NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of trabecular stent bypass microsurgery for open-angle glaucoma

Primary open-angle glaucoma is a progressive condition that causes long-term increase of pressure within the eye. This damages the nerve that connects the eye to the brain (optic nerve) and may gradually lead to permanent loss of sight. This procedure involves inserting a hollow metal tube (stent) into the eye to drain fluid from the front chamber of the eye. The aim is to reduce pressure within the eye.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in January 2016 and updated in October 2016.

Procedure name

- Trabecular stent bypass microsurgery for open-angle glaucoma

Specialist societies

- Royal College of Ophthalmologists.

Description

Indications and current treatment

Open-angle glaucoma is a chronic condition associated with elevated intraocular pressure and leads to progressive damage to the optic nerve. Early stages are usually asymptomatic but as the condition progresses it causes visual impairment and, if untreated, blindness.

Treatment is usually eye drops containing drugs that either reduce the production of aqueous humor or increase its drainage. Surgical procedures such as trabeculectomy, drainage tubes, deep sclerectomy, viscocanalostomy or laser trabeculoplasty may also be used.

What the procedure involves

Trabecular stent bypass microsurgery aims to reduce intraocular pressure by creating a bypass channel between the anterior chamber and Schlemm's canal to improve drainage of aqueous humor.

This procedure is often combined with phacoemulsification and intraocular lens insertion for the concomitant treatment of cataracts. Using local anaesthesia, a small corneal incision is made and viscoelastic is inserted into the anterior chamber. Under gonioscopic guidance and using a special applicator, a stent is slid through the trabecular meshwork (a small slit may be necessary) and into Schlemm's canal. The position of the stent is verified, then the applicator and viscoelastic are removed.

Either one or multiple stents may be inserted during the same procedure.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to trabecular stent bypass microsurgery for open-angle glaucoma. The following databases were searched, covering the period from their start to 27 October 2016: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with open-angle glaucoma.
Intervention/test	Trabecular stent bypass microsurgery.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 3096 patients from 2 systematic reviews and meta-analyses[1, 2], 5 randomised controlled trials (RCTs)[3-7] and 1 case series[8].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on trabecular stent bypass microsurgery for open-angle glaucoma

Study 1 Malvankar-Mehta MS (2015)

Details

Study type	**Systematic review and meta-analysis**
Country	18 studies from the US, 4 from the UK, 3 from Italy, 1 study in each country including Turkey, Spain, Germany, Finland, New Zealand, Japan and Israel.
Recruitment period	Search from 2000 to June 2014
Study population and number	n= **2,143 patients with glaucoma and cataract from 32 studies (4 RCTs, 2 case control, 21 case series, 5 cohort studies)** • **4 studies compared stent insertion with and without concurrent phacoemulsification** • **22 studies considered phacoemulsification as a solo procedure** • **6 studies assessed stent insertion with phacoemulsification**
Age and sex	Not reported
Patient selection criteria	Study population: adults above 18 years with open-angle glaucoma or ocular hypertension. Study selection criteria: minimum follow-up of 2 months, minimum sample size of 20 patients, studies in English language.
Technique	Insertion of 1, 2 or 3 stents (istent) and phacoemulsification or phacoemulsification alone.
Follow-up	**2 months to 7 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Not reported.

Study design issues:

- Only limited information was available on preoperative and postoperative contrast sensitivity, spherical equivalent, refractive status, stereopsis, and astigmatism and thus these parameters were excluded from the quantitative analysis.

- Some studies were excluded due to lack of necessary information. Data from these studies could have influenced the results.

Study population issues:

- No publication bias: visual inspection of funnel plots by follow-up and number of stents implanted for both pre- and postoperative percentage reduction in intraocular pressure (IOP) and topical medications did not reveal any asymmetry.

- There were significant variations between studies.

Other issues: The Samuelson (2011) study which is a shorter follow-up of the Craven (2012) study (included in table 2) was included in this meta-analysis. The Fea (2012) and (2010) studies which include the same patient population as the Fea (2015) study (included in table 2) were also included.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **2,143 patients with glaucoma and cataract from 32 studies (21 case series, 2 case control, 4 RCTs, 5 cohort studies)**

IOP

- Statistically significant decrease in IOP from baseline in the stent+phacoemulsification group compared with phacoemulsification-only group: SMD= −0.46, 95% confidence interval (CI;−0.87 to −0.06); based on 4 studies.
- I^2=47%, p=0.128

IOP reduction % from baseline based on RCTs comparing stent insertion with and without phacoemulsification

	1 stent + phacoemulsification (based on 3 studies)	2 stents + phacoemulsification (based on 1 study)	Phacoemulsification alone (based on 3 studies)
Weighted mean reduction in IOP reduction %	9%	27%	5%

% IOP reduction from baseline based on non-comparative studies

	1 stent + phacoemulsification (based on 4 case series)	2 stents + phacoemulsification (based on 1 case series and 1 cohort study)	3 stents + phacoemulsification (based on 1 cohort study)	Phacoemulsification alone (based on 22 studies considering phacoemulsification as a solo procedure)
Weighted mean reduction in IOP reduction %	26%	18%	20%	31%

Topical glaucoma medication use

- Statistically significant decrease in the number of medications used after the procedure in the stent+phacoemulsification group compared with phacoemulsification-only group: SMD = −0.65, 95% CI −1.18 to −0.12; based on 3 studies.
- I^2 =58%, p=0.092

Reduction in topical glaucoma medication use from baseline in RCTs comparing stent insertion with and without phacoemulsification

	1 stent + phacoemulsification (based on 3 studies)	2 stents + phacoemulsification (based on 1 study)	Phacoemulsification alone (based on 3 studies)
Weighted mean reduction in topical glaucoma medications	1.33	1.1	1.01

Reduction in the number of glaucoma medications from baseline based on non-comparative studies

	1 stent + phacoemulsification (based on 4 case series)	2 stents + phacoemulsification (based on 1 case series and 1 cohort study)	3 stents + phacoemulsification (based on 1 cohort study)	Phacoemulsification alone (based on 22 studies considering phacoemulsification as a solo procedure)
Weighted mean reduction in topical glaucoma medications	1.05	1.46	2.2	0.23

Reduction in the number of glaucoma medications from baseline based on non-comparative studies

	1 stent + phacoemulsification (based on 7 studies, I^2=87%, p=0.000)	2 stents + phacoemulsification (based on 3 studies, I^2=66%, p=0.085)	3 stents + phacoemulsification (based on 1 study)	Phacoemulsification alone (based on 20 studies considering phacoemulsification as a solo procedure, I^2 =89%, p=0.000)
SMD	SMD = -1.46, 95% CI −2.02 to −0.90	SMD = −2.07, 95% CI −2.94 to −1.2.	SMD = −2.30, 95% CI −3.02 to −1.58	SMD = −0.53, 95% CI −0.76 to −0.30

Postoperative change in topical glaucoma medication use by follow-up period for the studies examining phacoemulsification as a solo procedure

	6 months (4 studies; I^2=74%, p=0.021)	12 to less than 24 months (12 studies; I^2=92%, p=0.000)	24 months (3 studies; I^2=0%, p=0.888)	36 months and above (2 studies; I^2=92%, p=0.001)
SMD (95% CI)	−0.29, CI −0.65 to 0.06	−0.56, CI −0.9 to −0.22	−0.51 (−0.74 to −0.27)	−1.03 (−2.85 to 0.80)

Postoperative change in topical glaucoma medication use by follow-up period for the studies examining stent insertion and phacoemulsification

	6 months (2 studies; I^2=88%, p=0.003)	12 to less than 24 months (7 studies; I^2=81%, p=0.000)	4 years and above (1study)
SMD (95% CI)	−0.82, CI −1.84 to 0.21	-1.73, CI −2.23 to −1.23	−2.80 (−4.07 to −1.53)

Abbreviations used: IOP, intraocular pressure; SMD, standardised mean difference.

Safety

Complications reported in studies included in meta-analysis

Complication	Study	Intervention	Rate
Stent malposition	Belovay (2012)	2 stents + phacoemulsification	2% (N=28)
	Fea (2010)	Stent + phacoemulsification	6% (N=12)
	Fernandez-Barrientos (2010)	2 stents + phacoemulsification	18% (N=17)
	Spiegel (2008) – 6-month follow-up	Stent + phacoemulsification	2% (N=47)
	Spiegel (2009) – 12-month follow-up	Stent + phacoemulsification	17% (N=47)
	Samuelson (2011)	Stent + phacoemulsification	3% (N=123)
Stent occlusion	Ahmed (2012)	Stent + phacoemulsification	11% (N=27)
	Spiegel (2008) – 6-month follow-up	Stent + phacoemulsification	15% (N=47)
	Spiegel (2009) – 12-month follow-up	Stent + phacoemulsification	14% (N=47)
	Samuelson (2011)	Stent + phacoemulsification	4% (N=123)
Hyphema	Ahmed (2012)	Stent + phacoemulsification	4% (N=27)
	Belovay (2012)	2 stents + phacoemulsification	2% (N=28)
	Patel (2013)	Stent + phacoemulsification	2% (N=40)
IOP raise above 10 mmHg	Ahmed (2012)	Stent + phacoemulsification	48% (N=27)
IOP raise above 30 mmHg	Arriola-Villalobos (2013)	2 stents + phacoemulsification	15% (N=20)
Blockage of the opening of the stent lumen	Belovay (2012)	2 stents + phacoemulsification	15% (N=28, 8 eyes)
Anterior chamber collapse	Spiegel (2008)	Stent + phacoemulsification	2% (N=47)
Vitreous wick incarcerated in paracentesis	Spiegel (2008)	Stent + phacoemulsification	2% (N=47)
Cystoid macular oedema	Samuelson (2011)	Stent + phacoemulsification	1% (N=123)
Posterior capsule opacification	Samuelson (2011)	Stent + phacoemulsification	3% (N=123)
Subconjunctival haemorrhage	Samuelson (2011)	Stent + phacoemulsification	2% (N=123)
Epiretinal membrane	Samuelson (2011)	Stent + phacoemulsification	2% (N=123)
Iris atrophy	Samuelson (2011)	Stent + phacoemulsification	2% (N=123)
Iritis	Samuelson (2011)	Stent + phacoemulsification	1% (N=123)
Dry eye	Samuelson (2011)	Stent + phacoemulsification	1% (N=123)

Abbreviations used: IOP, intraocular pressure; SMD, standardised mean difference.

Study 2 Malvankar-Mehta M S (2015)

Details

Study type	**Systematic review and meta-analysis**
Country	5 studies from Canada (2), US (2) and France, Germany, Italy, Armenia and Spain (1).
Recruitment period	Search from 2000 to June 2014
Study population and number	n=**248 patients with mild to moderate glaucoma from 5 studies (1 RCT, 3 case series and 1 cohort)**
Age and sex	Age only reported for 2/5 studies: Voskanian (2014): mean 66.4 years and Singh (2012): mean 73 years. Sex not reported
Patient selection criteria	Study population: adults above 18 years old with mild to moderate glaucoma. Study selection criteria: minimum sample size of 20 patients, studies in English language.
Technique	Insertion of 1, 2 or 3 stents (istent).
Follow-up	**1 month to 18 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: For 1 of the 5 studies (Charters [2013]), no length of follow-up was reported.

Study design issues:

- All included articles were scored for quality using the Downs and Black checklist. Of the included papers, 1 was determined to be of high quality, 1 of medium quality and 3 were considered of poor quality.
- 1 study compared the impact of the insertion of 1, 2 or 3 stents, 2 studies examined the insertion of 2 stents and 2 studies examined the insertion of 1 stent.

Study population issues:

- No publication bias: Visual inspection of funnel plots by follow-up and number of stents implanted for both pre- and postoperative IOP and topical glaucoma medications did not reveal any asymmetry.

Other issues: Not reported.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **248 patients from 5 studies**

IOP

% reduction in IOP from baseline after 1-stent insertion at 18 months: 22% (1 study).

Weighted mean % reduction in IOP after 2-stent implantation at 6 months: 30% (2 studies).

% reduction in IOP from baseline after 3-stent insertion at 6 months: 41% (1 study).

IOP reduction from baseline by the number of stents inserted

	1 stent (based on 3 studies; I^2=96%, p=0.000, FU=6 to 18 months)	2 stents (based on 2 studies; I^2=98%, p=0.000, FU=6-12 months)	3 stents (based on 1 study, FU=6 months)
SMD (95% CI)	−1.95 (−3.41 to −0.49)*	−3.08 (−6.90 to 0.74)	−4.26 (−5.18 to −3.33)*

*Statistically significant reduction in IOP from baseline after implantation of 1 and 3 stents.

IOP reduction from baseline by follow-up

	Less than 6 months to 6 months (based on 3 studies; I^2=96%, p=0.000)	12 months (based on 2 studies; I^2=97%, p=0.000)	18 months (based on 1 study)
SMD (95% CI)	−2.84 (−4.38 to −1.29)*	−2.06 (−3.80 to −0.31)*	−0.70 (−1.14 to −0.25)*

*Statistically significant reduction in IOP from baseline at all follow-up but this suggests that, over a period of time, effect on IOP decreases.

Topical glaucoma medication use

Mean reduction in topical glaucoma medications from baseline after 1-stent insertion at 18 months: 1.2 bottles (1 study).

Weighted mean reduction in topical glaucoma medications from baseline after 2-stent implantation at 6 months: 1.45 bottles (2 studies).

Mean reduction in topical glaucoma medications from baseline after 3-stent insertion at 6 months: 1 bottle (1 study).

Reduction in number of medications used from baseline with regards to the number of stents inserted

	1 stent (based on 3 studies; I^2=94%, p=0.000, FU=6 to 18 months)	2 stents (based on 2 studies; I^2=0%, p=0.944, FU=6 to 12 months)	3 stents (based on 1 study, FU=6 months)
SMD (95% CI)	−1.68 (−2.74 to −0.61)*	−1.98 (−2.39 to −1.57)*	−2.00 (−2.62 to −1.38)*

*Statistically significant reduction in number of medications from baseline after implantation of 1, 2 and 3 stents.

Reduction in number of medications used from baseline by follow-up

	Less than 6 months to 6 months (based on 2 studies; I^2=0.0%, p=0.488)	12 months (based on 2 studies; I^2=12%, p=0.287)	18 months (based on 1 study)
SMD (95% CI)	−1.83 (−2.23 to −1.43)*	−2.21 (−2.53 to −1.88)*	−0.71 (−1.15 to −0.26)*

*Statistically significant reduction in number of medications used from baseline at all follow-up.

Safety

Complications reported in studies included in meta-analysis

Complication	Study	Intervention	Rate
Stent malposition	Buznego (2009)	1 stent	15% (N=41)
	Voskanyan (2014)	1 stent	1% (N=99)
Stent replacement	Buznego (2009)	1 stent	5% (N=41)
Stent reposition	Buznego (2009)	1 stent	2% (N=41)
Stent obstruction	Voskanyan (2014)	1 stent	3% (N=99)
Stent not visible upon gonioscopy	Voskanyan (2014)	1 stent	13% (N=99)
Elevated IOP	Voskanyan (2014)	1 stent	10% (N=99)
Hypotony	Ahmed (2012)	1, 2 or 3 stents	3% (N=90)
Hyphema	Ahmed (2012)	1, 2 or 3 stents	3% (N=90)
Intraocular inflammation	Voskanyan (2014)	1 stent	1% (N=99)
Subconjunctival haemorrhage	Voskanyan (2014)	1 stent	1% (N=99)
Goniosynechiae	Voskanyan (2014)	1 stent	1% (N=99)
Iris synechiae	Voskanyan (2014)	1 stent	1% (N=99)
Allergic reaction to medications	Voskanyan (2014)	1 stent	1% (N=99)
Posterior capsular opacification	Voskanyan (2014)	1 stent	1% (N=99)

Abbreviations used: CI, confidence interval, FU, follow-up; IOP, intraocular pressure; SMD, standardised mean difference.

Study 3 Craven E R (2012)

Details

Study type	**RCT**
Country	US
Recruitment period	Not reported
Study population and number	n= **239 (116 stent + phacoemulsification versus 123 phacoemulsification only)** patients with mild to moderate glaucoma (240 eyes)
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: Patients with mild to moderate glaucoma and with a medicated IOP of 24 mm Hg or lower on 1 to 3 medications. Exclusion criteria: angle-closure glaucoma, secondary glaucoma (except pseudoexfoliative and pigmentary), severely uncontrolled IOP, severe glaucomatous field defects, previous glaucoma surgery (except iridectomy), previous refractive procedures and monocular patients or patients with a corrected distance visual acuity worse than 20/200 in the fellow eye.
Technique	Standard phacoemulsification with intraocular lens implantation and stent (istent) implantation versus phacoemulsification alone. After the procedure, topical fluoroquinolone was prescribed for 1 week and prednisolone acetate 1% was started at 6 drops per day and tapered over 4 weeks. Ocular hypotensive medications were given when unmedicated IOP reached 21 mmHg or higher.
Follow-up	**2 years**
Conflict of interest/source of funding	Dr Craven was an investigator in the clinical trial of the istent. Dr Katz is a consultant to Glaukos and was the medical monitor for the clinical trial of the istent; he is also a stockholder in Glaukos. Mt Wells and Ms Giamporcaro are employees at Glaukos.

Analysis
Follow-up issues:
- After the procedure, patients were examined at 3 to 7 hours, 1 day, 1 to 2 weeks, and 3, 6, 12, 18, and 24 months.

Study design issues:
- Multicentre study.
- A medication-washout period was achieved before randomisation. Patients were randomly assigned in a 1:1 ratio to stent group or control group if the unmedicated IOP was between 22 and 36 mmHg. There was no postoperative medication-washout step before measurement of endpoints.
- The study was not designed with or statistically powered for 2-year endpoints.
- Each surgeon used his/her preferred standard phacoemulsification with intraocular lens implantation technique and anaesthesia regimen.
- Intention-to-treat analysis; patients receiving secondary surgical intervention (including repositioning) were treated as non-responders.
- The safety population comprised the eyes having surgery (116 versus 117).
- Additional analysis was done on a 'consistent cohort' defined as all eyes with IOP and ocular hypotensive medication data at screening, 12 months and 24 months who did not have secondary surgical intervention that may confound the results. At 2-year follow-up, the consistent cohort represented 84% (98/116) of patients in the stent group and 82% (101/123) of patients in the no-stent group.

Study population issues: Not reported.
Other issues: This is the 2-year follow-up of the Samuelson (2010) study which was included in the previous overview (now in Appendix A).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **239 (116 stent + phacoemulsification [117 eyes] versus 123 phacoemulsification only [123 eyes])** **IOP**	**Corrected distance visual acuity** **Corrected distance visual acuity loss (severe)**

Patients achieving IOP reduction at 24 months in the intent-to-treat population

	Stent (n=116)		Control (n=123)				
	%	90% CI	%	90% CI	Difference (%)	90% CI of difference	p value
IOP≤21 mmHg without medication	61% (71/116)	54 to 68	50% (61/123)	42 to 57	12%	1 to 22	0.036
IOP reduction ≥ 20% without medication	53% (61/116)	45 to 60	44% (54/123)	37 to 51	9%	−2 to 19	0.09

- Stent group: 1 patient

This occurred after a **stroke**.

- Control group: 1 patient

This occurred after macular traction, macular hole and macular oedema treated with vitrectomy.

Corrected distance visual acuity worse than 20/40 at 24 months

- Stent group: 7 eyes
- Control group: 9 eyes

Causes: **onset or progression of macular disease** (n=6), **posterior capsule opacification** (n=2) and **dry eye** (n=2).

Mean (±standard deviation [SD]) IOP in the 'consistent cohort'

	Stent (n=98, mm Hg)	Control (n=101, mm Hg)
Before the procedure – at screening	18.6±3.4	17.9±3.0
Before the procedure – after medication washout	25.4±3.6	25.2±3.6
12 months	17.0±2.8	17.0±3.1
24 months	17.1±2.9	17.8±3.3

Intraoperative complications (stent group only)

Outcomes	Rate
Intraoperative stent removal and replacement	1/116
Stent malposition (2nd stent inserted – no effect on outcome)	1/116

Mean (±SD) number of ocular hypotensive medications used in the 'consistent cohort'

	Stent (n=98)	Control (n=101)	p value
Before the procedure – at screening	1.6±0.8	1.5±0.6	
12 months	0.2±0.6	0.4±0.7	0.011
24 months	0.3±0.6	0.5±0.7	NS

Corrected distance visual acuity

% of eyes with corrected distance visual acuity of 20/40 or better

	Stent	Control
Before the procedure	45% (49 eyes)	44% (53 eyes)
12 months	94% (99 eyes)	90% (101 eyes)

Frequently reported postoperative ocular

	Stent (n=116 eyes)	No stent (n=117 eyes)
Stent repositioning	3% (3/116)	NA
Stent removal and replacement	1% (1/116)	NA
Nd:YAG laser for stent obstruction	1% (1/116)	NA
Trabeculoplasty	1% (1/116)	2% (2/117)
Focal argon laser photocoagulation	1% (1/116)	0%
Deep sclerectomy/ sclerostomy	0%	1% (1/117)
Intraocular lens removal and replacement	0%	1% (1/117)
Laser in situ keratomileusis	0%	1% (1/117)
Pupilloplasty	0%	1% (1/117)
Vitrectomy	0%	1% (1/117)
Wound resuture due to wound leak	0%	1% (1/117)
Total patients (some had more than 1 surgical intervention)	4% (5/116)	5% (6/117)

*Includes early postoperative corneal oedema, anterior chamber cells, corneal abrasion, discomfort, subconjunctival haemorrhage, blurry vision and floaters.

Secondary surgical interventions through 24 months in the safety population

complications (≥3%) through 24 months in the safety population

Outcome	Stent (n=116 eyes)	No stent (n=117 eyes)
Anticipated early postoperative event*	17% (20/116)	19% (22/117)
Posterior capsule opacification	6% (7/116)	10% (12/117)
Elevated IOP	4% (5/116)	7% (8/117)
Elevated IOP ('other')	3% (4/116)	4% (5/117)
Elevated IOP requiring treatment with oral or intravenous medications or surgical intervention	1% (1/116)	3% (3/117)
Stent obstruction	4% (5/116)	NA
Blurry vision or visual disturbance	3% (4/116)	7% (8/117)
Stent malposition	3% (3/116)	NA
Iritis	1% (1/116)	5% (6/117)
Conjunctival irritation due to hypotensive medication	1% (1/116)	3% (3/117)
Disc haemorrhage	1% (1/116)	3% (3/117)

Abbreviations used: CI, confidence interval; IOP, intraocular pressure; NA, not applicable; NS, not significant; SD, standard deviation.

Study 4 Fea A M (2014)

Details

Study type	**Prospective RCT**
Country	Italy, Spain, Poland, Germany, United Kingdom and Armenia
Recruitment period	Not reported
Study population and number	n=**192 (94×2 stents versus 98 medical therapy)** patients with open-angle glaucoma not controlled on 1 medication
Age and sex	Mean 64 years; 56% (107/192) female
Patient selection criteria	Inclusion criteria: Patients presenting with a post-washout IOP between 22 mmHg or more and less than 38 mmHg, minimum BCVA of 20/200 or better, scleral spur clearly visible by gonioscopy, able and willing to attend follow-up visits for 1 year after the procedure and informed consent. Exclusion criteria: Known non-responders to latanoprost, had secondary glaucoma (with the exception of pseudoexfoliative and pigmentary), prior incisional glaucoma surgery or procedure such as trabeculectomy shunt or collagen implant, cloudy cornea inhibiting gonioscopic view, signs of traumatic or uveitic, neovascular, or angle-closure glaucoma. Prior selective laser trabeculoplasty in the study eye was allowed as long as the procedure was not performed within 90 days before the screening visit.
Technique	• The stent group was treated with 2 istent inject devices (GTS400). The study was initiated using the first generation G2-0 injector, which allows for insertion of 1 stent at a time. Subsequently, the second-generation injector G2-M-IS system, which allows for insertion of multiple stents at a time, was introduced to the study. After the procedure, the patients received topical anti-inflammatory and anti-infective medications for 4 weeks. • The medical therapy group was treated with a fixed combination of latanoprost/timolol (Xalacom).
Follow-up	**1 year**
Conflict of interest/source of funding	Glaukos Corporation provided study devices, sponsorship for performing this study, editorial assistance in the preparation of this manuscript and payment of the article processing charges. Dr Fea received financial support from Glaukos for his work as an investigator in this study and has also received non-study financial support from Glaukos. Drs Belda, Rekas, Jünemann, Chang, Pablo and Voskanyan received financial support from Glaukos for their work as investigators in this study. Dr Katz received financial support from Glaukos for his work as a medical monitor in this study and has also received non-study financial support from Glaukos. The authors report no conflicts of interest in this work.

Analysis

Follow-up issues:

- Evaluations occurred at day 1, month 1, 3, 6, 9, and 12 in both groups. IOP was measured between 8 am and 11 am to control for diurnal variation in IOP.
- 229 patients were screened for the trial, 192 qualified and were enrolled.
- At 12 months, 100% (94/94) of patients in the stent group and 93% (91/98) of patients in the medical therapy group were available for follow-up. There was a nonresponse assumption for missing data.

Study design issues:

- Multicentre study conducted at 8 investigational sites.
- Unblinded RCT.
- Before randomisation, patients were washed out of their current glaucoma medication in the study eye. There was either a 4-week washout for prostaglandin analogues and beta-blockers or a 2-week washout for alpha-adrenergic agonists and carbonic anhydrase inhibitors.

Study population issues:

- The majority of eyes in both groups were phakic (98% versus 97% for the stent and medication groups, respectively).
- No patients enrolled in the trial had undergone prior selective laser trabeculoplasty.
- As an alternative to the use of Xalacom (latanoprost/timolol), 8 patients took Duotrav (travoprost/timolol).
- Four eyes in the iStent inject group were taking medication at the month 12 examination.
- Enrolment of Caucasian population only.

Other issues: Not reported.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **192 (94 x 2 stents versus 98 medical therapy)**

% of eyes with IOP reduction at 1 year versus baseline unmedicated IOP

IOP reduction	Stent group (n=94 eyes; %, 95% CI)	Medical therapy group (n=98 eyes; %, 95% CI)	p value
≥50%	53% (43 to 64)	36% (26 to 46)	0.02
≥40%	81% (71 to 88)	76% (66 to 84)	NR
≥30%	94% (87 to 98)	89% (81 to 94)	NR
≥20%	95% (89/94, 95% CI 88 to 98)	92% (88/98, 95% CI 85 to 96)	NR

% of eyes with IOP of 18 mmHg or less at 1 year

IOP reduction	Stent group (n=94 eyes; %, 95% CI)	Medical therapy group (n=98 eyes; %, 95% CI)
≤15 mmHg	85% (76 to 92)	82% (73 to 89)
≤18 mmHg	93% (85 to 97)	90% (82 to 95)

Mean IOP and IOP change by visit (mmHg)

IOP	Screening	Baseline washout	1 month	3 months	6 months	9 months	1 year
2 stents (N=94)							
Mean (SD) IOP over time	21.1 (1.7) (N=94)	25.2 (1.4) (N=94)	13.3 (4.1) (N=93)	12.8 (3.2) (N=94)	12.7 (3.2) (N=93)	12.9 (2.9) (N=94)	13.0 (2.3) (N=94)
Mean (SD) IOP change from screening			−7.7 (4.2)	−8.3 (3.3)	−8.5 (2.8)	−8.2 (3.0)	−8.1 (2.6)
Mean (SD) IOP change from baseline			−11.8 (4.2)	−12.4 (3.4)	−12.5 (3.2)	−12.3 (3.0)	−12.2 (2.5)
2 medications (N=98)							
Mean (SD) IOP over time	20.7 (1.78) (N=98)	24.8 (1.7) (N=98)	12.8 (2.6) (N=96)	12.5 (2.8) (N=95)	12.2 (2.2) (N=91)	12.8 (2.9) (N=92)	13.2 (2.0) (N=90)
Mean (SD) IOP change from screening			−7.9 (2.9)	−8.1 (2.6)	−8.3 (2.4)	−7.7 (2.8)	−7.3 (2.2)
Mean (SD) IOP change from baseline			−12.0 (2.9)	−12.3 (2.8)	−12.6 (2.4)	−11.9 (2.8)	−11.6 (2.2)

Safety

Ocular adverse events and other postoperative observations

	Stent group (N=94)	Medical therapy group (N=98)	Treatment
Eye burning	0	1% (1/98)	
IOP decompensation	1% (1/94)	0	The patient was treated with medication and the IOP was lowered from 48 mmHg to 25 mmHg.
Medication allergy	0	1% (1/98)	
1 stent not visible	1% (1/94)	0	This was treated with Nd:YAG laser to remove an apparent obstruction.
Soreness/ discomfort	1% (1/94)	0	This was treated with nonsteroidal anti-inflammatory medications.

Proportion of eyes with BCVA of 20/40 or better

	Stent group	Medical therapy group
Before the procedure	84%	87%
1 year	79%	84%

Five patients in the stent group and 9 patients in the medication group had a slight decrease in BCVA.

Vertical cup-to-disc ratio change from baseline

	1 month	3 months	6 months	9 months	1 year
2 stents (N=94)					
Better	2% (2/92)	0	0	1% (1/93)	0
No change	97% (89/92)	98% (89/91)	99% (91/92)	96% (89/93)	97% (90/93)
Worse	0	1% (1/91)	1% (1/92)	2% (2/93)	1% (1/93)
2 medications (N=98)					
Better	1% (1/94)	0	2% (2/92)	0	1% (1/89)
No change	98% (92/94)	99% (92/93)	98% (90/92)	100% (91/91)	99% (88/89)
Worse	0	0	0	0	0

Better: decrease >0.2; No change: change within ±0.2; Worse: increase >0.2.

Abbreviations used: BCVA, best corrected visual acuity; CI, confidence interval; IOP, intraocular pressure; NR, not reported; SD, standard deviation.

Study 5 Katz L J (2015)

Details

Study type	**Prospective RCT**
Country	Armenia
Recruitment period	Not reported
Study population and number	n= **119 (38×1 stent versus 41×2 stents versus 40×3 stents)** patients (eyes) with primary open-angle glaucoma not controlled on ocular hypotensive medication.
Age and sex	1-stent and 2-stent groups: Mean 68 years; 3-stent group: Mean 61 years 45% (53/118) female
Patient selection criteria	Inclusion criteria: open-angle glaucoma (pigmentary and pseudoexfoliative were allowed) not controlled on 2 preoperative medications, with preoperative medicated IOP ≥18 mmHg and ≤30 mmHg and ≥ 22 mmHg and ≤38 mmHg without medication), mild to moderate glaucomatous optic neuropathy, cup:disk ratio ≤0.9, normal angle anatomy, absence of peripheral anterior synechia, rubeosis, or other angle abnormalities that could impair proper stent placement, and a willingness to attend scheduled follow-up examinations for 5 years postoperatively. Exclusion criteria: pseudophakia with anterior-chamber intraocular lens, prior stent implantation in study eye, traumatic, uveitic, neovascular, or angle-closure glaucoma, glaucoma associated with vascular disorders, functionally significant visual field loss, prior incisional glaucoma surgery, prior selective laser trabeculoplasty within 90 days of screening, prior argon laser trabeculoplasty, iridectomy, or laser iridotomy, visual field status at risk by washout period, unmedicated IOP expected to be >38 mmHg after washout period, active corneal inflammation or oedema, clinically significant corneal dystrophy, corneal surgery of any type, corneal opacities, congenital or traumatic cataract, retinal or optic nerve disorders, elevated episcleral venous pressure, clinically significant sequelae from trauma, chronic ocular inflammatory disease, BCVA worse than 20/200, fellow eye in the trial, and pregnant or nursing women.
Technique	Patients were treated with 1, 2 or 3 istent(s). At the end of each surgical procedure, patients were prescribed topical antibiotic medication (moxifloxacin) for 1 week and corticosteroid medication (dexamethasone 0.1%) for 4 weeks, tapered from 4times per day to once a day over the 4-week period. Postoperative ocular hypotensive medication was administered for elevated IOP (IOP >18 mmHg).
Follow-up	**18 months**
Conflict of interest/source of funding	The study was sponsored by Glaukos.

Analysis

Follow-up issues:

- The evaluation schedule was postoperative days 1 and 7 and months 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60.
- Patients on postoperative medication needed to undergo annual postoperative medication-washout periods at months 12, 24, 48, and 60, then return 1 month later for clinical evaluation and reinstitution of medication if needed.
- 251 patients were screened for the study, 152 proceeded to medication washout and the baseline exam. Of the 152 subjects, 33 did not pass the baseline exam (IOP not in range after medication washout, or did not complete medication washout). The remaining qualified patients (n=119, ITT population) were randomised to 1 of the 3 groups.

Study design issues:

- Single-centre study.
- Open-label study.
- Patients who met the screening criteria were instructed to undergo a 4-week washout for prostaglandin analogues, beta-blockers, and combination medications, a 2-week washout for alpha-adrenergic agonists, and a 5-day washout for carbonic anhydrase inhibitors.
- Randomisation treatment assignments were generated using a pseudorandom number generator.
- Procedures were done by 1staff surgeon and 5 visiting surgeons at the clinical facility in Armenia.
- Postoperative examinations were conducted by the staff surgeon and investigational site staff.
- The qualifying IOP at the baseline visit was not measured on multiple days.
- The study did not examine postural considerations of IOP measurements.

Study population issues:

- The majority of eyes in both groups were phakic (97% for the 1-stent and 3-stent groups, and 100% for the 2-stent group).
- Enrolment of Caucasian population only.

Other issues: Not reported.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **119 (38 x 1 stent versus 41 x 2 stents versus 40 x 3 stents)**

% of patients with IOP reduction at 1 year versus baseline unmedicated IOP

IOP reduction	1-stent group % (n/N) (95% CI)	2-stent group % (n/N) (95% CI)	3 -stent group % (n/N) (95% CI)
≥20%	89% (33/37) (75% to 97%)	90% (37/41) (77% to 97%)	92% (35/38) (79% to 98%)
IOP ≤ 18 mmHg	89% (33/37) (75% to 97%)	90% (37/41) (77% to 97%)	92% (35/38) (79% to 98%)
IOP ≤ 15 mmHg	65% (24/37) (48% to 80%)	85% (35/41) (71% to 94%)	92% (35/38) (79% to 98%)

The analysis was done on the modified ITT population (subset of patients who did not have cataract surgery before Month 12).

Medication use within 18 months after the procedure

	1-stent group	2-stent group	3-stent group
Number of patients needing medication	18% (7/38)	10% (4/41)	8% (3/40)

93% (13/14) of patients were prescribed 1 medication and 1 patient in the 2-stent group was prescribed 2 medications.

Mean IOP (mmHg) and proportion of eyes on medications (data included for all patients who had not had secondary surgical interventions)

	Screening	Baseline washout	1 month	3 months	6 months	12 months	Months 12-13*	18 months
1-stent group								
n	38	38	38	38	38	37	37	36
Mean IOP (SD)	19.8 (1.3)	25.0 (1.1)	12.2 (3.1)	12.8 (2.3)	13.1 (1.7)	14.4 (1.2)	14.9 (1.9)	15.6 (1.5)
On medication, n (%)	100% (38/38)	0	0	3% (1/38)	8% (3/38)	11% (4/37)	0	11% (4/36)
2-stent group								
n	41	41	41	41	41	41	41	41
Mean IOP (SD)	20.1 (1.6)	25.0 (1.7)	12.5 (2.7)	13.0 (2.1)	13.5 (2.3)	12.8 (1.4)	13.6 (2.1)	13.8 (1.3)
On medication, n (%)	100% (41/41)	0	0	0	2% (1/41)	10% (4/41)	0	10% (4/41)
3-stent group								
n	40	40	40	40	40	38	38	38
Mean IOP (SD)	20.4 (1.8)	25.1 (1.9)	12.0 (2.7)	12.8 (2.0)	12.9 (2.0)	12.2 (1.5)	12.7 (2.1)	12.1 (1.2)
On medication, n (%)	100% (40/40)	0	0	0	3% (1/40)	8% (3/38)	0	8% (3/38)

*11 eyes were washed out of medication at month 12. Months 12–13 IOP = month 12 IOP for 105 eyes on no medication, and month 13 IOP for 11 eyes washed out of medication at month 12.

Mean IOP (mmHg) and change in mean IOP at 18 months versus screening and baseline examinations for available eyes without medication (for patients who had not had secondary surgical interventions).

Mean IOP and change in mean IOP at month 18	1-stent group, n=32	2-stent group, n=37	3-stent group, n=35
Mean ± SD IOP for eyes without medication	15.93±0.90	14.07±1.00	12.24±1.12
Change (%) from screening medicated IOP	−3.94 (−20%)	−5.99 (−30%)	−8.19 (−40%)
Change (%) from baseline unmedicated IOP	−9.04 (−36%)	−10.77 (−43%)	−12.61 (−51%)

Pairwise group comparisons of unmedicated IOP reduction at 18 months

- 3 stents versus 2 stents: −1.84 mmHg (95% CI 0.96 to 2.73, p<0.001)
- 2 stents versus 1 stent: −1.73 mmHg (95% CI 0.83 to 2.64, p<0.001)
- 3 stents versus 1 stent: −3.58 mmHg (95% CI 2.66 to 4.49, p<0.001)

Proportion of eyes with BCVA of 20/40 or better

	1-stent group	2-stent group	3-stent group
Before the procedure	68% (26/38)	61% (25/41)	73% (29/40)
18 months	79% (30/38)	66% (27/41)	80% (32/40)

Cup-to-disc ratio: At 18 months, mean cup-to-disc ratio values were the same as preoperative values.

Safety

Cataract progression: 3% (4/119) of patients (2 in the 1-stent and 2 in the 3-stent groups). The patients were treated with cataract surgery.

Visual field

Mean visual field (mean deviation) values at 18 months of -4.9±4.71 dB (1 stent), −5.96±5.84 dB (2 stents), and −5.24±4.13 dB (3 stents) were generally similar to preoperative values.

Abbreviations used: BCVA, best corrected visual acuity; CI, confidence interval; IOP, intraocular pressure; ITT, intent-to-treat; SD, standard deviation.

Study 6 Pfeiffer N (2015)

Details

Study type	**Prospective RCT**
Country	Germany, Spain, The Netherlands and Italy.
Recruitment period	2011-12
Study population and number	n=**100 (50 cataract surgery + stent versus 50 cataract surgery alone)** patients with open-angle glaucoma and cataract
Age and sex	Cataract surgery + stent group: Mean 73 years; cataract surgery alone group: Mean 72 years 51% (51/100) female
Patient selection criteria	Inclusion criteria: concurrent cataract and open-angle glaucoma. Only 1 eye per patient was eligible for treatment, IOP of 24 mmHg or less with no more than 4 hypotensive medications, Shaffer grade III or IV chamber angle in all quadrants, and Humphrey visual field changes characteristic of glaucoma or glaucomatous optic nerve damage confirmed by ophthalmoscopy and nerve fibre layer imaging. Glaucoma severity was limited to patients considered capable of safely undergoing medication washout. After the washout, the diurnal IOP had to be between 21 and 36 mmHg. Exclusion criteria: angle-closure glaucoma, secondary glaucomas except pseudoexfoliation or pigment dispersion syndromes, exudative age-related macular degeneration ,proliferative diabetic retinopathy, or significant risk of glaucomatous vision loss because of washout of IOP-lowering medications, narrow angle or other angle abnormality visible on gonioscopy, central corneal thickness of less than 480 mm or more than 620 mm, or clinically significant corneal dystrophy, patients with prior corneal surgery, argon laser trabeculoplasty, cycloablation, or any incisional glaucoma procedure, such as trabeculectomy, tube shunts, deep sclerectomy, or canaloplasty.
Technique	Patients received preoperative medications according to the standard practice of each site for cataract surgery. All patients were treated with cataract surgery with phacoemulsification through a clear corneal or limbal incision. Miotics were administered at the surgeon's discretion. The stent delivery cannula was inserted through the same incision used for the cataract surgery or through a 1- to 1.5-mm secondary incision when the view of the anterior chamber angle was not optimal or if the target implantation site could not be accessed with the cataract incisions. Postoperative care included a topical antibiotic for 4 to 7 days and a tapering dose of a topical corticosteroid for up to 4 weeks. The type of stent used in the combined group was Hydrus.
Follow-up	**2 years**
Conflict of interest/source of funding	Ivantis funded the study.

Analysis

Follow-up issues:

- Follow-up examinations were conducted per protocol at 1 day, 1 week, and 1, 3, 6, 12, 18, and 24 months. Interim visits were conducted at any time at the discretion of the treating physician.
- Ocular hypotensive medications could be reintroduced if follow-up IOP exceeded 19 mmHg or at any IOP level with evidence of progression of optic nerve damage or visual field loss. For patients taking hypotensive medications at 12 and 24 months, a safety visit was conducted with IOP measurement before instructing the patient to cease hypotensive medications in the study eye, and the diurnal IOP was measured according to the same washout schedule as the baseline visit.
- Before the 12-month visit, 2 patients from the stent + cataract surgery group and 1 patient from the cataract surgery only group exited the study for none health-related reasons, for a 12-month patient accountability rate of 97% (97/100). Between 12 and 24 months,4 additional patients exited from the study: 1 patient died of cardiac disease, 1 patient developed lung cancer, 1 declined further participation after secondary glaucoma surgery, and 1 patient was lost to follow-up, all in the cataract surgery only group, for a 24-month accountability rate of 93% (93/100).
- Total number of evaluable washed out patients: 93% (90/97) at 12 months and 87% (78/90) at 24 months.

Study design issues:

- Single-masked study conducted at 7 European sites. Patients remained masked to treatment assignment for the course of the study.
- Patients were assigned randomly in a 1:1 ratio according to a computer-generated listing just before surgery to undergo either cataract surgery (phacoemulsification and intraocular lens implantation) with microstent or cataract surgery alone.
- Before surgery, patients were washed out of all hypotensive medications in the study eye for a variable period, depending on the class of medication in use at the time of screening.

Study population issues:

- Study population almost completely white.
- Statistically significant differences in baseline characteristics:
    - Visual field mean deviation (±SD): −5.6±5.4 (Stent+cataract surgery) versus −8.4±7.8 (cataract surgery alone), p=0.0449.
    - Use of carbonic anhydrase inhibitor: 28% (14/50) versus 52% (26/50), p=0.0242.

Other issues: None reported.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **100 (50 cataract surgery + stent versus 50 cataract surgery alone)**

Successful stent implantation rate: 96% (48/50)

- The microstent was implanted in the nasal hemisphere in 90% (43/48) of patients and in the inferior temporal quadrant in 10% (5/48) of patients.
- One of the unsuccessful implantation was the result of excessive eye movement possibly related to inadequate anaesthesia. The second unsuccessful implantation was the result of hyphema, which led to an obscured gonioscopic view, precluding a second attempt. Both of these patients were followed up for the duration of the study and remained in the intention-to-treat population.

Proportion of patients with a minimum of 20% reduction in mean washed out diurnal IOP* compared with baseline

Follow-up	Stent + CS group	CS group	p value
12-month	88%	74%	NS
24-month	80% (40/50)	46% (23/50)	0.0008

* Diurnal IOP value was obtained by averaging 3 Goldmann tonometry measurements obtained 4 hours apart between 8am and 4pm. The tonometry protocol used a 2-person system (an observer and a reader), and 2 readings were obtained at each time point during the day. If the difference in the 2 measurements was more than 2 mmHg, a third measurement was obtained. The average of 2 measurements or the median value of 3 was used for the time point, and the average of the IOP measurements at all 3 time points was the mean DIOP.

Washed out mean (±SD) diurnal IOP through 2-year follow-up (mmHg)

Follow-up	Stent + CS group	CS group	p value
Baseline	26.3 (n=50)	26.6 (n=50)	NS
12-month	16.6±2.8 (n=46)	17.4±3.7 (n=44)	NS
24-month	16.9±3.3 (n=44)	19.2±4.7 (n=34)	0.0093

Medication use at 24 months

	Stent + CS group	CS group	p value
Mean medications per patient	0.5±1.0	1.0±1.0	0.0189
% patients using 2 or more medications	15%	27%	0.1996
% medication-free patients	73%	38%	0.0008

BCVA

- It decreased by 2 lines in 2 patients in the stent+cataract surgery group, but resolved by 1 month.
- There were no significant differences in BCVA between groups throughout the remainder of follow-up.
- Most patients in both groups showed an increase in BCVA of 2 lines or more, although there was 1 patient with persistent BCVA loss of more than 2 lines in the cataract surgery group.
- By 3 months, BCVA was 20/40 or better in 96% of stent plus cataract surgery patients and in 90% of cataract surgery patients.

Safety

Descemet folds were noted in 1 patient at 1 month in each group. They both resolved by the 3-month visit.

Secondary glaucoma surgery during 2nd year of follow-up

- Stent + cataract surgery group: 1/50
- Cataract surgery only group : 2/50

Adverse events at year 1 and year 2

	Year 1			Year 2		
	Stent + CS group	CS group	p value	Stent + CS group	CS group	p value
IOP spike (>10 mmHg more than baseline)	4% (2/50)	4% (2/50)	1	0	0	-
Macular oedema	2% (1/50)	4% (2/50)	1	0	0	-
Vitreomacular traction	0	2% (1/50)	1	2% (1/48)	0	0.49
Focal peripheral anterior synechiae	12% (6/50)	2% (1/50)	0.1117	19% (9/48)	2% (1/50)	0.0077
Optic disc haemorrhage	2% (1/50)	0	1	0	0	-

Abbreviations used: BCVA, best corrected visual acuity; CS, cataract surgery; IOP, intraocular pressure; NS, not statistically significant; SD, standard deviation.

Study 7 Fea A M (2015)

Details

Study type	**Prospective RCT**
Country	Italy
Recruitment period	Not reported
Study population and number	n= **36 (12 cataract surgery + stent versus 24 cataract surgery alone)** patients with primary open-angle glaucoma and cataract.
Age and sex	Age and gender not reported
Patient selection criteria	Inclusion criteria: IOP of more than 18 mmHg in 3 different visits while using at least 1 ocular hypotensive medication and a corrected distance visual acuity worse than 20/80. Exclusion criteria: glaucoma other than primary open-angle glaucoma, cloudy cornea, potentially inhibiting gonioscopic view of the angle, peripheral anterior synechiae, prior ocular surgery, diabetic retinopathy, and age-related macular degeneration.
Technique	All patients had standard clear corneal phacoemulsification with intraocular lens implantation. The stent group was treated with 1 Istent after intraocular lens implantation.
Follow-up	**4 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- 67% (24/36) of patients (10 versus 14) were available for 4-year follow-up assessment. 5 patients died, 5 were lost to follow-up, 1 refused washout, and 1 could not travel to the clinic.
- The patients available for long-term follow-up undertook an initial long-term evaluation before discontinuing ocular hypotensive medication and were told to return 1 month later for an unmedicated assessment (washout evaluation).

Study design issues:

- After the first 12 months patients were referred back to their ophthalmologists, so IOP-lowering medications were not prescribed based on a standardised protocol.

Study population issues: Not reported.
Other issues: Not reported.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 36 (12 cataract surgery + stent versus 24 cataract surgery alone)

Mean IOP (mmHg) by visit
<table>
<tr><td></td><td>Baseline</td><td>12 months</td><td>12 months washout</td><td>48 months</td><td>48 months washout</td></tr>
<tr><td>Stent group (SD)</td><td>17.8 (2.7)</td><td>14.7 (1.3)</td><td>16.1 (2)</td><td>15.9 (2.3)</td><td>17.5 (2.3)</td></tr>
<tr><td>Control group (SD)</td><td>16.7 (3)</td><td>15.6 (1.1)</td><td>18.4 (3.1)</td><td>17 (2.5)</td><td>20.4 (3.2)</td></tr>
<tr><td>p value for the difference between groups</td><td>NS</td><td></td><td>0.05</td><td>NS</td><td>0.02</td></tr>
</table>
Ocular hypotensive medications by visit (mean values)
<table>
<tr><td></td><td>Baseline</td><td>12 months</td><td>p value (12 months vs baseline)</td><td>48 months</td><td>p value (48 months vs baseline)</td></tr>
<tr><td>Stent group (SD)</td><td>1.9 (0.9)</td><td>0.4 (0.7)</td><td>0.003</td><td>0.5 (0.8)</td><td>0.005</td></tr>
<tr><td>Control group (SD)</td><td>1.8 (0.7)</td><td>1 (1.1)</td><td>0.01</td><td>0.9 (1)</td><td>0.01</td></tr>
</table>
No statistically significant difference between groups at any visit.

Visual acuity
The majority of patients had an improvement of UDVA and CDVA after phacoemulsification and intraocular lens implantation.</td><td>No postoperative stent-related adverse events were observed through 48 months.

No secondary surgical intervention was required to control IOP throughout the entire follow-up period.</td></tr>
<tr><td colspan="2">Abbreviations used: CDVA, corrected distance visual acuity; IOP, intraocular pressure; NS, not statistically significant; SD, standard deviation; UDVA, uncorrected distance visual acuity.</td></tr>
</table>

Study 8 Arriola-Villalobos PA (2012)

Details

Study type	**Prospective case series**
Country	Spain
Recruitment period	Not reported
Study population and number	n= **19** patients with primary open-angle, pigmentary or pseudoexfoliative glaucoma and cataract.
Age and sex	Mean 75 years; 53% (10/19) female
Patient selection criteria	Inclusion criteria: prior diagnosis of mild or moderate open-angle glaucoma (including pseudoexfoliative or pigmentary glaucoma) with an IOP above 18 mmHg (as measured at the last 2 consecutive visits) and the use of 1 or more pressure lowering medications, a concurrent diagnosis of cataract with a preoperative BCVA no better than 0.5, age 18 years or older and a scleral spur visible on gonioscopy. The patients were also required to understand the information given to provide their consent for the procedure and to express a willingness to attend scheduled follow-up visits for at least 3 years. Exclusion criteria: patients with any type of glaucoma other than primary open-angle, pseudoexfoliative or pigmentary, cloudy corneas likely to impair gonioscopic observation of the nasal angle, peripheral anterior synechiae, prior eye surgery, prior trauma or ocular surface disease, as well as a history of any significant ocular condition that could interfere with the tests required. Patients with demonstrated elevated episcleral venous pressure, active thyroid orbitopathy, carotid-cavernous fistula, Sturge–Weber syndrome and orbital tumours or orbital congestive disease.
Technique	• Standard clear corneal phacoemulsification with foldable acrylic intraocular lens implantation was conducted under topical anaesthesia (oxybuprocaine 0.40% plus tetracaine 0.10%, Alcon Cusi). A single iStent was then implanted through the clear corneal incision placed for phacoemulsification. • Postoperative care included antibiotic (tobramycin 0.3%) plus steroid (dexamethasone 0.1%) eye drops 5 times a day for 1 week with tapering of the dose for a further 3 weeks. Antiglaucoma topical therapy was introduced after the procedure if the desired target IOP range, as judged by the investigator, was not achieved.
Follow-up	**Mean 54 months**
Conflict of interest/source of funding	The authors have no commercial or proprietary interest in any of the products or companies mentioned in this article. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. One of the authors is a consultant to Glaukos Corporation.

Analysis

Follow-up issues:

- Follow-up visits were scheduled for day 1, week 1, months 1 and 3 and years 1, 2, 3, 4 and 5.
- All the patients included in this study completed at least 3 years of follow-up.
- 84% (16/19) of patients completed 4 years of follow-up and 68% (13/19) of patients completed the full 5 years. The other patients could not complete the required visits for logistic reasons (n=1), mortality (n=3) and other reasons.

Study design issues:

- There was no washout of ocular hypotensive medications before surgery. After surgery, patients had to discontinue all previous glaucoma medications.
- All surgical procedures were performed by 2 of the authors.
- The patients included in the study were the first to be treated by this procedure at this centre meaning that the surgeons were at an early stage in the learning curve.

Study population issues:

- All patients were white.
- 79% (15/19) of patients had primary open-angle glaucoma, 10.5% had pigmentary glaucoma and 10.5% had pseudoexfoliative glaucoma.

Other issues: Not reported.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **19**

Surgery

- The stent was successfully implanted in all eyes.
- In 2 patients the applicator had to be replaced after an initial attempt.
- Implantation was successful after 1 or 2 attempts in 94% (18/19) of the patients. In the remaining patient, 3 attempts were needed to implant the stent.

Mean IOP (mmHg) by visit

	Before the procedure	24 hours	1 week	1 month	3 months	1 year	2 years	3 years	4 years	5 years	Final
Mean IOP ±SE	19.42 ±1.89	19.84	17.16	17.37	14.39	17.28	16.11	15.94	16.46	16.08 ±4.25	16.26 ±4.23

Statistically significant reduction in IOP between final follow-up and baseline, p=0.002.

- By the end of follow-up, 68% (13/19) of patients showed an IOP≤18 mm Hg and 89% (17/19) of patients an IOP≤21 mm Hg, including medicated patients.
- Among the patients under no medication, 32% (6/19) of patients achieved an IOP≤18 mm Hg and 42% (8/19) of patients an IOP≤21 mm Hg at the end of the follow-up.

Antiglaucoma medications

	Before the procedure	24 hours	1 week	1 month	3 months	1 year	2 years	3 years	4 years	5 years	Final
Mean number of antiglaucoma medications ±SE	1.32 ±0.48	0.11	0.05	0.05	0.11	0.17	0.32	0.56	0.5	1.15 ±0.48	0.84 ±0.89

Statistically significant reduction in number of antiglaucoma medications between final follow-up and baseline, p=0.046.

42% (8/19) of patients did not need any hypotensive medication by the end of follow-up**.**

Visual acuity

BCVA was statistically significantly improved, increasing from 0.29±0.13 before the procedure to 0.62±0.3 at the end of follow-up (p<0.001).

Safety

Stent malposition: 21% (4/19)
None of them required re-intervention.

Stent occlusion: 11% (2/19)
The stents were partially occluded by peripheral anterior synechiae; these patients received no treatment.

In these 6 patients, the stent was functional since a satisfactory drop in IOP was produced.

Loss of visual acuity: 1/19

This was caused by macular degeneration.

Transient IOP elevation to more than 30 mm Hg: 21% (4/19) at 1-day follow-up.

In these patients, IOP was checked 1 day later and only in 1 patient temporary topical treatment was required (2 drugs). Normal pressures were recovered in all 4 eyes in the 1-week visit.

Abbreviations used: BCVA, best corrected visual acuity; IOP, intraocular pressure; SE, standard error.

Efficacy

Intraocular pressure (IOP)

In a systematic review and meta-analysis of 2,143 patients from 32 studies, comparing stent insertion combined with phacoemulsification against phacoemulsification alone in patients with glaucoma and cataract, there was a statistically significant decrease in intraocular pressure (IOP) from baseline in the combined group compared against the phacoemulsification-only group at a follow-up of 12 to 58 months (standardised mean deviation [SMD] −0.46, 95% confidence interval [CI] −0.87 to −0.06, n=4 RCTs, I^2=47%, p=0.128). There was a 9% weighted mean IOP reduction from baseline after insertion of 1 stent combined with phacoemulsification (based on 3 RCTs), a 27% weighted mean IOP reduction from baseline after insertion of 2 stents combined with phacoemulsification (based on 1 RCT) and a 5% weighted mean IOP reduction from baseline after phacoemulsification alone (based on 3 RCTs).[1]

In a systematic review and meta-analysis of 248 patients (n=5 studies) with mild to moderate glaucoma treated by stent insertion alone, there was a statistically significant reduction in IOP from baseline after implantation of 1 stent at a follow-up of 6 to 18 months (SMD −1.95, 95% CI −3.41 to −0.49, n= 3 studies; I^2=96%, p=0.000) and of 3 stents at 6-month follow-up (SMD -4.26, 95% CI −5.18 to −3.33, n=1 study). But there was not a statistically significant reduction in IOP from baseline after implantation of 2 stents at 6 to 12 months (SMD −3.08, 95% CI −6.90 to 0.74, n=2 studies; I^2=98%, p=0.000). In the same study there was a 22% reduction in IOP from baseline after 1-stent insertion at 18-month follow-up (n=1 study), and at 6-month follow-up there was a 30% reduction in IOP after 2-stent implantation (n=2 studies) and a 41% reduction after 3-stent insertion (n=1 study).[2]

In an RCT of 239 patients comparing stent insertion combined with phacoemulsification (n=116) with phacoemulsification alone (n=123) in patients with open-angle glaucoma not controlled on 1 medication, there was statistically significantly more patients with an IOP of 21 mmHg or less without medication 2 years after the procedure in the combined group (61% [71/116] compared with 50% [61/123], p=0.036 for the difference between groups). In the same study, an IOP reduction of 20% or more without medication was reported in 53% (61/116) of patients in the combined group and in 44% (54/123) of patients in the phacoemulsification-only group at 2 years (p=0.09 for the difference between groups). Mean IOP (± standard deviation, SD, mmHg) in the consistent cohort (defined as all eyes with IOP and ocular hypotensive medication data which did not have secondary surgery that may confound the results) was 18.6±3.4 at screening, 25.4±3.6 after medication washout, 17.0±2.8 at 12 months and 17.1±2.9 at 24 months in the combined group (n=98). In the phacoemulsification-only group (n=101), mean IOP (±SD, mmHg) was 17.9±3.0 at screening, 25.2±3.6 after medication washout, 17.0±3.1 at 12 months and 17.8±3.3 at 24 months.[3]

In an RCT of 192 patients comparing implantation of 2 stents (n=94) with medical therapy (n=98) in patients with open-angle glaucoma not controlled on 1 medication, there was statistically significantly more patients with an IOP reduction of 50% or more at 1 year versus baseline unmedicated IOP in the stent group than in the medical therapy group: 53%, 95% CI 43% to 64% compared with 36%, 95% CI 26% to 46%, p=0.02. In the same study, the proportion of patients with IOP of 18 mmHg or less at 1 year was 93%, 95% CI 85% to 97% in the stent group and 90%, 95% CI 82% to 95% in the medical therapy group (level of statistical significance not reported). The mean (±SD) IOP values in the stent group were 21.1±1.7 mmHg at screening, 25.2±1.4 mmHg at baseline washout and 13.0±2.3 mmHg at 1 year (−8.1±2.6 mmHg from screening); in the medical therapy group, they were 20.7±1.78 mmHg at screening, 24.8±1.7 mmHg at baseline washout and 13.2±2.0 mmHg at 1 year (−7.3±2.2 mmHg from screening).[4]

In an RCT of 119 patients comparing implantation of 1 stent (n=38) with implantation of 2 stents (n=41) or 3 stents (n=40) in patients with primary open-angle glaucoma not controlled on ocular hypotensive medication, the rates of patients with 20% reduction or more in IOP at 1 year versus baseline unmedicated IOP were 89% (33/37), 95% CI 75% to 97% in the 1-stent group, 90% (37/41), 95% CI 77% to 97% in the 2-stent group and 92% (35/38), 95% CI 79% to 98% in the 3–stent group. The values were identical for the rates of patients with IOP of 18mmHg or less at 1 year. Mean IOP values (±SD) at 18 months were 15.6±1.5 mmHg for patients in the 1-stent group, 13.8±1.3 mmHg in the 2-stent group and 12.1±1.2 mmHg in the 3-stent group (data from all patients who had not had secondary surgical interventions). Changes in mean IOP at 18 months versus screening medicated IOP and baseline unmedicated IOP for patients without medication who had not had secondary surgical interventions were −3.94 mmHg (−20%) and −9.04 mmHg (−36%) in the 1-stent group, −5.99 mmHg (−30%) and −10.77 mmHg (−43%) in the 2-stent group, and −8.19 mmHg (40%) and 12.61 mmHg (−51%) in the 3-stent group. The mean unmedicated IOP reduction was statistically significantly greater with 3 stents compared with 1 stent (3.58 mmHg, 95% CI 2.66 to 4.49 mmHg, p<0.001) or 2 stents (−1.84 mmHg, 95% CI 0.96 to 2.73 mmHg, p<0.001); it was also statistically significantly greater with 2 stents than with 1 stent (−1.73 mmHg, 95% CI 0.83 to 2.64 mmHg, p<0.001).[5]

In an RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) and phacoemulsification alone (n=50) in patients with open-angle glaucoma and cataract, the rates of patients with a minimum of 20% reduction in mean washed out diurnal IOP compared with baseline were statistically significantly higher in the combined group at 24 months (80% [40/50] versus 46% [23/50], p=0.0008). At 12 months, the rates were 88% in the combined group compared with 74% in the cataract surgery only group (p value not statistically significant). The mean washed out diurnal IOP (±SD) was statistically significantly higher in the combined group than in the cataract surgery

group at 2 years (16.9±3.3 mmHg, n=44 compared with 19.2±4.7 mmHg, n=34; p=0.0093).[6]

In an RCT of 36 patients comparing stent insertion combined with cataract surgery (n=12) and cataract surgery alone (n=24) in patients with open-angle glaucoma and cataract, the mean IOP± SD (mmHg) values were 17.8±2.7 in the combined group and 16.7±3 in the cataract surgery only group before the procedure (medicated values, p value not statistically significant); 48 months after the procedure (after washout), the mean IOP± SD (mmHg) values were 17.5±2.3 in the combined group and 20.4±3.2 in the cataract surgery only group (p=0.02).[7]

In a prospective case series of 19 patients with primary open-angle, pigmentary or pseudoexfoliative glaucoma and cataract treated with stent implantation and phacoemulsification, there was a statistically significant decrease in the mean IOP ± standard error (SE) from 19.42 ±1.89 mmHg before the procedure to 16.26 ±4.23 mmHg at final follow-up (mean 54 months, p=0.002). By the end of follow-up, the IOP was18 mmHg or less in 68% (13/19) of patients and 21 mm Hg or less in 89% (17/19) of patients, including medicated patients. Among the patients under no medication, the IOP was18 mm Hg or less in 32% (6/19) of patients and 21 mm Hg or less in 42% (8/19) of patients at the end of follow-up.[8]

Medication use

In the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone, there was a statistically significant reduction in the number of topical glaucoma medications used after the procedure in the combined group compared against the phacoemulsification-only group (SMD −0.65, 95% CI −1.18 to −0.12, n=3 studies; I^2 =58%, p=0.092). There was a weighted mean reduction in topical glaucoma medications per patient of 1.33 from baseline after insertion of 1 stent combined with phacoemulsification (n=3 RCTs), of 1.1 from baseline after insertion of 2 stents combined with phacoemulsification (n=1 RCT) and of 1.01 after phacoemulsification alone (n=3 RCTs).[1]

In the systematic review and meta-analysis of 248 patients treated with stent insertion alone, there was a statistically significant reduction in the number of topical glaucoma medication use from baseline after implantation of 1 stent (−1.68, 95% CI −2.74 to −0.61, n= 3 studies; I^2=94%, p=0.000), 2 stents (−1.98, 95% CI −2.39 to −1.57, n=2 studies; I^2=0%, p=0.944) and 3 stents (−2.00, 95% CI −2.62 to −1.38, n=1 study). In the same study, there was a mean reduction of 1.2 bottles per patient of glaucoma medications from baseline after 1-stent insertion at 18 months (n=1 study), of 1.45 bottles after 2-stent implantation at 6 months (n=2 studies) and of 1 bottle after 3-stent insertion at 6 months (n=1 study). [2]

In the RCT of 239 patients comparing stent insertion combined with phacoemulsification (n=116) with phacoemulsification alone (n=123), there was

statistically significantly less ocular hypotensive medications (mean ±SD) used at 12 months in the combined group of the consistent cohort (0.2±0.6) than in the phacoemulsification-only group of the consistent cohort (0.4±0.7), p=0.011 for the difference between groups. At 24 months, the mean number of ocular hypotensive medications used in the consistent cohort was 0.3±0.6 (combined group) compared with 0.5±0.7 (phacoemulsification-only group) and the difference between groups was no longer statistically significant. [3]

In the RCT of 119 patients comparing implantation of 1 stent (n=38) with implantation of 2 stents (n=41) or 3 stents (n=40), 18% (7/38) of patients in the 1-stent group, 10% (4/41) of patients in the 2-stent group and 8% (3/40) of patients in the 3-stent group needed medication 18 months after the procedure; 93% (13/14) of patients were prescribed 1 medication and 1 patient in the 2-stent group was prescribed 2 medications. [5]

In the RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) to phacoemulsification alone (n=50), there was statistically significantly less medication use per patient at 24 months in the combined group than in the cataract surgery only group (0.5±1.0 versus 1.0±1.0, p=0.0189). The rate of patients without medication at 24 months was also statistically significantly higher in the combined group (73% compared with 38%, p=0.0008). The rates of patients using 2 or more medications were 15% in the combined group and 27% in the cataract surgery only group (p=0.1996). [6]

In the RCT of 36 patients comparing stent insertion combined with cataract surgery (n=12) and cataract surgery alone (n=24), there was a statistically significant decrease in the mean ± SD number of ocular hypotensive medications used in both groups from 1.9±0.9 before the procedure to 0.5±0.8 at 48 months in the combined group (p=0.005) and from 1.8±0.7 to 0.9±1 in the cataract surgery only group (p=0.01). [7]

In the prospective case series of 19 patients treated with stent implantation and phacoemulsification, there was a statistically significant decrease in the mean number of antiglaucoma medications used ± SE from 1.32 ±0.48 before the procedure to 0.84 ±0.89 at final follow-up (mean 54 months, p=0.046). By the end of follow-up, 42% (8/19) of patients did not need any hypotensive medication. [8]

Visual acuity

In the RCT of 239 patients comparing stent insertion combined with phacoemulsification (n=116) against phacoemulsification alone (n=123) in patients with open-angle glaucoma not controlled on 1 medication, the proportions of eyes with CDVA of 20/40 or better in the combined group were 45% (49 eyes) before the procedure and 94% (99 eyes) at 12-month follow-up. In the phacoemulsification-only group, the proportions were 44% (53 eyes) before the procedure and 90% (101 eyes) 12 months after the procedure. [3]

In the RCT of 192 patients comparing implantation of 2 stents (n=94) against medical therapy (n=98), the proportions of eyes with BCVA of 20/40 or better in the stent group were 84% before the procedure and 79% at 12-month follow-up. In the medical therapy group, the proportions were 87% before the procedure and 84% at 12-month follow-up. Five patients in the stent group and 9 patients in the medication group experienced a slight decrease in BCVA.[4]

In the RCT of 119 patients comparing implantation of 1 stent (n=38) with implantation of 2 stents (n=41) or 3 stents (n=40), the proportions of eyes with BCVA of 20/40 or better were 68% (26/38) before the procedure and 79% (30/38) at 18 months in the 1-stent group, 61% (25/41) and 66% (27/41) in the 2-stent group, and 73% (29/40) and 80% (32/40) in the 3-stent group. [5]

In the RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) to phacoemulsification alone (n=50), BCVA was 20/40 or better in 96% of patients in the combined group and in 90% of cataract surgery only patients within 3 months of the procedure.[6]

In the prospective case series of 19 patients treated with stent implantation and phacoemulsification, there was a statistically significant increase in BCVA from 0.29±0.13 before the procedure to 0.62±0.3 at final follow-up (mean 54 months, $p<0.001$).[8]

Vertical cup-to-disc ratio

In the RCT of 192 patients comparing implantation of 2 stents (n=94) against medical therapy (n=98), the vertical cup-to-disc ratio had not changed from baseline (change within ±0.2) in 97% (90/93) of patients in the stent group at 1-year follow-up, and was worse than baseline (increase of more than 0.2) in 1 patient (n=93). In the medication group, the vertical cup-to-disc ratio had not changed from baseline in 99% (88/89) of patients in the stent group at 1-year follow-up and was better than baseline (decrease of more than 0.2) in 1 patient (n=89).[4]

In the RCT of 119 patients comparing implantation of 1 stent (n=38) against implantation of 2 stents (n=41) or 3 stents (n=40), the mean cup-to-disc ratios at 18-month follow-up were the same as preoperative values.[5]

Successful stent implantation

In the RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) against phacoemulsification alone (n=50) in patients with open-angle glaucoma and cataract, the successful stent implantation rate was 96% (48/50). One of the unsuccessful implantation was the result of

excessive eye movement possibly related to inadequate anaesthesia; the second unsuccessful implantation was the result of hyphema, which led to an obscured gonioscopic view, precluding a second attempt.[6]

In the prospective case series of 19 patients treated by stent implantation and phacoemulsification, the stent was successfully implanted in all eyes (19/19). [8]

Safety

Loss of visual acuity

Severe loss of corrected distance visual acuity (CDVA) was reported in 1 patient each in the combined group and in the phacoemulsification-only group in a randomised controlled trial (RCT) of 239 patients with open-angle glaucoma not controlled on 1 medication comparing stent insertion combined with phacoemulsification (n=116) against phacoemulsification alone (n=123). In the combined group, the loss of CDVA occurred after a stroke; in the phacoemulsification-only group, it occurred after macular traction, macular hole and macular oedema treated with vitrectomy. In the same study, CDVA worse than 20/40 was reported in 7 eyes in the combined group and in 9 eyes in the phacoemulsification group at 24-month follow-up. The causes reported were onset or progression of macular disease (n=6), posterior capsule opacification (n=2) and dry eye (n=2). Blurry vision or visual disturbance were also reported in 3% (4/116) of eyes in the combined group and in 7% (8/117) of eyes in the phacoemulsification-only group. [3]

Loss of visual acuity was reported in 1 patient in the prospective case series of 19 patients with primary open-angle, pigmentary or pseudoexfoliative glaucoma and cataract treated with stent implantation and phacoemulsification; this was caused by macular degeneration. [8]

Elevation of intraocular pressure (IOP)

Increase in intraocular pressure (IOP) above 10 mmHg after the procedure was reported in 48% of patients in the combined group of 1 of the 32 studies included in a systematic review and meta-analysis of 2,143 patients with glaucoma and cataract comparing stent insertion combined with phacoemulsification against phacoemulsification alone. In the same systematic review, rise in IOP above 30 mmHg after the procedure was reported in 15% of patients in the combined group in 1 of the studies.[1]

Elevated IOP was reported in 10% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated by stent insertion alone.[2]

Elevated IOP was reported in 4% (5/116) of eyes in the combined group and in 7% (8/117) of eyes in the phacoemulsification-only group in the RCT of 239 patients comparing stent insertion combined with phacoemulsification with

phacoemulsification alone within 24 months of follow-up. Among these patients, 1 patient in the combined group and 3 patients in the phacoemulsification-only group needed treatment with oral or intravenous medications or surgical intervention. [3]

IOP decompensation was reported in 1 patient in the stent group in an RCT of 192 patients comparing implantation of 2 stents (n=94) with medical therapy (n=98) in patients with open-angle glaucoma not controlled on 1 medication; the patient was treated with medication and the IOP was lowered from 48 mmHg to 25 mmHg.[4]

IOP spike (10 mmHg more than baseline) was reported in 4% (2/50) of patients in each group of an RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) to phacoemulsification alone (n=50) in patients with open-angle glaucoma and cataract, during the first year of follow-up. [6]

Transient IOP elevation to more than 30 mm Hg was reported in 21% (4/19) of patients at 1-day follow-up in the prospective case series of 19 patients treated with stent implantation and phacoemulsification; in these patients, IOP was checked 1 day later and only in 1 patient temporary topical treatment was needed. Normal pressures were recovered in all 4 eyes in the 1-week visit.[8]

Macular oedema

Cystoid macular oedema was reported in 1% of patients in the combined group of 1 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone.[1]

Macular oedema was reported in 2% (1/50) of patients in the combined group and in 4% (2/50) of patients in the phacoemulsification-only group in the RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) against phacoemulsification alone (n=50), during the first year of follow-up. [6]

Optic disc haemorrhage

Optic disc haemorrhage was reported in 1% (1/116) of eyes in the combined group and in 3% (3/117) of eyes in the phacoemulsification group in the RCT of 239 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone within 24 months of follow-up. [3]

Optic disc haemorrhage was reported in 1 patient in the combined group in the RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) against phacoemulsification alone (n=50), during the first year of follow-up. [6]

Hyphema

Hyphema was reported in 2% to 4% of patients in 3 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone.[1]

Hyphema was reported in 3% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated with stent insertion alone.[2]

Subconjunctival haemorrhage

Subconjunctival haemorrhage was reported in 2% of patients in the combined group in 1 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone.[1]

Subconjunctival haemorrhage was reported in 1% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated by stent insertion alone.[2]

Hypotony/anterior chamber collapse

Hypotony was reported in 3% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated with stent insertion alone.[2]

Anterior chamber collapse was reported in 2% of patients in the combined group in 1 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone.[1]

Intraocular inflammation

Intraocular inflammation was reported in 1% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated by stent insertion alone.[2]

Cataract progression

Cataract progression was reported in 3% (4/119) of patients (2 in the 1-stent group and 2 in the 3-stent group) in an RCT comparing implantation of 1 stent (n=38) against implantation of 2 stents (n=41) or 3 stents (n=40) in patients with primary open-angle glaucoma not controlled on ocular hypotensive medication; the patients were treated by cataract surgery.[5]

Synechiae

Goniosynechiae were reported in 1% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated by stent insertion alone.[2]

Iris synechiae were reported in 1% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated by stent insertion alone.[2]

Focal peripheral anterior synechiae were reported in 30% (15/50) of patients in the combined group and in 4% (2/50) of patients in the phacoemulsification-only group in the RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) against phacoemulsification alone (n=50), within 2 years of follow-up. [6]

Vitreous wick incarcerated in paracentesis

Vitreous wick incarcerated in paracentesis was reported in 2% of patients in the combined group in 1 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone.[1]

Vitreomacular traction

Vitreomacular traction was reported in 2% (1/50) of patients in each group in the RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) against phacoemulsification alone (n=50), within 2 years of the procedure. [6]

Posterior capsule opacification

Posterior capsule opacification was reported in 3% of patients in the combined group of 1 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone.[1]

Posterior capsule opacification was reported in 1% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated by stent insertion alone.[2]

Posterior capsule opacification was reported in 6% (7/116) of eyes in the combined group and in 10% (12/117) of eyes in the phacoemulsification group in the RCT of 239 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone within 24 months of the procedure. [3]

Epiretinal membrane

Epiretinal membrane was reported in 2% of patients in the combined group in 1 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone.[1]

Changes in the iris

Iris atrophy was reported in 2% of patients in the combined group in 1 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone.[1]

Uveitis

Uveitis (iritis) was reported in 2% of patients in the combined group in 1 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification to phacoemulsification alone.[1]

Iritis was reported in 1 (n=116) eye in the combined group and in 5% (6/117) of eyes in the phacoemulsification-only group in the RCT of 239 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone within 24 months of follow-up. [3]

Eye discomfort

Dry eye was reported in 2% of patients in the combined group in 1 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone.[1]

Soreness or discomfort was reported in 1 patient in the RCT of 192 patients comparing implantation of 2 stents (n=94) against medical therapy (n=98); this was treated with nonsteroidal anti-inflammatory medications.[4]

Descemet folds

Descemet folds were reported in 1 patient in each group at 1-month follow-up in the RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) against phacoemulsification alone (n=50); they resolved before the 3-month follow-up visit.[6]

Stent-related issues

Stent malposition

Stent malposition was reported in 2 to 18% of patients in 6 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification to phacoemulsification alone.[1]

Stent malposition was reported in 1% to 15% of patients from 2 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated with stent insertion alone.[2]

Stent malposition was reported in1 patient during the procedure in the RCT of 239 patients comparing stent insertion combined with phacoemulsification (n=116) with phacoemulsification alone (n=123); a second stent was inserted, with no effect on clinical outcome. In the same study, stent malposition within 24 months of follow-up was reported in 3% (3/116) of patients in the combined group. [3]

Stent malposition was reported in 21% (4/19) of patients in the prospective case series of 19 patients treated with stent implantation and phacoemulsification; re-intervention was not needed in any of the patients. [8]

Stent reposition

A need to reposition the stent was reported in 2% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated by stent insertion alone.[2]

Stent occlusion

Stent occlusion was reported in 4 to 15% of patients in 4 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification with phacoemulsification alone.[1]

Stent obstruction was reported in 3% of patients from 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated with stent insertion alone.[2]

Stent obstruction was reported in 4% (5/116) of patients in the combined group in the RCT of 239 patients comparing stent insertion combined with phacoemulsification with phacoemulsification alone within 24 months of follow-up. [3]

Stent obstruction was reported in 1 patient in the RCT of 192 patients comparing implantation of 2 stents (n=94) with medical therapy (n=98); this was treated with Nd:YAG laser. [4]

Stent occlusion was reported in 11% (2/19) of patients in the prospective case series of 19 patients treated with stent implantation and phacoemulsification; the

stents were partially occluded by peripheral anterior synechiae; these patients received no further treatment. [8]

Blockage of the opening of the stent lumen

Blockage of the opening of the stent lumen was reported in 15% of patients in 1 of the 32 studies included in the systematic review and meta-analysis of 2,143 patients comparing stent insertion combined with phacoemulsification to phacoemulsification alone.[1]

Stent not visible upon gonioscopy

Stent not visible upon gonioscopy was reported in 13% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated by stent insertion alone.[2]

Secondary surgical interventions

Secondary surgical interventions were needed in 4% (5/116) of eyes in the combined group and in 5% (6/117) of eyes in the phacoemulsification-only group in the RCT of 239 patients comparing stent insertion combined with phacoemulsification against phacoemulsification alone within 24 months of follow-up (including patients who had more than 1 surgical re-intervention). In the combined group of 116 patients, the secondary surgical interventions were stent repositioning (3% [3/116]), stent removal and replacement (1 patient), Nd:YAG laser for stent obstruction (1 patient), trabeculoplasty (1 patient) and focal argon laser photocoagulation (1 patient). [3]

Secondary glaucoma surgery was reported in 1 patient in the combined group and in 2 patients in the phacoemulsification-only group in the RCT of 100 patients comparing stent insertion combined with phacoemulsification (n=50) against phacoemulsification alone (n=50), during the second year of follow-up.[6]

Stent replacement was reported in 5% of patients in 1 of the 5 studies included in the systematic review and meta-analysis of 248 patients treated with stent insertion alone.[2]

Stent removal and replacement during the procedure was reported in 1 patient in the RCT of 239 patients comparing stent insertion combined with phacoemulsification (n=116) with phacoemulsification alone (n=123).[3]

Validity and generalisability of the studies

- Some patients were treated with stent bypass microsurgery during cataract surgery, while others had the procedure done as a stand-alone treatment.
- Some patients were treated with 2 or 3 stents.

- A second generation of devices was used in some of the studies.
- Some IOP outcomes are measured on hypotensive medication following the procedure and some after washout, making comparison between studies difficult.
- In the studies included in table 2, the longest follow-up was 5 years. [8]

Existing assessments of this procedure

Preferred Practice Pattern® guidelines were published in January 2016 by the American Academy of Ophthalmology[9]. They stated: '' *Trabecular microbypass stent: The trabecular microbypass stent, or iStent (Glaukos Corporation, Laguna Hills, CA), is a snorkel-shaped device manufactured from heparin-coated titanium. A preloaded inserter is used to implant the device into the Schlemm canal under gonioscopic guidance. The iStent has received FDA approval for implantation in combination with cataract extraction in patients with mild to moderate OAG treated with topical ocular hypotensive agents. Several studies have reported a small reduction of IOP and glaucoma medical therapy with the combined phacoemulsification and iStent placement compared with phacoemulsification alone. A decrease in IOP and topical ocular hypotensive agents has been described with the iStent alone in the treatment of secondary OAG. Recent studies suggest that implantation of multiple stents may provide better IOP lowering than a single stent. Low rates of surgical complications have been reported with the iStent, and most commonly they relate to stent malposition or obstruction.*''

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Trabeculotomy ab interno for open-angle glaucoma. NICE interventional procedure guidance 397 (2011). Available from https://www.nice.org.uk/guidance/ipg397
- Canaloplasty for primary open-angle glaucoma. NICE interventional procedure guidance 260 (2008). Available from https://www.nice.org.uk/guidance/ipg260

NICE guidelines

- Glaucoma: diagnosis and management. NICE clinical guideline 85 (2009). Available from https://www.nice.org.uk/guidance/cg85

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Four Specialist Adviser Questionnaires for trabecular stent bypass microsurgery for open-angle glaucoma were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent 50 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received no completed questionnaires.

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Potential short-term impact of phacoemulsification alone on IOP makes evaluating the efficacy of the procedure difficult.
- In the Arriola-Villalobos (2012) study[8], patients with pigmentary or pseudoexfoliative glaucoma were also included.
- In the Pfeiffer (2015) study[6], the patients were treated with the Hydrus device, which is not yet available outside of research to the NHS.
- Primary open-angle glaucoma is 3 to 4 times more common in Afro-Caribbean people in whom it tends to present earlier and is more severe. However, in

most of the studies included in table 2 where ethnicity was reported, all patients were Caucasian.

- Ongoing studies:
  - NCT01443988 Subjects With Open-angle Glaucoma, Pseudoexfoliative Glaucoma, or Ocular Hypertension Naïve to Medical and Surgical Therapy, Treated With Two Trabecular Micro-bypass Stents (iStent) or Travoprost. Location: Armenia. RCT. Active, not recruiting. Estimated enrolment: 100 patients. Estimated Completion Date: April 2017.
  - NCT01444040 Subjects With Open-angle Glaucoma, Pseudoexfoliative Glaucoma, or Ocular Hypertension Naïve to Medical and Surgical Therapy, Treated With Two Trabecular Micro-bypass Stents (iStent Inject) or Travoprost. Location: Armenia. RCT. Recruiting. Estimated enrolment: 200 patients. Estimated Completion Date: April 2017.
  - NCT02024464 Compare the Hydrus Microstent(TM) to the iStent for Lowering IOP in Glaucoma Patients Having Cataract Surgery (Hydrus III). Location: United States. RCT. Recruiting. Estimated enrolment: 300 patients. Estimated Completion Date: January 2017.
  - NCT01455467 Open-angle Glaucoma Subjects on One Topical Hypotensive Medication Randomized to Treatment With One or Two Trabecular Micro-bypass Stents in Conjunction With Cataract Surgery. Location: Armenia. RCT. Active, not recruiting. Estimated enrolment: 80 patients. Estimated Completion Date: April 2017.
  - NCT01517477 Safety and Efficacy of One, Two, or Three iStents for the Reduction of Intraocular Pressure in Open-angle Glaucoma Subjects. Location: Armenia. RCT. Recruiting. Estimated enrolment: 120 patients. Estimated Completion Date: October 2017.
  - NCT01252849 Purpose of This Study is to Evaluate the Safety and Efficacy of One, Two, or Three iStents for the Reduction of Intraocular Pressure in Open-angle Glaucoma Subjects. Location: Armenia. RCT. Active, not recruiting. Estimated enrolment: 120 patients. Estimated Completion Date: December 2016.
  - NCT01444105 Open-angle Glaucoma Subjects on One Ocular Hypotensive Medication Randomized to Treatment With Two Trabecular Micro-bypass Stents or Selective Laser Trabeculoplasty. Location: Armenia. RCT. Active, not recruiting. Estimated enrolment: 80 patients. Estimated Completion Date: January 2017.
  - NCT02023242 Comparing Effectiveness of the Hydrus Microstent (TM) to Two iStents to Lower IOP in Phakic Eyes (Hydrus V). Location: United States. RCT. Recruiting. Estimated enrolment: 150 patients. Estimated completion date: January 2018.

References

1. Malvankar-Mehta MS, Iordanous Y, Chen YN et al. (2015) IStent with phacoemulsification versus phacoemulsification alone for patients with glaucoma and cataract: A meta-analysis. PLoS ONE 10(7): e0131770. doi:10.1371/journal.pone.0131770.
2. Malvankar-Mehta MS, Chen YN, Iordanous Y et al. (2015) iStent as a Solo Procedure for Glaucoma Patients: A Systematic Review and Meta-Analysis. PLoS ONE 10(5): e0128146. doi:10.1371/journal.pone.0128146.
3. Craven ER, Katz LJ, Wells JM et al. (2012) Cataract surgery with trabecular micro-bypass stent implantation in patients with mild-to-moderate open-angle glaucoma and cataract: two-year follow-up. Journal of Cataract & Refractive Surgery 38:1339-1345.
4. Fea AM, Belda JI, Rekas M et al. (2014) Prospective unmasked randomized evaluation of the iStent inject versus two ocular hypotensive agents in patients with primary open-angle glaucoma. Clinical Ophthalmology 8:875-882.
5. Katz LJ, Erb C, Guillamet AC et al. (2015) Prospective, randomized study of one, two, or three trabecular bypass stents in open-angle glaucoma subjects on topical hypotensive medication. Clinical Ophthalmology 9:2313-2320.
6. Pfeiffer N, Garcia-Feijoo J, Martinez-de-la-Casa JM et al. (2015) A Randomized Trial of a Schlemm's Canal Microstent with Phacoemulsification for Reducing Intraocular Pressure in Open-Angle Glaucoma. Ophthalmology 122:1283-1293.
7. Fea AM, Consolandi G, Zola M et al. (2015) Micro-Bypass Implantation for Primary Open-Angle Glaucoma Combined with Phacoemulsification: 4-Year Follow-Up. Journal of ophthalmology http://dx.doi.org/10.1155/2015/795357.
8. Arriola-Villalobos P, Martinez-de-la-Casa JM, Diaz-Valle D et al. (2012) Combined iStent trabecular micro-bypass stent implantation and phacoemulsification for coexistent open-angle glaucoma and cataract: a long-term study. British Journal of Ophthalmology 96:645-649.
9. Prum BE, Rosenberg LF, Gedde SJ et al. (2016). Primary Open-Angle Glaucoma Preferred Practice Pattern® Guidelines. Ophthalmology 123(1):41-111. doi: 10.1016/j.ophtha.2015.10.053.

Appendix A: Additional papers on trabecular stent bypass microsurgery for open-angle glaucoma

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Ahmed II, Katz LJ, Chang DF et al. (2014) Prospective evaluation of microinvasive glaucoma surgery with trabecular microbypass stents and prostaglandin in open-angle glaucoma. Journal of Cataract & Refractive Surgery 40:1295-1300	Prospective case series n= 39 FU=18 months	Patients with OAG treated with 2 trabecular microbypass stents and 1 presumptive postoperative medication achieved a significant and sustained reduction in IOP and medication through 18 months.	Larger studies or studies with longer follow-up are already included in table 2.
Arriola-Villalobos P, Martinez-de-la-Casa JM, Diaz-Valle D et al. (2013) Mid-term evaluation of the new Glaukos iStent with phacoemulsification in coexistent open-angle glaucoma or ocular hypertension and cataract. British Journal of Ophthalmology 97:1250-1255	Prospective case series n=20 FU=1 year	Combined cataract surgery with implantation of 2 stents seems to be an effective and safe procedure.	Larger studies or studies with longer follow-up are already included in table 2.
Belovay GW, Naqi A, Chan BJ et al. (2012) Using multiple trabecular micro-bypass stents in cataract patients to treat open-angle glaucoma. Journal of Cataract & Refractive Surgery 38:1911-1917	Comparative case series n= 53 (28x2 stents, 25x3 stents) FU=1 year	Using multiple microbypass stents with concurrent cataract surgery led to a mean postoperative IOP of less than 15 mm Hg and allowed patients to achieve target pressure control with significantly fewer medications through 1 year.	Study included in the Malvankar-Mehta (2015) systematic review and meta-analysis which is included in Table 2.
Buchacra O, Duch S, Milla E et al. (2011) One-year analysis of the istent trabecular microbypass in secondary glaucoma. Clinical ophthalmology (Auckland, N.Z.) 5:321-326	Prospective case series n=10 FU=1 year	This procedure is a safe and effective treatment option in patients with secondary open-angle glaucoma, and reduces the use of glaucoma medications.	Larger studies or studies with longer follow-up are already included in table 2.
Donnenfeld ED, Solomon KD, Voskanyan L et al. (2015) A prospective 3-year follow-up trial of implantation of two trabecular microbypass stents in open-angle glaucoma. Clinical Ophthalmology 9:2057-2065	Prospective case series n=39 FU=3 years	In a pilot study, 2 trabecular microbypass stents to treat open-angle glaucoma patients on 1 preoperative medication provided statistically significant, sustained, and safe reduction of IOP to <15 mmHg without medication through 36 months.	Larger studies or studies with longer follow-up are already included in table 2.

El Wardani M, Bergin C, Achache F et al. (2015) Evaluating the trabecular micro-bypass stent combined with phacoemulsification compared to phacoemulsification alone. Klinische Monatsblatter fur Augenheilkunde 232:442-445	Retrospective consecutive comparative study n=131 eyes (31 phacoemulsification and 1 stent, 22 phacoemulsification and 2 stents, 78 phacoemulsification alone) FU=6 months	Stent implantation resulted in similar IOP reduction to phacoemulsification alone but achieved a significantly greater reduction in glaucoma medications.	Larger studies or studies with longer follow-up are already included in table 2.
Fea AM. (2010) Phacoemulsification versus phacoemulsification with micro-bypass stent implantation in primary open-angle glaucoma: randomized double-masked clinical trial. Journal of Cataract & Refractive Surgery 36: 407-412	RCT n = 36 (12 stent, 24 no stent) FU= 16 months (median)	Phacoemulsification with stent implantation was more effective in controlling IOP than phacoemulsification alone; the safety profiles were similar.	Same patient population as in Fea (2015) study which is already included in table 2.
Fea AM, Dogliani M, Machetta F et al. (2008) The trabecular bypass stent in a pseudophakic glaucoma patient: a 1-year follow-up. Clinical Ophthalmology 2: 931-934	Single case report FU=1 year	The intraocular pressure was controlled with topical beta-blockers for 6 months and without therapy for 6 months. Two diurnal curves demonstrated achievement of target pressure during the day. The 1-year visual field was unchanged.	Larger studies or studies with longer follow-up are already included in table 2.
Ferandez-Barrientos Y, Garcia-Feijoo J, Martinez-de-la-casa et al (2010) Fluorophotometric study of the effect of the Glaukos trabecular micro-bypass stent on aqueous humour dynamics. Investigative Ophthalmology & Visual Science 51: 3327-3332	RCT n = 37 (17 stent, 16 no stent) FU= 12 months (median)	Compared with cataract surgery alone, implantation of the iStent concomitant with cataract extraction significantly increased trabecular outflow facility, reduced IOP, and reduced the number of medications at 1 year. Longer follow-up is needed to assess the long-term effect on outflow facility.	Larger studies or studies with longer follow-up are already included in table 2.
Ferguson TJ, Berdahl JP, Schweitzer JA et al. (2016) Clinical evaluation of a trabecular microbypass stent with phacoemulsification in patients with open-angle glaucoma and cataract. Clinical Ophthalmology.10 (pp 1767-1773)	Retrospective, consecutive case series n= 350 eyes FU= 2 years	The insertion of the iStent trabecular microbypass stent in combination with cataract surgery effectively lowers IOP in OAG patients. The magnitude of IOP reduction was more significant in patients with higher preoperative pressure. Medication use was also significantly reduced postoperatively. The safety profile appears favorable with a low rate of IOP spikes and only two eyes (<1%) requiring additional surgery.	No new complication reported. RCTs and studies with longer follow-up are already included in table 2.

Ferguson TJ, Berdahl JP, Schweitzer JA et al. (2016) Evaluation of a Trabecular Micro-Bypass Stent in Pseudophakic Patients With Open-Angle Glaucoma. Journal of Glaucoma.(no pagination)	Retrospective, consecutive case series n= 42 eyes FU= 2 years	The insertion of the iStent Trabecular Micro-Bypass stent effectively lowers IOP in pseudophakic patients with open-angle glaucoma. Although medication use was not significantly reduced postoperatively at 1 year, 80% of patients either experienced a reduction or no change in medication use. The safety profile appears favorable with a low rate of IOP spikes and only 1 patient requiring additional surgery.	No new complication reported. Larger studies or studies with longer follow-up are already included in table 2.
Khan M, Saheb H, Neelakantan A et al. (2015) Efficacy and safety of combined cataract surgery with 2 trabecular microbypass stents versus ab interno trabeculotomy. Journal of Cataract and Refractive Surgery 41:1716-1724	Retrospective comparative case series n=101 (49 phacoemulsification and 2 stents, 52 phacoemulsification and trabeculotomy) FU=1 year	Both types of surgery achieved a significant reduction in IOP and medication use at 12 months, with the stent group achieving higher success and a reduced incidence of postoperative hyphema.	Larger studies or studies with longer follow-up are already included in table 2.
Klamann MK, Gonnermann J, Pahlitzsch M et al. (2015) iStent inject in phakic open-angle glaucoma. Graefes Archive for Clinical & Experimental Ophthalmology 253:941-947	Retrospective case series n=35 FU= 6 months	This procedure has the ability to lower the postoperative IOP significantly in primary open-angle glaucoma and pseudoexfoliation glaucoma after a short follow-up of 6 months with a favorable risk profile. However, limitation of this surgical procedure in phakic pigmentary glaucoma may exist and need to be investigated in further studies.	Larger studies or studies with longer follow-up are already included in table 2.
Kurji Keal. (2016) Phaco-trabectome versus phaco-iStent in patients with open-angle glaucoma. Canadian Journal of Ophthalmology	Retrospective comparative study n= 55 (25 phaco-iStent versus 30 phaco-trabectome) FU= 1 year	At 12 months of follow-up, both techniques significantly lowered IOP, but fewer complications were observed in the phaco-iStent group.	No new complication reported. RCTs and studies with longer follow-up are already included in table 2.
Larsen, C. L. and Samuelson, T. W (2016) Managing coexistent cataract and glaucoma with iStent. Survey of Ophthalmology (*article in press*).	Review	Among microinvasive glaucoma surgeries, the iStent currently provides a promising benefit for mild or moderate open-angle glaucoma patients with a favorable safety profile and sparing of conjunctival tissue should more aggressive intervention be necessary in the future.	Recent review of the literature without meta-analysis on the iStent device. No new study was listed.

Lindstrom R, Lewis R, Hornbeak DM et al. (2016) Outcomes Following Implantation of Two Second-Generation Trabecular Micro-Bypass Stents in Patients with Open-Angle Glaucoma on One Medication: 18-Month Follow-Up. Advances in Therapy.(pp 1-9)	Prospective case series n= 57 eyes FU = 18 months	The standalone implantation of 2 second-generation trabecular micro-bypass stents in OAG patients on 1 preoperative medication resulted in IOP reduction to <15 mmHg and elimination of medication through 18 months, with favorable safety.	No new complication reported. Larger studies or studies with longer follow-up are already included in table 2.
Morales-Fernandez L, Martinez-de-la-Casa JM, Garcia-Feijoo J et al. (2012) Glaukos() trabecular stent used to treat steroid-induced glaucoma. European Journal of Ophthalmology 22:670-673.	Single case report FU= 1 year	This trabecular bypass seems a safe and effective therapeutic option for IOP control when there is a poor response to conventional treatment in this type of secondary glaucoma.	Larger studies or studies with longer follow-up are already included in table 2.
Neuhann TH. (2015) Trabecular micro-bypass stent implantation during small-incision cataract surgery for open-angle glaucoma or ocular hypertension: Long-term results. J Cataract Refract Surg. 41:2664-2671. doi:10.1016/j.jcrs.2015.06.032	Prospective case series n=43 patients (62 eyes) FU=36 months	Trabecular microbypass stent implantation during cataract surgery was safe and effective in patients with ocular hypertension or glaucoma as measured by a sustained reduction in IOP and medication use and an excellent safety profile through 3 years after surgery.	Larger studies or studies with longer follow-up are already included in table 2.
Patel I, de Klerk TA, Au L. (2013) Manchester iStent study: early results from a prospective UK case series. Clin Experiment Ophthalmol. 41(7):648-52.	Prospective case series n= 44 eyes (40 stent alone, 4 stent+ cataract surgery)	The procedure proved to be safe and effective for patients with open-angle glaucoma over a 6-month follow-up period. Insertion resulted in a significant decrease in intraocular pressure as well as the number of topical antiglaucoma medications required for adequate intraocular pressure control.	Larger studies or studies with longer follow-up are already included in table 2.

Resende AF, Patel NS, Waisbourd M et al. (2016) iStent(R) Trabecular Microbypass Stent: An Update. J Ophthalmol. 2731856-	Review of the literature	Current data suggest that the iStent is a safe and effective tool in the management of mild-to-moderate glaucoma, notable for its limited complications and absence of serious adverse events following implantation. As valuable experience is gained performing ab interno MIGS, increasing familiarity with angle anatomy and iStent placement, and as newer stent designs are developed, there is promise of continual improvement in the surgical management of glaucoma.	Recent review of the literature without meta-analysis on the iStent device. No new study was listed.
Roelofs K, Arora S, and Dorey MW. (2014) Implantation of 2 trabecular microbypass stents in a patient with primary open-angle glaucoma refractory to previous glaucoma-filtering surgeries. Journal of Cataract & Refractive Surgery 40:1322-1324	Single case report FU= more than 2 years	The IOP decreased by 11 mm Hg to 17 mm Hg after surgery and has remained stable for 2 years.	Larger studies or studies with longer follow-up are already included in table 2.
Samuelson TW, Katz LJ, Wells JM et al. (2011) Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology 118(3):459-67	RCT n = 240 (117 stent, 123 no stent) FU= 12 months (median)	Pressure reduction on fewer medications was clinically and statistically significantly better 1 year after stent plus cataract surgery versus cataract surgery alone, with an overall safety profile similar to that of cataract surgery alone.	Same patient population as in Craven (2012) study which is already included in table 2.
Seibold LK, Gamett KM, Kennedy JB et al. (2016) Outcomes after combined phacoemulsification and trabecular microbypass stent implantation in controlled open-angle glaucoma. Journal of Cataract & Refractive Surgery 42:1332-1338.	Retrospective case series n= 64 eyes in 45 patients FU= 1 year	Combined cataract surgery and trabecular microbypass stent implantation was statistically effective in reducing IOP and/or medication burden in OAG patients with a low preoperative IOP. During the informed surgical consent process, the physician and patient should consider the clinical benefit of modest IOP lowering and/or a decrease in medication use.	No new complication reported. Larger studies or studies with longer follow-up are already included in table 2.
Spiegel D, Wetzel W, Neuhann T et al. (2009) Coexistent primary open-angle glaucoma and cataract: interim analysis of a trabecular micro-bypass stent and concurrent cataract surgery. European Journal of Ophthalmology 19: 393-399	Case series n=58 FU=1 year (median)	In patients undergoing concurrent cataract and glaucoma surgery, the iStent was safe and efficacious for the reduction of IOP and medication therapy.	Larger studies or studies with longer follow-up are already included in table 2.

Spiegel D, Wetzel W, Haffner DS et al. (2007) Initial clinical experience with the trabecular micro-bypass stent in patients with glaucoma. Advances in Therapy 24:161-170	Case series n=6 FU= 1 year (median)	The microstent was effective in reducing IOP and in decreasing the number of glaucoma medications required to control IOP. Implantation procedures were safe, and stents remained in place throughout the follow-up period. None of the complications traditionally associated with filtering surgery were reported.	Larger studies or studies with longer follow-up are already included in table 2.
Tan SZ and Au L. (2016) Manchester iStent study: 3-year results and cost analysis. Eye (Basingstoke).30 (10) (pp 1365-1370)	Prospective case series n= 41 FU= 3 years	Combined phaco-iStent proved to be a safe and effective way of managing patients with OAG over our 3-year follow-up period. The cost-effectiveness of the procedure may vary depending on whether brand name or generic eye drops are used.	No new complication reported. Larger studies or studies with longer follow-up are already included in table 2.
Vandewalle E, Zeyen T, Stalmans I. (2009) The iStent trabecular micro-bypass stent: a case series. Bulletin de la Societe belge d'ophtalmologie 311: 23-29	Case series n=8 (10 eyes) FU= 1 year (median)	The procedure is safe and not associated with complications traditionally associated with filtering surgery. The trabecular bypass results in significant mid-term reduction of intraocular pressure as well as the number of medications.	Larger studies or studies with longer follow-up are already included in table 2.
Vold SD, Voskanyan L, Tetz M et al. (2016) Newly Diagnosed Primary Open-Angle Glaucoma Randomized to 2 Trabecular Bypass Stents or Prostaglandin: Outcomes Through 36 Months. Ophthalmol.Ther	RCT n= 101 (54 with 2 stents versus 47 prostaglandin) FU=3 years	In this randomised comparison of patients with newly diagnosed POAG naive to therapy, substantial IOP reduction with a favorable low complication rate was shown through 3 years after either 2 trabecular stents implanted as the sole procedure or topical travoprost therapy. These data suggest 2-stent implantation may be a viable initial treatment option comparable to topical prostaglandin in newly diagnosed POAG patients.	No new complication reported. Larger studies or studies with longer follow-up are already included in table 2.
Voskanyan L, Garcia-Feijoo J, Belda JI et al. (2014) Prospective, unmasked evaluation of the iStent inject system for open-angle glaucoma: synergy trial. Advances in Therapy 31:189-201	Prospective case series n=99 FU= 1 year	In this series, implantation of 2 trabecular microbypass second generation stents in subjects with OAG resulted in IOP and medication reduction and favorable safety outcomes.	Study included in the Malvankar-Mehta (2015) systematic review and meta-analysis which is included in Table 2.

Appendix B: Related NICE guidance for trabecular stent bypass microsurgery for open-angle glaucoma

Guidance	Recommendations
Interventional procedures	**Trabeculotomy ab interno for open angle glaucoma. NICE interventional procedure guidance 397 (2011)** 1.1 Current evidence on the safety and efficacy of trabeculotomy ab interno for open angle glaucoma is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Patient selection should be carried out in units that specialise in glaucoma treatment that can offer a range of treatment options. 9.3 NICE encourages the collection and publication of further data on long-term efficacy. **Canaloplasty for primary open-angle glaucoma. NICE interventional procedure guidance 260 (2008)** 1.1 Current evidence on the safety and efficacy of canaloplasty for primary open-angle glaucoma is inadequate in both quality and quantity. Therefore, this procedure should only be used in the context of research or formal prospective data collection. Clinicians are encouraged to collaborate in the collection and publication of data. 1.2 Further publication of safety and efficacy outcomes will be useful. The Institute may review the procedure upon publication of further evidence.

NICE guidelines	**Glaucoma: diagnosis and management. NICE clinical guideline 85 (2009)** 1.4.6 Check the person's adherence to their treatment and eye drop instillation technique in people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss despite pharmacological treatment. If adherence and eye drop instillation technique are satisfactory offer one of the following: • alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP • laser trabeculoplasty • surgery with pharmacological augmentation (MMC or 5-FU1) as indicated If the pharmacological treatment option is chosen, after trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5-FU1) as indicated or laser trabeculoplasty. 1.4.7 Offer surgery with pharmacological augmentation (MMC or 5-FU1) as indicated to people with COAG who are at risk of progressing to sight loss despite treatment. Offer them information on the risks and benefits associated with surgery. 1.4.9 After surgery offer people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss one of the following: • pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP • further surgery • laser trabeculoplasty or cyclodiode laser treatment. 1.4.10 Offer people with COAG who prefer not to have surgery or who are not suitable for surgery: • pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); more than one agent may be needed concurrently to achieve target IOP • laser trabeculoplasty or cyclodiode laser treatment.

Appendix C: Literature search for trabecular stent bypass microsurgery for open-angle glaucoma

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	27/10/2016	Issue 10 of 12, October 2016
Cochrane Central Database of Controlled Trials - CENTRAL	27/10/2016	Issue 9 of 12, September 2016
HTA database (Cochrane)	27/10/2016	Issue 3 of 4, July 2016
MEDLINE (Ovid)	27/10/2016	1946 to October Week 3 2016
MEDLINE In-Process (Ovid)	27/10/2016	October 25, 2016
EMBASE (Ovid)	27/10/2016	1974 to 2016 Week 43
PubMed	27/10/2016	n/a
JournalTOCS [for update searches only]	27/10/2016	n/a

Trial sources searched on 19/01/2016

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 19/01/2016

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Glaucoma/

2 Glaucoma, Open-Angle/

3 (glaucoma* adj4 (compensat* or pigment* or simple* or open angle* or open-angle* or simplices or chronic)).tw.

4 POAG.tw.

5 Ocular Hypertension/

6 OHT.tw.

7 ((ocular* or intraocul*) adj4 hypertens*).tw.

8 Intraocular Pressure/

9 (intraocul* adj4 pressur*).tw.

10 IOP.tw.

11 or/1-10

12 Ophthalmologic Surgical Procedures/

13 Glaucoma Drainage Implants/

14 (bypass* or micro-bypass*).tw.

15 or/12-14

16 Stents/

17 (stent* or tube*).tw.

18 or/16-17

19 15 and 18

20 (microtrabecular adj4 (surgery* or microsurgery*)).tw.

21 (trabecular adj4 stent*).tw.

22 istent*.tw.

23 glaukos.tw.

24 or/19-23

25 11 and 24

26 Animals/ not Humans/

27 25 not 26

28 2016*.ed.

29 27 and 28