (n = 200; CI 37.0 to 51.2) of the phacoemulsification + microstent group and 40.9% and 28.3% (n = 52; CI 16.8 to 42.3) of the control group achieved a medication free IOP ≤ 18 mmHg at 24 months and 60 months respectively.

Proportion of participants who achieved an IOP ≤ 14 mmHg

This outcome was not reported in the included trial.

Proportion of participants who required further glaucoma surgery, including laser, as recorded by the investigators of the included trial

In the COMPASS Trial, four participants from the control group (4/131) and three participants from the intervention group (3/374) required further intervention for IOP control in the intention-to-treat population (RR 0.26, 95% CI 0.07 to 1.04), although the nature of the intervention was not described.

Mean change in health-related quality of life (HRQoL)

This outcome was not reported in the included trial.

Proportion of participants experiencing intraoperative and postoperative complications

See Table 1.

No participants in the control group and 1.1% of participants in the phacoemulsification + microstent group lost more than two lines of vision at 24 months.

At 60 months, 6.0% of the control group and 11.2% of the phacoemulsification + microstent group lost more than two lines of vision. Two participants (0.9%) in the phacoemulsification + microstent group lost more than 3 lines of vision (epiretinal membrane; cystoid macular oedema).

No participants in the control group and 2.7% of participants in the phacoemulsification + microstent group developed hyphaema (described as transient intraoperative).

There were no reported cases of endophthalmitis in either assigned group.

Postoperative IOP spikes (IOP ≥ 10 mmHg above baseline) occurred transiently in 2.3% of participants in the control group and 4.3% of participants in the phacoemulsification + microstent group. Transient hypotony was reported in 2.9% of participants in the phacoemulsification + microstent group.

Seven (1.9%) (7/374) participants in the phacoemulsification + microstent group developed a cyclodialysis cleft, no associated hypotony occurred, and no additional surgical intervention was required.

Sixty-month post-surgery data from an FDA-mandated post-approval safety study (NCT03273907) identified an elevated rate of endothelial cell density (ECD) reduction, with 27.16% (44/162) of microstented cases showing > 30% loss (FDA 2018; Reiss 2019, Table 2). There appeared to be an association between the extent of protrusion of the microstent into the anterior chamber and the rate of ECD loss. Three participants showed asymptomatic evidence of focal cornea oedema in the region of the microstent.

Four (1.9%) cases required a microstent trimming procedure.

DISCUSSION

Summary of main results

We found one completed RCT, the COMPASS Trial, evaluating the efficacy and safety of supraciliary microstent surgery for the treatment of OAG, comparing phacoemulsification + supraciliary microstent surgery with phacoemulsification alone.

This review found moderate-certainty evidence that the insertion of a Cypass supraciliary microstent combined with phacoemulsification increased the proportion of participants who were medication-free at medium-term follow-up from 59% to 85% (RR 1.27, 95% CI 1.09 to 1.49).

High-certainty evidence shows that a greater improvement in mean IOP occurred in the phacoemulsification + microstent group - mean (SD) change in IOP from baseline of -5.4 (3.9) mmHg in the control group, compared to -7.4 (4.4) mmHg in the phacoemulsification + microstent group at 24 months (mean difference -2.0, 95% CI -2.9 to -1.1).

Moderate-certainty evidence shows that mean IOP-lowering drop use in the phacoemulsification + microstent group was associated with a reduction of 1.2 medications compared to 0.7 medications in the control group.

Moderate-certainty evidence indicates that fewer participants in the microstent group required further glaucoma intervention to control IOP at a later stage: three phacoemulsification + microstent participants (3/374) compared to four control participants (4/131).

There is moderate-certainty evidence relating to the proportion of participants experiencing postoperative complications over 24 months (medium-term): anticipated absolute effect (95% CI) of 360 per 1000 and 390 per 1000 in the control and phacoemulsification plus microstent groups, respectively.

Concerns have emerged from five-year post-approval data regarding the safety of the Cypass supraciliary microstent (Alcon.com, Alcon Laboratories, a division of Novartis, Basel, Switzerland), the device featured in the COMPASS Trial, in terms of ECD loss rate and an enhanced risk of future cornea decompensation. At the time of this review, this device has been withdrawn from the market.

There are no current published RCT data on health-related quality of life outcomes or visual field progression in people receiving supraciliary microstent surgery to achieve IOP-lowering drop reduction.

Overall completeness and applicability of evidence

This review has shown that RCT evidence exists to assess the efficacy and safety of supraciliary microstent surgery for the treatment of OAG. The COMPASS trial has provided important data to support the primary outcome of this review and also several IOP-associated secondary outcomes, importantly also including safety data (COMPASS Trial; Lass 2019; Reiss 2019). However, the COMPASS Trial only addresses one of the four subgroups of glaucoma interventions that the scope of this review set out to compare.

Although 60-month safety and effectiveness data has been published, this study extension was not powered to allow statistical analysis beyond description to be presented. Twenty per cent of case data at 60 months required retrospective collection, the observations were unmasked, and only 253 of the original 505 cohort of cases completed the entire study extension period, raising additional concerns over selection bias (44% declined enrolment without a reason). At 60 months, endothelial cell density data were collected on only 163 participants from the 355 phacoemulsification + microstent cases that completed the initial 24-month COMPASS Trial.

The results of another RCT, NCT01461278, are awaited, featuring an alternative supraciliary microstent.

Quality of the evidence

Although only one RCT exists (comprising 505 enrolled participants) relating to one of the five glaucoma intervention types sought in this review, the evidence presented was assessed to be of moderate- to high-certainty. While the COMPASS Trial is well designed, this study also acknowledges the presence of unmasked investigators in the follow-up period as a limitation, potentially introducing performance bias.

Potential biases in the review process

This review was conducted in line with the methods outlined by Cochrane. To ensure a high level of completeness in the search of electronic databases and trial registries, an Information Specialist was used. Selection of studies meeting the review inclusion criteria was performed independently by two of the review authors. Our review method ensured that only data from RCTs were included in this review.

Agreements and disagreements with other studies or reviews

We found no other systematic reviews to form a comparison.

AUTHORS' CONCLUSIONS

Implications for practice

This review has identified RCT data showing a superiority in effectiveness of supraciliary microstent surgery when combined with phacoemulsification compared to phacoemulsification alone in achieving drop-free control of OAG, an aspect of importance to people with OAG. However, there are associated safety concerns with the device used in the single published RCT (COMPASS Trial), with particular focus on the health of the cornea endothelium after device implantation leading to its withdrawal form the market at the time of this review.

Additionally, this review highlights the lack of high-quality trial data comparing supraciliary microstent surgery to standard medical, laser or surgical glaucoma treatments. This should be a consideration when clinicians and other decision makers discuss management options with people in the treatment of OAG.

Implications for research

This review demonstrates that RCTs can be performed to assess the effectiveness and safety of supraciliary microstents, one of several minimally-invasive glaucoma devices proposed as alternatives to standard glaucoma interventions. However, as this review highlights, there is a lack of high-quality trial data comparing supraciliary microstent surgery to standard medical, laser or surgical glaucoma treatments that should be addressed.

The emergence of safety concerns in the five-year post-approval safety study for the Cypass supraciliary microstent device also reminds us of the important value of long-term study data, particularly in the assessment of new interventions.

Although clinical outcome measures are important, future study design should also consider including outcome measures on health-related quality of life and other aspects important to people with OAG.

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We thank the members of the MIGS Consortium for their input into this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

COMPASS Trial

Study characteristics	
Methods	**Study design:** Prospective, randomised, multicentre, controlled, interventional study
Participants	**Country:** USA **Total number of participants:** 505 (505 eyes) **Number (%) of men and women**: 47% male; 53% female **Age range:** mean age 70 years **Ethnic group:** 84% white; 9% black origin **Inclusion criteria:** • Age ≥ 45 years • Primary open-angle glaucoma - mild to moderate • Unmedicated baseline diurnal IOP 21 to 33 mmHg • BCVA ≤ 20/40 **Exclusion criteria:** • > 3 IOP-lowering topical medications • Risk to glaucoma from medication washout • Previous cornea/glaucoma surgery • Ocular comorbidity other than glaucoma/cataract • Pseudoexfoliation, pigmentary glaucoma • Other secondary glaucomas including: traumatic, congenital, malignant, uveitic, and also acute angle closure
Interventions	Intervention (n = 332): phacoemulsification combined with insertion of Cypass supraciliary microstent Comparator (n = 116): phacoemulsification only
Outcomes	**Primary outcome (all at 24 months):** • Proportion achieving an unmedicated ≥ 20% diurnal lowering of IOP from baseline **Secondary outcomes (all at 24 months):** • Mean unmedicated change in IOP • Percentage of eyes with unmedicated IOP ≥ 6 and ≤ 18 mmHg • Change in number of glaucoma medications required to maintain target IOP • Incidence and type of ocular adverse events • Percentage of participants with BCVA ≥ 20/40
Notes	**Date conducted:** 07/2011 to completion 03/2015 **Sample size calculations:** To detect a ≥ 20% difference in IOP effect between the two patient groups at 24 months, it was determined using Fisher's Exact Test with a power of 90% and significance interval of 5% that 266 microstent subjects and 95 control subjects were required. To identify one safety event,

COMPASS Trial *(Continued)*

where the rate is ≥ 1%, and a probability of ≥ 0.95 at 24 months, required a total sample size of 505 subjects, 372 in the microstent group and 133 in the control group, assuming a 10% annual attrition rate.

Sources of funding: Study support received from Transcend Medical, Inc. - also involvement in study design, performance, analysis and reporting

Declaration of interest: Authors have disclosed fees for review activities, research funding, and consultation from Transcend Medical, Inc. One author also holds Transcend Medical, Inc. Stock options.

One author acknowledges financial support from 31 other sources for research, speaking honoraria, and consultation.

Trial ID: NCT01085357

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Restricted randomisation was performed centrally, ensuring a 3:1 ratio of microstented:control groups. Stratified randomisation also occurred by trial site.
Allocation concealment (selection bias)	Low risk	After central randomisation, group assignment was informed only after completion of cataract surgery. Allocation concealment occurred up to this point.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Although participants were masked to their treatment group throughout the study period, as were IOP reading technicians, surgeons/investigators were not.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	IOP reading technicians were masked to group assignment - both primary and secondary outcomes relied upon IOP measurements, including the algorithm for the reintroduction of IOP-lowering medications.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	88.7% of recruited study participants that underwent surgery completed per protocol analyses (448 of 505); attrition rates were similar in each assignment group (11.2% microstent + cataract surgery vs 11.4% cataracts surgery alone), however, other than 11 deceased cases (2% of total), detail on the causes for this attrition was minimal.
Selective reporting (reporting bias)	Low risk	The study outcomes were described within the study methods, and the outcome results were reported in the prespecified way.
Other bias	Unclear risk	The reintroduction of IOP-lowering medication decisions, in participants with IOP > 18 and < 21 mmHg, were made on a 'case by case basis' giving rise to potential bias given that decision-making investigators may be aware of group assignment.

BCVA: best-corrected visual acuity; **IOP:** intraocular pressure

Characteristics of ongoing studies *[ordered by study ID]*

NCT01461278

Study name	A prospective, randomised, single-masked, controlled, parallel groups, multicentre clinical investigation of the Glaukos® Suprachoroidal Stent model G3 In conjunction with cataract surgery
Methods	Prospective, randomised, single-masked, controlled, parallel-group, multicentre study to evaluate the safety and efficacy of the Glaukos Suprachoroidal Stent model G3 (also known as the Is-

NCT01461278 *(Continued)*	tent Supra) in subjects with mild to moderate primary open-angle glaucoma, in conjunction with cataract surgery, compared to cataract surgery alone
Participants	**Inclusion criteria:** • Mild to moderate primary open-angle glaucoma • Use of 1 to 3 medications at screening • Age ≥ 45 years **Exclusion criteria:** • Pigmentary or pseudoexfoliative glaucoma • Prior incisional glaucoma surgery
Interventions	Intervention: cataract surgery + insertion of Istent Supra Comparator: cataract surgery alone
Outcomes	Current primary outcome: ≥ 20% reduction in intraocular pressure from baseline to 24 months Current secondary outcome: diurnal intraocular pressure reduction from baseline to 24 months
Starting date	October 2011
Contact information	Study Director: Jeff Wells, Glaukos Corp.
Notes	Study information from www.clinicaltrials.gov, last update 03/2019. Study completion expected 12/2020

DATA AND ANALYSES

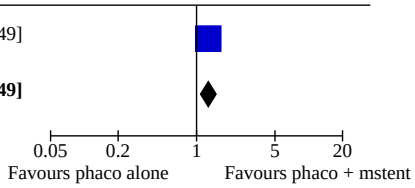
Comparison 1. Phacoemulsification + supraciliary microstent surgery versus phacoemulsification alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Proportion of participants medication-free at 24 months	1	448	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.09, 1.49]
1.2 Mean change in unmedicated IOP at 24 months	1	448	Mean Difference (IV, Fixed, 95% CI)	-2.00 [-2.85, -1.15]
1.3 Mean change in number of IOP-lowering medications taken per day	1	448	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.68, -0.32]

Analysis 1.1. Comparison 1: Phacoemulsification + supraciliary microstent surgery versus phacoemulsification alone, Outcome 1: Proportion of participants medication-free at 24 months

Study or Subgroup	Phaco + microstent Events	Total	Phaco alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
COMPASS Trial	255	332	70	116	100.0%	1.27 [1.09 , 1.49]
Total (95% CI)		**332**		**116**	**100.0%**	**1.27 [1.09 , 1.49]**
Total events:	255		70			

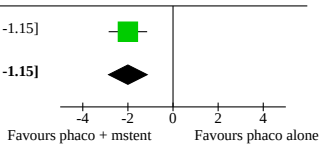
Heterogeneity: Not applicable
Test for overall effect: Z = 2.97 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Phacoemulsification + supraciliary microstent surgery versus phacoemulsification alone, Outcome 2: Mean change in unmedicated IOP at 24 months

Study or Subgroup	Phaco + microstent Mean [mmHg]	SD [mmHg]	Total	Phaco alone Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mmHg]
COMPASS Trial	-7.4	4.4	332	-5.4	3.9	116	100.0%	-2.00 [-2.85 , -1.15]
Total (95% CI)			**332**			**116**	**100.0%**	**-2.00 [-2.85 , -1.15]**

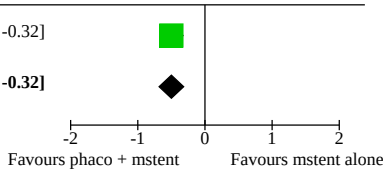
Heterogeneity: Not applicable
Test for overall effect: Z = 4.60 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Phacoemulsification + supraciliary microstent surgery versus phacoemulsification alone, Outcome 3: Mean change in number of IOP-lowering medications taken per day

Study or Subgroup	Phaco + microstent Mean	SD	Total	Phaco alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
COMPASS Trial	-1.2	0.75	332	-0.7	0.9	116	100.0%	-0.50 [-0.68 , -0.32]
Total (95% CI)			**332**			**116**	**100.0%**	**-0.50 [-0.68 , -0.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.37 (P < 0.00001)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Ocular adverse events after phacoemulsification + supraciliary microstent surgery versus phacoemulsification, at 60 months

	Intervention			
	Phacoemulsification surgery		Phacoemulsification surgery + microstent	
	%	n	%	n
Outcomes				
BCVA loss of > 3 lines or more compared to best BCVA reported in COMPASS study	0	0	0.9	2

Table 1. Ocular adverse events after phacoemulsification + supraciliary microstent surgery versus phacoemulsification, at 60 months *(Continued)*

Retinal detachment	1.5	1	0	0
Treatment of elevated intraocular pressure not satisfactorily managed with ocular hypotensive medication	1.5	1	0.5	1
Macular oedema	1.5	1	1.4	3
Other maculopathies	1.5	1	1.4	3
Corneal oedema	0	0	1.4	3
Events requiring unplanned surgical intervention	1.5	1	0.9	2

Results from the COMPASS XT publication. Phacoemulsification n = 200; phacoemulsification + microstent group n = 53, completing 60 months
Unmasked observational data. Similar baseline characteristics between groups.
Approximately 20% of the 60-month data from the 253 participants cases completing the COMPASS XT study was obtained retrospectively.

Table 2. Corneal endothelial cell loss after phacoemulsification + supraciliary microstent or phacoemulsification alone

Mean endothelial cell density (cells/mm^2)

	Baseline				At 60 months			
	mean	Lower CI	Upper CI	n	mean	Lower CI	Upper CI	n
Phacoemulsification	2434.5	2356.5	2512.4	67	2189.1	2069	2309.2	40
Phacoemulsification + supraciliary microstent	2432.6	2382.8	2482.4	214	1931.2	1851.2	2011.2	163

Change from baseline (cells/mm^2)

	mean	Lower CI	Upper CI	n
Phacoemulsification	-249.6	-341	-158.2	40
Phacoemulsification + supraciliary microstent	-507.6	-581.7	-433.6	163

Proportion of eyes with > 30% reduction in endothelial cell density from baseline at 60 months

	%	n	%	n	%	n
Number of retention rings visible on gonioscopy	< 1 microstent retention ring		1 microstent retention ring		≥ 2 microstent retention rings	
Phacoemulsification + supraciliary microstent	20.6	13/63	21.9	16/73	57.7	15/26
Phacoemulsification alone	10.0	4/40				

Results from the COMPASS trial safety extension publication. Extended interval specular microscopy performed subsequent to enrolment into the COMPASS extension trial (COMPASS XT)
Unmasked observational data

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glaucoma, Open-Angle] explode all trees
#2 MeSH descriptor: [Intraocular Pressure] explode all trees
#3 MeSH descriptor: [Ocular Hypertension] explode all trees
#4 OAG or POAG or IOP or OHT
#5 simple near/3 glaucoma*
#6 open near/2 angle near/2 glaucoma*
#7 chronic near/2 glaucoma*
#8 secondary near/2 glaucoma*
#9 low near/2 tension near/2 glaucoma*
#10 ow near/2 pressure near/2 glaucoma*
#11 normal near/2 tension near/2 glaucoma*
#12 normal near/2 pressure near/2 glaucoma*
#13 pigment near/2 glaucoma*
#14 MeSH descriptor: [Exfoliation Syndrome] this term only
#15 exfoliat* near/2 syndrome*
#16 exfoliat* near/2 glaucoma*
#17 pseudoexfoliat* near/2 syndrome*
#18 pseudoexfoliat* near/2 glaucoma*
#19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 MeSH descriptor: [Stents] explode all trees
#21 (micro-bypass* or microbypass* or micro* or bypass*) near/2 stent*
#22 bypass near/3 (trabecul* or interno)
#23 (supraciliary or suprachoroidal) near/3 (microstent* or micro stent* or implant* or drainage or device*)
#24 (Gold Micro Shunt or SOLX Gold Shunt or iStent Supra or Cypass or Aquashunt or STARflo or Esnoper)
#25 #20 or #21 or #22 or #23 or #24
#26 #19 and #25

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma open angle/
14. exp intraocular pressure/
15. ocular hypertension/
16. (OAG or POAG or IOP or OHT).tw.
17. (simple$ adj3 glaucoma$).tw.
18. (open adj2 angle adj2 glaucoma$).tw.
19. (primary adj2 glaucoma$).tw.
20. (chronic adj2 glaucoma$).tw.
21. (secondary adj2 glaucoma$).tw.
22. (low adj2 tension adj2 glaucoma$).tw.
23. (low adj2 pressure adj2 glaucoma$).tw.
24. (normal adj2 tension adj2 glaucoma$).tw.
25. (normal adj2 pressure adj2 glaucoma$).tw.
26. (pigment$ adj2 glaucoma$).tw.
27. exfoliation syndrome/
28. (exfoliat$ adj2 syndrome$).tw.
29. (exfoliat$ adj2 glaucoma$).tw.

30. (pseudoexfoliat$ adj2 syndrome$).tw.
31. (pseudoexfoliat$ adj2 glaucoma$).tw.
32. or/13-31
33. exp Stents/
34. ((micro-bypass$ or microbypass$ or micro$ or bypass$) adj2 stent$).tw.
35. (bypass adj3 (trabecul$ or interno)).tw.
36. ((supraciliary or suprachoroidal) adj3 (microstent$ or micro stent$ or implant$ or drainage or device$)).tw.
37. (Gold Micro Shunt or SOLX Gold Shunt or iStent Supra or Cypass or Aquashunt or STARflo or Esnoper).tw.
38. or/33-37
39. 32 and 38
40. 12 and 39

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. open angle glaucoma/
34. intraocular pressure/
35. intraocular hypertension/
36. (OAG or POAG or IOP or OHT).tw.
37. (open adj2 angle adj2 glaucoma$).tw.
38. (primary adj2 glaucoma$).tw.
39. (chronic adj2 glaucoma$).tw.
40. (secondary adj2 glaucoma$).tw.
41. (low adj2 tension adj2 glaucoma$).tw.
42. (low adj2 pressure adj2 glaucoma$).tw.
43. (normal adj2 tension adj2 glaucoma$).tw.
44. (normal adj2 pressure adj2 glaucoma$).tw.
45. (pigment$ adj2 glaucoma$).tw.
46. exfoliation syndrome/

47. (exfoliat$ adj2 syndrome$).tw.
48. (exfoliat$ adj2 glaucoma$).tw.
49. (pseudoexfoliat$ adj2 syndrome$).tw.
50. (pseudoexfoliat$ adj2 glaucoma$).tw.
51. or/33-50
52. Stent/
53. ((micro-bypass$ or micro$ or bypass$) adj2 stent$).tw.
54. (bypass adj3 (trabecul$ or interno)).tw.
55. ((supraciliary or suprachoroidal) adj3 (microstent$ or micro stent$ or implant$ or drainage or device$)).tw.
56. (Gold Micro Shunt or SOLX Gold Shunt or iStent Supra or Cypass or Aquashunt or STARflo or Esnoper).tw.
57. or/52-56
58. 51 and 57
59. 32 and 58

Appendix 4. ISRCTN search strategy

(Supraciliary microstent OR Suprachoroidal microstent OR Cypass OR iStent Supra OR Gold Micro Shunt OR SOLX Gold Shunt OR Aquashunt OR STARflo OR Esnoper)

Appendix 5. ClinicalTrials.gov search strategy

(Supraciliary microstent OR Suprachoroidal microstent OR Cypass OR iStent Supra OR Gold Micro Shunt OR SOLX Gold Shunt OR Aquashunt OR STARflo OR Esnoper)

Appendix 6. WHO ICTRP search strategy

(Supraciliary microstent OR Suprachoroidal microstent OR Cypass OR iStent Supra OR Gold Micro Shunt OR SOLX Gold Shunt OR Aquashunt OR STARflo OR Esnoper)

Appendix 7. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	· **Parallel-group RCT** *i.e. people randomised to treatment* · **Within-person RCT** *i.e. eyes randomised to treatment* · **Cluster RCT** *i.e. communities randomised to treatment* · **Cross-over RCT** · Other, specify	Number of study arms Method of randomisation Exclusions after randomisation Losses to follow-up Number randomised/analysed Method of masking How were missing data handled? *e.g. available case analysis, imputation methods* Reported power calculation (Y/N)*, if yes, sample size and power* Unusual study design/issues
Eyes Unit of randomisation/unit of analysis	· **One eye included in study**, *specify how eye selected* · **Two eyes included in study, both eyes received same treatment**, *briefly specify how analysed (best/worst/average/both and adjusted for within-person correlation/both and not adjusted for within-person correlation) and specify if mixture of one eye and two eyes* · **Two eyes included in study, eyes received different treatments,** *specify if correct pair-matched analysis done*	
Participants		
Country	-	Setting Ethnic group Method of recruitment

(Continued)

Total number of participants Number (%) of men and women Average age and age range	*This information should be collected for total study population recruited into the study. If these data are reported for the people who were followed up only, please indicate.*	Participation rate Equivalence of baseline characteristics (Y/N) Diagnostic criteria
Inclusion criteria	-	
Exclusion criteria	-	
Interventions		
Intervention (n =) Comparator (n =)	· Number of people randomised to this group · Intervention name · Comparator name · Specify whether phacoemulsification, or other intervention, performed at same time as intervention	Comparator parameters, *e.g. dosage of drugs*
Outcomes		
Primary and secondary outcomes *as defined in study reports*	· IOP at baseline · IOP at follow-up · Number of glaucoma medications at baseline · Number of glaucoma medications at follow-up · Intraoperative complications · Postoperative complications · Secondary surgery · Duration of follow-up · Loss to follow-up · Intervals at which outcomes assessed Adverse events reported (Y/N)	Planned/actual length of follow-up
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: *(if applicable)* Date of publication Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding	-	
Declaration of interest	-	

HISTORY

Protocol first published: Issue 9, 2017

CONTRIBUTIONS OF AUTHORS

Review:
AS, HJ screened the search results.
AS extracted the data for the review.
AS and HJ wrote the review.
KH, CB, GG commented on the draft.

DECLARATIONS OF INTEREST

Amanjeet Sandhu has received travel and subsistence support for training during his Glaucoma Fellowship in the use of the Cypass microstent.

Hari Jayaram has no competing interests with this work, but receives grant support from the Royal College of Surgeons of Edinburgh, Fight For Sight and Glaucoma UK, honoraria for lectures from Thea Pharmaceuticals, Santen and Allergan, honoraria for the peer review of basic science grants (Velux Stiftung) and has received travel support and consultancy honoraria from Allergan.

Kuang Hu has lectured on 'Constructing clinical trials for MIGS - the lack of evidence and what to do about it' at the Moorfields International Glaucoma Symposium 2016, sponsored by Laboratoires Thea, which has contributed an educational grant to Moorfields Eye Hospital.

Catey Bunce has no conflicts to declare.

Gus Gazzard has in the last five years received travel funding and his host organisation has received both educational and unrestricted research funding from pharmaceutical and equipment manufacturers that are involved in the treatment of glaucoma but none that are otherwise related to (or competing with) the subject of this report.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research (NIHR), UK
  * Richard Wormald, Co-ordinating Editor for Cochrane Eyes and Vision (CEV) received financial support for his CEV research sessions from the Department of Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology.
  * This review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the CEV UK editorial base.

  The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.
- Moorfields Eye Charity, UK
  * Hari Jayaram acknowledges financial support for his research sessions from Moorfields Eye Charity.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The follow-up times for the outcomes were decided after the protocol was published.
- The protocol included combination therapy with phacoemulsification as a separate comparison and also for subgroup analysis. After discussion within the review team and MIGS Consortium, we opted to include it as a separate comparison as this is likely to be a different indication.
- We added the following secondary outcomes:
  * Mean change in number of IOP-lowering drops taken per day;
  * Proportion of participants who achieved an IOP 21 mmHg or less; an IOP 17 mmHg or less; IOP 14 mmHg or less;
  * Proportion of participants who required further glaucoma surgery, including laser;
  * Rate of visual field progression (decibels (dB)/time) or proportion of participants whose field loss progressed in the follow-up period.
- In the 'Summary of findings' table, intraoperative and postoperative complications were pooled as a single outcome.