NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes

The cornea is the clear outer layer at the front of the eyeball that acts as a window to the eye. Injury, surgery or disease can make the cornea cloudy, affecting vision.

A corneal graft–keratoprosthesis is an artificial cornea surrounded by a corneal graft from a human donor. It is implanted to replace a severely diseased cornea in wet eyes with good blinking function.

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 2015.

Procedure name

- Implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes

Specialist societies

- Royal College of Ophthalmologists (RCO)

Description

Indications and current treatment

Injury or disease of the cornea can make it opaque, stopping light from entering the eye and resulting in loss of vision. Some severe corneal diseases can also affect the eye's blink and tear mechanisms. Corneal injuries can be caused by direct trauma, including surgery, as well as chemical or thermal

burns. Diseases that can cause corneal opacity include autoimmune diseases, bullous keratopathy, keratoconus, keratitis and corneal stromal dystrophies.

The standard treatment for significant corneal opacity is a corneal transplant (penetrating keratoplasty). Penetrating keratoplasty removes the opaque cornea using a trephine, replacing it with a donor cornea. Some patients cannot have a standard corneal transplant for reasons including: disease severity; severe involvement of the conjunctiva; a failed previous corneal transplant, or when measures needed to prevent graft rejection are contraindicated. For these patients, penetrating keratoplasty using an artificial cornea (keratoprosthesis) may be an option.

What the procedure involves

A corneal graft–keratoprosthesis is an artificial clear central corneal window surrounded by a human donor cornea. Implantation is generally done if a standard corneal transplant has failed, or when it is inappropriate. The procedure is used to treat only the most severe corneal opacity.

A type I corneal graft–keratoprosthesis is the most commonly implanted artificial corneal device and is suitable for patients whose blink and tear mechanisms are reasonably intact (wet blinking eyes) and who have had multiple graft failures. The device is custom-made to have a range of dioptric powers to match the axial length of the patient's aphakic eye. It is shaped like a collar button, with a refractive front and porous back plate and a titanium locking ring.

Implantation of the fully assembled corneal graft–keratoprosthesis is done under general or local anaesthesia. A human donor corneal graft with a central hole is positioned between the front and back plate, and held in place by the titanium ring. The central portion of the patient's opaque cornea is removed, and if the natural lens is in place, it is also removed. The corneal graft–keratoprosthesis is then transferred to the patient's corneal opening and secured with multiple interrupted sutures. Finally, a soft bandage contact lens is placed on the surface of the eye.

Postoperatively, patients wear a soft contact lens and use prophylactic antibiotic drops for the rest of their lives. In addition, topical steroids are usually recommended and patients need frequent follow-up and monitoring for life.

Outcome measures

Visual acuity

Visual acuity is the minimal angle (or object size) that can be recognised at a given distance. It is usually tested by asking people to read a letter chart presented at a set distance. The most commonly used letter chart is the Snellen chart, which presents progressively smaller letters. Measurements may be uncorrected, corrected by glasses or contact lenses, or through a pin hole (that corrects refractive error). Snellen notation uses a numerator and denominator, such as 6/9. The top figure represents the test distance (6 metres). The lower figure (9 metres) represents the distance at which a person with normal vision can see a particular letter size. A visual acuity of 6/6 (20/20 if measured in feet) is normal vision, whereas 6/12 is reduced vision and lower values (for example, 20/200) correspond to subnormal vision. It is possible to have vision superior to 6/6, such as 6/4.

Visual acuity is sometimes presented on a logMAR (logarithm of the minimum angle of resolution) scale, where 0.0 is normal vision, negative values represent better than normal vision, and positive values represent worse than normal vision. For example, logMAR 0.3 is the same as 6/12. If people cannot see the eye chart letters they may be able to count fingers presented in front of them, see hand movement or perceive changes in light intensity (light perception).

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes. The following databases were searched, covering the period from their start to 28 January 2015: 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 severe corneal opacity.
Intervention/test	Corneal graft–keratoprosthesis (Boston keratoprosthesis type I).
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 1095 patients (1144 eyes) from 10 retrospective[1–4, 6–11], 1 prospective[5] case series and 4 case reports[12–15].

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 implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes

Study 1 Ciolino JB (2013)

Details

Study type	**Prospective case series (cohort study)**
Country	USA (multicentre:18 sites, 19 surgeons)
Recruitment period	2003–8
Study population and number	n=**300 (300 eyes)** Indications: patients with severe autoimmune disease (ocular cicatricial pemphigoid [OCP]; Stevens–Johnson Syndrome [SJS]), 31; chemical injuries; 31, herpes simplex [HSV], 21; Fuchs endothelial dystrophy, 8; keratoconus, 11; infectious keratitis,19; neurotrophic keratitis, 4; limbal stem cell deficiency, 9; pseudophakic bullous keratopathy [PBK], 55; trauma, 13; aniridia, 7; miscellaneous, 35; failed graft, 50; and unknown, 6. Indications for surgery: repeat penetrating keratoplasty, 86.2% (244/300) [average 2.3±1.3 prior transplants]; primary keratoprosthesis implantation, 13.3% (39/300) with high risk of graft failure; replacement of a prior keratoprosthesis, 7.5% (22/300). Concomitant surgical procedures: intracameral steroids, 143; cataract extraction, 55; tarsorrhaphy, 20; glaucoma surgery, 21; pars plana vitrectomy, 70; intraocular lens removal, 32; iridectomy, 36; iriodoplasty,16; iridocorneal synechiolysis,15; punctual occlusion, 6; miscellaneous,17.
Age and sex	Mean 62.6 years; 52% male
Patient selection criteria	Not reported
Technique	Boston Keratoprosthesis type I device implanted (as described in procedure description section). Procedure was performed in right eye for 53.6% (161/300) of the cases. At the time of implantation many patients underwent additional surgical procedures. Prophylactic antibiotics were used in all.
Follow-up	**Mean 17.1±14.8 months (range 1 week to 6.1 years)** **422.1 cumulative life years of device implantation**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up reported at 1 week, 1 month, 6 months, 12 months and yearly thereafter. 53.7% (161/300) eyes had 1 year follow-up and 30.3% (90/300) eyes had 2 years follow-up.

Study design issues: A large prospective multicentre cohort study; data were analysed using SAS. Only data from the first implant were included in this study. Patients who received a replacement keratoprosthesis for graft failure during the study and the second eye of those who underwent bilateral keratoprosthesis implantation were excluded from the analysis.

Study population issues: Varied indications for surgery, study included more eyes with autoimmune corneal diseases. There was no difference between eyes that retained the prosthesis or those that failed in terms of age (p=0.278) or gender (p=1.00).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **300 (300 eyes)**

Keratoprosthesis retention (survival)* (assessed using Kaplan–Meier curves)

Overall retention rate at last follow-up % (n)	93 (279/300)
Retention time (patient years/years)	396 patient years or 1.42 years/keratoprosthesis
Probability of retention after 1 year (%)	94
Probability of retention after 2 years (%)	89
Mean survival time (years)	3.8±0.09
Retention rate for non-autoimmune eyes after 1 year (%)	95

* defined as anatomical retention at the last follow-up date.

Keratoprosthesis failure % (n)

Keratoprosthesis failure*	7 (21/300)
Reasons for failure	
Sterile keratolysis (5 sterile tissue necrosis with an intact prosthesis, 4 keratoprosthesis extrusion)	9
Fungal infections (7 keratitis cases, 1 fungal endophthalmitis)	8
Dense retroprosthetic membranes (keratoprosthesis replaced)	3
Bacterial endophthalmitis	1

* defined as a lack of anatomical retention, which includes removal, extrusion or loss of the eye.

16 patients received a replacement keratoprosthesis, 2 had standard penetrating keratoplasty without a keratoprosthesis, 1 developed a self-sealing membrane and 2 eyes were enucleated.

Failure rate of keratoprosthesis by surgical indication (Kaplan–Meier curves)

Aetiology	**Failure (n=21)**		**Retention (n=279)**	**p value (log-rank test)**
	rate %	n	n	
Autoimmune disease	29.0 (9/31)	9	22	<0.0001
Chemical injury	3.2 (1/31)	1	30	0.508
Herpes simplex virus	4.8 (1/21)	1	20	0.790
Fuchs dystrophy	12.5 (1/8)	1	7	0.621
Keratoconus	9.1 (1/11)	1	10	0.969
Infectious keratitis	5.3 (1/19)	1	18	0.643
Neuropathic keratitis	0	0	4	0.617
Limbal stem cell deficiency	0	0	9	0.440
Pseudophakic bullous keratopathy (PBK)	1.8 (1/55)	1	54	0.064
Trauma	15.4 (2/13)	2	11	0.520
Aniridia	14.3 (1/16)	1	6	0.566
Miscellaneous	8.6 (3/35)	3	32	0.889
Failed graft	0	0	50	0.098
Unknown	0	0	6	0.390

Risk factors for keratoprosthesis failure (multivariate analysis)

Multivariate analysis demonstrated 3 independent risk factors for keratoprosthesis failure: autoimmune aetiology such as SJS, OCP (hazard ratio [HR] 11.94; 95% CI 3.31 to 43.11, p=0.0002), ocular surface exposure requiring a concomitant tarsorrhaphy (HR 3.43; 95% CI 1.05 to 11.22; p=0.042) and a number of prior failed penetrating keratoplasties (HR 1.64; 95% CI 1.18 to 2.28; p=0.003).

Abbreviations used: CI, confidence interval; HR, hazard ratio; IOL, intraocular lens; SJS, Stevens–Johnson Syndrome; OCP, ocular cicatricial pemphigoid.

Study 2 Aldave AJ (2012)

Details

Study type	**Retrospective comparative case series**
Country	International (Armenia, India, Indonesia, Nepal, Philippines, Russia, and Saudi Arabia, USA) (11 centres)
Recruitment period	2006–11 (international series), 2004–11 (USA)
Study population and number	n=**194 (205 eyes, 223 procedures)** **International series 100 (107 eyes, 113 procedures) versus 94 (98 eyes, 110 procedures) USA series** Main indications: corneal transplant failure (44%, [n=50] vs 64%, [n=64]; p=0.005), chemical injury (27% [n=30] vs 7% [n=8]; p=0.0001). Other indications: Stevens–Johnson syndrome; repeat keratoprosthesis; mucus membrane pemphigoid; thermal injury; herpetic keratitis; infectious keratitis; limbal stem cell deficiency; corneal vascularisation; aniridia; atopic keratoconjuctivitis. Indications for surgery: repeat penetrating keratoplasty: 69.2% (74/107) vs 83.6 (82/98) Comorbid ocular conditions: glaucoma 40% (43/107) eyes vs 78% (76/98); p<0.0001. Previous ocular surgeries: 19% eyes (20/107) vs 59% (58/98); p<0.0001. Concomitant surgical procedures: cataract extraction, anterior vitrectomy, tube shunt implantation and intraocular lens removal.
Age and sex	Mean age: 46 years vs 63 years Sex: 70% vs 50% male (p=0.018)
Patient selection criteria	Patients considered poor candidates for either initial or repeat corneal transplantation both within and outside USA were included.
Technique	Boston keratoprosthesis type I device implanted (as described in procedure description section). Implantation techniques used were similar with only minor differences. Other surgical procedures were commonly performed with keratoprosthesis implantation. Contact lens was placed in 97% of the procedures. All patients were maintained on topical antibiotic prophylaxis and in a bandage soft contact lens indefinitely; the lens was exchanged once a month by a relative or a local eye care provider.
Follow-up	**Mean 14.2 months (range 0-48 months) versus 24 months (range 0-84 months)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Average follow-up times differed between the 2 studies, huge losses to follow-up in the international and USA series beyond 2 years.

Study design issues: Large retrospective case series, study compares the procedures performed outside USA with those performed by a training surgeon at 1 centre in USA. 59% (67/113) of the surgeries were performed in 1 centre in India. Patients' charts were reviewed and data collected. Implantations were performed by trained surgeons in major ophthalmology centres who also had access to the expertise and assistance of glaucoma, retina and oculoplastic specialists.

Study population issues: Varied indications for surgery but the most common indication was for corneal transplant failure. Chemical injury was another more common indication in the international series than in the US series.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **100 (107 eyes) vs 94 (98 eyes)**

Visual outcomes at different follow-up periods (using Snellen chart)

	Baseline	**6 months**	**1 year**	**2 years**	**5 years**
Number of eyes with CDVA >20/100 % (n)					
International series	1 (1/107)	52(45/87)	50.8 (33/65)	52.9 (18/34)	0
US series	0	60 (54/98)	55 (42/77)	47 (22/47)	71 (5/7)
Number of eyes with CDVA >20/200 % (n)					
International series	2 (2/98)	70 (61/87)	68(44/65)	59 (20/34)	0
US series	6 (6/98)	69 (62/91)	63 (48/77)	60 (28/47)	0

In the international series, in eyes that retained keratoprosthesis, the final post-operative CDVA was better than the preoperative CDVA in 82% (74/90) eyes, same in 13% (12/90) eyes, and worse in 4 (4/90) eyes.

Keratoprosthesis retention and failure rate (Kaplan–Meier survival analysis)

	International series % (n=113 implants)	**USA series % (n=110 implants)**	**p value**
Mean follow-up (months/ cumulative years)	14.2 (133.4)	24.1	
Retention survival rate			
1 year	79.2	91.7	
2 years	74.6	78.4	
3 years	74.6	75.5	
Final follow-up	80.5 (91/113)	80 (88/110)	
Retention failure rate^			
1 year	20.8 (n=58)	8.3% (n=74)	
2 years	25.4 (n=18)	21.6 (n=45)	
3 years	NR	38.4 (n=29)	
Final follow-up	19.5 (22/113) n=19 (20 eyes)*	20 (22/110)	
All eyes	22 per 133.4 eye years, 0.165/eye year	22 per 220.9 eye years, 0.100/eye year	0.24
Eyes with transplant failure	8 per 62.1 eye years, 0.129/eye year	8 per 148.1 eye years, 0.054/eye year	0.08
Eyes with chemical injury	7 per 37.5 eye years, 0.187/eye year	1 per 20.9 eye years, 0.048/eye year	0.47

^ number of keratoprosthesis that were removed per eye years

*in 6 eyes, another keratoprosthesis was implanted.

Safety

Complications

	International series % (n=101 eyes)*	**USA series % (n=94 eyes)***	**p value**
Retroprosthetic membrane	**26.7 (27/101)**	**48.9 (46/94)**	**0.002**
YAG laser membranectomy	9.9 (10/101)	34 (32/94)	<0.0001
Surgical membranectomy	4 (4/101)	7.4 (7/94)	0.36
Sterile corneal stromal necrosis	**17.8 (18/101)**	**16 (15/94)**	**0.85**
Keratoprosthesis replacement	20.8 (21/101)	18.1 (17/94)	0.72
Elevated IOP (>25 mmHg)	**13.9 (14/101)**	**20.2 (19/94)**	**0.26**
Glaucoma surgery	8.9 (9/101)	6.4 (6/94)	0.60
Corneal infiltrate	**11.9 (12/101)**	**9.6 (9/94)**	**0.65**
Persistent epithelial defect	**9.9 (10/101)**	**36.2 (34/94)**	**<0.0001**
Tarsorrhaphy	12.9 (13/101)	21.3 (20/94)	0.13
Infectious endophthalmitis	**8.9 (9/101)**	**1.1 (1/94)**	**0.019**
Vitreous tap and injections	6.9 (7/101)	11.7 (11/94)	0.32
Retinal detachment	**5 (5/101)**	**16 (15/94)**	**0.017**
Repair of detachment	2 (2/101)	9.6 (9/94)	0.029
Sterile vitritis	**4 (4/101)**	**10.6 (10/94)**	**0.096**
Cystoid macular oedema	**3 (3/101)**	**9.6 (9/94)**	**0.074**
Intravitreal injection	1 (1/101)	5.3 (5/94)	0.11

*eyes with more than 1 month follow-up.

Abbreviations used: CDVA, corrected distance visual acuity; IOP, intraocular pressure; NR, not reported; PK, penetrating keratoplasty; YAG, yttrium-aluminium-garnet.

Study 3 Srikumaran D (2014)

Details

Study type	**Retrospective case series (longitudinal cohort study)**
Country	USA (multicentre, 5 sites)
Recruitment period	2003–7
Study population and number	n=**150 (158 eyes)** Indications: Ocular surface disease (OSD), 23%; congenital corneal abnormalities, 12.9%; infectious keratitis, 12.2%; bullous keratopathy/dystrophy, 35.3%; unknown, 16.5%. Indications for surgery: prior failed graft (penetrating keratoplasty), 72.6%; primary keratoprosthesis, 27.3%. Glaucoma status: known history of glaucoma, 58.3%; previous glaucoma surgery, (e.g. tube shunt, diode, trabeculectomy), 30.4% Retinal disease: 33.1%, with retinal detachment in13.7%. Concomitant surgical procedures: 70% (97/139) eyes had at least 1 procedure (anterior vitrectomy in 25% eyes, glaucoma surgery in 21% eyes).
Age and sex	Mean age 63.9 years; 45.3% male
Patient selection criteria	Not reported
Technique	Boston keratoprosthesis type 1 device implanted (as described in procedure description section). All eyes received a device with 7-mm or 8.5-mm fenestrated back plate. 6 patients had bilateral implantation.
Follow-up	**Mean 46.7±26 months (range 6 weeks to 8.7 years);** **52.5% eyes had >4-years follow-up; 15 eyes had 7-years follow-up.**
Conflict of interest/source of funding	One author was a consultant to Allergan and received grants from Johnson & Johnson and Bausch & Lomb. One author received payment for lectures from Bausch & Lomb, one author was a consultant to OCULUS GmbH.

Analysis

Follow-up issues: 4 (4 eyes) were lost to follow-up. 4 included patients had a postoperative follow-up of less than 6 months (2 were lost to follow-up and 1 died of unrelated causes 2 months after surgery, 1 with severe OSD underwent device explantation 6 weeks after implantation due to corneal necrosis).

Study design issues: Longest longitudinal cohort study; data collected from medical records were reviewed by 2 authors. Patients with at least 1 postoperative visit were included in the analyses. In the eyes that underwent a repeat keratoprosthesis implantation (n=19), only the outcomes of initial surgery were analysed. For retention analyses, repeat implantations were counted as failures. Visual acuity analyses were performed for all eyes and also for those that retained the initial implantation. Patients younger than 18 years at the time of surgery (n=13; 15 eyes) or without at least 1 postoperative follow-up visit (n=4; 4 eyes) were excluded from the analysis. 1 patient (1 eye) with severe learning difficulties was excluded from the visual acuity analysis but included for other outcome analyses. Subgroup analyses were performed for each indication.

Study population issues: Varied indications for surgery; study included more eyes with OSD (such as severe keratoconjunctivitis sicca, cicatrising conjunctivitis mucous membrane pemphigoid, Stevens–Johnson syndrome and, atopic disease) and bullous keratopathy/corneal dystrophies.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **133 (139 eyes)**

Distribution of best-corrected visual acuity (measured using Snellen chart) for entire cohort

	Preoperative % (n=138)	Best ever vision at any time point % (n=138)	At last follow-up* % (n=130)
BCVA >20/200	7	60	44
BCVA 20/200–20/400	15	16	11
Counting fingers - hand motion	63	20	23
Light perception	15	1	8
No light perception^		1	14

* 8 eyes with device removal were excluded from the analysis. ^ the eye was enucleated during follow-up.

Distribution of best-corrected visual acuity (measured using Snellen chart) in eyes that retained the initial implantation

	Preoperative % (n=138)	Best ever vision at any time point^ % (n=138)	At last follow-up* % (n=103)
BCVA >20/200	9	70	51
BCVA 20/200-20/400	16	7	6
Counting fingers - hand motion	62	20	24
Light perception	14	2	10
No light perception^	0	1	10

^ median time of 6.3 months (range 3.5-11.5 months)

* Only eyes that were able to retain the device were included. ^ the eye was enucleated during follow-up. 30% (41/138) eyes never achieved BCVA 20/200 or better because of pre-existing posterior segment conditions.

Maintenance of >20/200 visual acuity at last follow-up (estimated with Kaplan–Meier survival curves) (97 eyes): probability was 50% at 7 years.
Keratoprosthesis retention rate (estimated using Kaplan–Meier survival curve)

2 years	84%
7 years (84 months)	67% (89/133)

Device failure: In 25% (35/139) eyes, the device was removed (30/139) or the eye underwent enucleation (5/139) as a result of device related complications during the entire follow-up.

Subgroup analyses according to initial diagnosis

Subgroup analyses show that eyes with a history of bullous keratopathy/corneal dystrophies had the highest device retention rate (85% at 84 months). Eyes with OSD had significantly lower retention rates (35% at 84 months) compared with eyes without OSD (78% at 84 months; log rank test p<0.001).

No differences in retention rate were noted between eyes that had a primary implantation versus those that had previously failed 1 or more donor grafts and eyes that had an aphakic versus pseudophakic device implanted.

Safety

Complications n=133 (139 eyes)

	Years after surgery				
% (n) Complication	**1**	**2**	**3**	**5**	**7**
Device removal	5.9	16.2	20.9	33.2	33.2 (44/133)
Retroprosthetic membrane formation*	29.5	35.5	44.9	49.7	49.7 (66/133)
Glaucoma requiring additional surgery^	7.8	10.4	13.6	18.9	21.6 (29/133)
Sterile corneal necrosis	6.7	11.1	12.2	19.5	19.5 (26/133)
Retinal detachment	4.6	8.1	11.2	16.1	18.6 (25/133)
Infectious endophthalmitis	3.1	4.8	4.8	10.5	15.5 (20/133)
Persistent epithelial defect	4.4	6	7.1	8.2	8.2 (11/133)
Infectious corneal infiltrate (keratitis not progressing to endophthalmitis)	0.8	3.4	3.4	3.4	3.4 (4/133)
Cystoid macular oedema	NR	NR	NR	NR	10.1 (13/133)

* 33% had a YAG membranectomy, 18.6% needed a surgical membranectomy.

^ included tube shunt surgery or diode ciliary body ablation. The need for glaucoma surgery did not differ when comparing eyes with and without glaucoma (20.6% versus 17.2%, p=0.99).There was an increased need for glaucoma surgery postoperatively in eyes without glaucoma compared with eyes with prior or concurrent glaucoma surgery (31.4% versus 18.9%, p=0.10).

Abbreviations used: BCVA, best corrected visual acuity; NR, not reported; OSD, ocular surface disease; YAG, yttrium-aluminium-garnet.

Study 4 Dunlap K (2010)

Details

Study type	**Retrospective case series**
Country	USA (multicentre, 2 sites, 2 surgeons)
Recruitment period	2004–8
Study population and number	n=**122 (126 eyes) patients with corneal diseases deemed ineligible for donor corneal transplants.** Indications: bullous keratopathy, 29.5% (33); Fuchs dystrophy, 15.2% (17); keratoconus, 10.7% (12); penetrating trauma, 9.8% (11); infectious keratitis, 9.8% (11); herpetic keratitis, 6.3% (7); chronic uveitis, 5.4% (6); Sjogren's syndrome, 3.6% (4); mucous membrane pemphigoid, (5); Peters anomaly, 1.8% (2); chemical trauma, (5); trachoma, (2); Axenfeld Rieger, (1); gelatinous drop dystrophy, (1); Lattice dystrophy, (1); interstitial keratitis, (1); sclerocornea, (2); neurotrophic corneal ulcer with severe neovascularisation, (2); bullous keratopathy with severe neovascularisation, (2); Stevens–Johnson syndrome (1). Indications for surgery: prior failed graft (penetrating keratoplasty), 88.9% (112/126); primary keratoprosthesis surgery, 11.1% (14/126). Comorbid conditions (n): glaucoma, (32); retinal detachment, (10); diabetic retinopathy, (4); pre-phthisical state, (4); age-related macular degeneration, (3); hypotony, (2); amblyopia, (2); retinal vein occlusion, (1); retinal hole, (1); macular oedema, (1). Concomitant surgical procedures (n): anterior vitrectomy, (32); intraocular lens explantation, (29); synechiolysis and excision of corneal or pupillary membrane, (28); cataract extraction, (25); pars plana vitrectomy and retinal procedures, (22); pupilloplasty, (16); glaucoma valve placement or revision, (12); peripheral iridectomy, (8); canthotomy, (1).
Age and sex	Median age 72 years; 54% (66/122) male
Patient selection criteria	Patients with corneal diseases that were deemed ineligible for corneal transplantation: with little or no chance of success with standard penetrating keratoplasty, those with a history of multiple graft failures, presence of limbal stem cell deficiency, or significant ocular surface diseases such as severe dry eye or cicatrising conjunctivitis, with a visual acuity of <20/200 and the fellow eye with better vision.
Technique	Boston keratoprosthesis type 1 device implanted (as described in procedure description section). 4 patients underwent bilateral procedures. It was more often performed as part of a combined procedure.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis

Study design issues: Medical records of patients were reviewed retrospectively. Uncorrected visual acuity and manifest refraction were obtained preoperatively, postoperatively at day 1, 1 week, 1 month, 3 months and 6 months. Paediatric patients aged under 5 years who could not provide reliable visual acuity measurements were excluded from the analyses.

Study population issues: Heterogeneous population with different indications, eligibility criteria of the 2 sites differed slightly. 47.3% (53/122) patients were aphakic after prosthesis implantation.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **122 (126 eyes)**

Best corrected visual acuity (measured using Snellen chart)

Follow-up	% of eyes (n) with 20/200 vision or better
1st day	7.1
1st week	24.6 (31/126)
1st month*	56 (59/104)
3 months^	54% eyes had 20/200 vision or better and 18% had 20/40 or better vision
6 months	82.5 (104/126)

* By 1 month the number of patients with severe visual loss (hand motion to light perception) at baseline was reduced by more than half, from 50 to 22 patients.

^ 7.4% (22/126) eyes did not have improved vision, mostly attributed to comorbid conditions. 8 eyes lost vision.

Refractive outcomes at the time of BCVA (dioptres [D])

Mean spherical refraction error	−0.57 (range +10.00 to −10.00)
Mean astigmatism	0.10 (range, 0 to 1.25)

Safety

Complications during 6 months follow-up

Complication	% (n)
Intraoperative	
Choroidal haemorrhage (mild, did not need draining)	1.6 (2)
Postoperative	
Retroprosthetic membrane (needed a YAG laser)	14.3 (18)
Endophthalmitis	4.8 (6)
Retinal detachment	4.8 (6)
Choroidal haemorrhage	3.2 (4)
Cystoid macular oedema	2.4 (3)
Choroidal detachment	2.4 (3)
Extrusion/corneal melt	2.4 (3)
New onset glaucoma	2.4 (3)
Vitreous haemorrhage	1.6 (2)
Sterile uveitis	1.6 (2)
Hyphema	0.8 (1)
Wound dehiscence	0.8 (1)
Phthisis	0.8(1)
Blepharospasm	0.8 (1)
Macular pucker	0.8 (1)
Scleritis	0.8 (1)

Abbreviations used: BCVA, best-corrected visual acuity; YAG, yttrium-aluminium-garnet.

Study 5 Lekhanont K (2014)

Details

Study type	**Prospective case series**
Country	Thailand (single centre)
Recruitment period	2006–13
Study population and number	n=**40 (42 eyes) patients with poor prognosis for standard keratoplasty.** Indications (n): bullous keratopathy, (11); corneal dystrophies: Fuchs dystrophy, (4); gelatinous drop like dystrophy, (5); macular dystrophy, (1); chemical injury, (12); Stevens–Johnson syndrome [SJS], (13); herpetic keratitis, (1); Acanthamoeba keratitis, (1); traumatic corneal scar, (1); congenital corneal opacity, (1); congenital glaucoma with multiple surgery, (1); limbal stem cell deficiency of unknown cause, (4); limbal stem cell deficiency in patients with neurofibromatosis, (4). Indications for surgery: prior failed penetrating keratoplasty [mean 2.2], 59.5% (25/42); primary keratoprosthesis surgery, 40.5% (17/42). Comorbid conditions: glaucoma, 42.9% (18/42); diabetes, 25% (10/42). Concomitant surgical procedures: 83% (35/42): cataract extraction, 21; intraocular lens explantation, 12; anterior vitrectomy, 7; pupilloplasty, 3; iridotomy, 3; silicone oil removal, 1; symblepharon lysis, 1; pars plana vitrectomy, 1.
Age and sex	Mean age, 49.3 years; 69.1% male
Patient selection criteria	Inclusion criteria: patients with poor prognosis for primary or repeat penetrating keratoplasty, only patients with SJS or mucous membrane pemphigoid [MMP] who had wet eye, no symblepharon and normal blinking, compliant with postoperative regimen and a minimum follow-up of 4 years were included. Exclusion criteria: patients with less than 4-years follow-up (n=10) were excluded to improve the assessment of medium term effects of this treatment.
Technique	Boston keratoprosthesis type 1 device implanted (as per the Boston keratoprosthesis international protocol). Aphakic keratoprosthesis implanted in 88% (37/42) eyes. In most eyes the device was implanted in the corneal allograft and only 2 eyes had it implanted in their own corneas. The diameter of the corneal button ranged between 8 and 9.5 mm. 83% (35/42) had a backplate diameter of 8.5 mm and 17% (7/42) had a backplate diameter of 7 mm. 3 patients had sequential bilateral procedures. Bandage contact lenses and lateral tarsorrhapies were used in conjunction to minimise the risk of epithelial defect formation and corneal melting. Permanent topical antibiotic prophylaxis was also given to decrease the risk of infection. Postoperatively, follow-up was done on day 1, weeks 1, 2 and 4 and then every 1-3 months.
Follow-up	**Mean 64.9±15.2 months (range 48–88 months)**
Conflict of interest/source of funding	None, study supported by a research grant from Mahidol university.

Analysis

Follow-up issues: No patients were lost to follow-up.

Study design issues: Implants with polymethyl methacrylate (PMMA) backplate were used in the study. Data on all preoperative, intraoperative and postoperative variables were recorded for all patients. Simultaneously glaucoma surgery was not performed.

Study population issues: Heterogeneous population with different indications.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **40 (42 eyes)**

Best spectacle corrected visual acuity (BSCVA)

Follow-up	Improvement (≥2 lines) % (n)	Unchanged % (n)	Worsened % (n)
1 week	90.5 (38/42)	7.1 (3/42)**	2.4 (1/42)^^
6 months -best ever BCVA			
Eyes with improved BSCVA	100 (38/38)^		
Last follow-up (mean 64 months)			
All eyes	54.8 (23/42)	16.7 (7/42)	28.6 (12/42)
Eyes with improved BSCVA			39.5 (15/38)*

**1 due to amblyopia, 1 pre-existing advanced glaucoma, 1 postoperative bacterial endophthalmitis. ^^1 due to glaucoma progression. ^78.9% (30/38) achieved by 1 month and 21.1% (8/38) by 6 months. *The major cause of visual deterioration was glaucoma (60%, 9/15) and recurrent corneal melts with device extrusion needing PK (n=5).

Percentage of eyes with BSCVA ≥20/200

1, 2, 3 years	4 years	5 years	6 years
52.4	50	47.6	42.9 (18/42)

Refractive outcomes (dioptres [D])

Mean spherical refraction error	+0.52±3.16
Cylindrical refraction error	-0.78±1.11

Keratoprosthesis retention and failure rate (measured using Kaplan–Meier method) (mean 64.9 months)

Retention rate^	80.9% (34/42)
Failure rate*	4 per 100 eye years or 0.04/eye year

^defined as anatomical retention at last follow-up.

*defined as lack of retention because of extrusion or removal. 19% (8/42) devices were explanted (2 as a result of early and late postoperative endophthalmitis, 6 had device extrusion from severe corneal melting).

Multivariate analysis revealed that autoimmune cause was the only independent risk factor for keratoprosthesis failure [HR, 5.68; 95% CI 1.41 to 22.85; p=0.014].

The retention rate in 8 eyes with an autoimmune disease was 50% (4/8), corresponding to a failure rate of 0.14.eye year, whereas it was 88.2% (30/34) in eyes with non-autoimmune aetiology, resulting in a significantly lower failure rate of 0.02/eye year (log rank test p=0.006).

Repeat keratoprosthesis implantation

11.9% (5/42) eyes had a repeated keratoprosthesis because of recurrent corneal melts with device extrusion.

Safety

Intraoperative complications

Complication	n=42
Posterior capsule tear	1

Postoperative complications at each follow-up period*

	Years					
Complications	**1 n=42**	**2 n=42**	**3 n=42**	**4 n=42**	**5 n=34**	**Total % (n)**
Glaucoma (5 SJS, 29 non SJS)^						**80.9 (34/42)**
IOP elevation	0	4	3	1	0	19 (8/42)
Newly diagnosed	2	6	3	1	1	30 (13/42)
Progression (3 became blind)	5	4	3	1	0	30 (13/42)
RPM	8	10	4	0	0	52.4 (22/42)
Corneal melting^^	6	3	1	0	0	23.8 (10/42)
Infectious keratitis	2	3	1	1	2	21.4 (9/42)
Endophthalmitis (occurred days to years after surgery)	3	1	1	0	0	11.9 (5/42)
Vitreous haemorrhage	4	0	0	0	0	9.5 (4/42)
Retinal detachment	2	0	0	0	0	4.7 (2/42)
Cystoid macular oedema	1	0	0	0	0	2.4 (1/42)
Epiretinal membrane	1	0	0	0	0	2.4 (1/42)
Total	**34**	**31**	**16**	**4**	**3**	

*some eyes had more than 2 complications. 97.6% (41/42) eyes developed at least 1 complication (range 1-6) after surgery.

^ treated with anti-glaucoma drugs, 12 needed subsequent surgical interventions at mean 22.1 months.

^^ in patients with Stevens–Johnson syndrome and the melt led to further morbidity, infection and implant extrusion

No sterile viritis was observed.

Abbreviations used: BSCVA, best spectacle corrected visual acuity; CI, confidence interval; HR, hazard ratio; IOP, intraocular pressure; SJS, Stevens–Johnson syndrome; PK, penetrating keratoplasty; RPM, retroprosthetic membrane.

Study 6 Cortina MS (2015)

Details

Study type	**Prospective case series**
Country	USA (single centre)
Recruitment period	2011–14
Study population and number	n=**24** Indications for surgery (n): multiple failed grafts (6), aniridia (5), chemical burns (3), infectious keratitis (1), corneal dystrophy (1), other causes of limbal stem cell deficiency (3), Steven–Johnson syndrome (1), and hypotony (4). Mean VFQ-25 composite baseline score: 44.6±21.4 Preoperative visual acuity: 20/00 (n=1), 20/600 (n=1), count fingers (n=11), hand motion (n=8), and light perception (n=3). Preoperative vision in contralateral eye: 20/200 or better (n=10), worse than 20/200 (n=14).
Age and sex	Mean 53.5 years; 37.5%(9/24) male
Patient selection criteria	Not reported
Technique	Boston keratoprosthesis type I (in 23) and type II (in 1) were implanted. Implantations were performed by 1 surgeon.
Follow-up	**Mean 16 months (range 2–36 months)**
Conflict of interest/source of funding	No conflicts of interest.

Analysis

Follow-up issues: At the first follow-up, 2 patients in the cohort missed their data collection.

Study design issues: Small sample size, the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) was used to assess the impact of keratoprosthesis on patient reported visual function. Data were collected by administering an interview at 3, 6 and 12 months and yearly thereafter. Patients under 18 years at the time of surgery or without at least 1 postoperative follow-up visit were excluded from the analyses. Patients who underwent device removal or repeat implantation in the same eye during the study period were included only once.

Visual acuity was assessed using a Snellen chart with manifest refraction. If the patient was unable to identify <20/200 Snellen letters, visual acuity was assessed as counting fingers, hand motion and light perception.

Only 1 patient had a type II device.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **22**

Postoperative NEI VFQ-25 and vision-related quality of life outcomes (baseline versus first average follow-up)

VFQ-25 (n=22)	Baseline	3-month follow-up	Mean change	p value
Overall score	43.1	70.0	26.8	<0.001
General health	54.5	56.8	2.3	0.58
General vision	31.2	68.2	37.0	<0.001
Ocular pain	75.6	83.0	7.4	0.14
Near activities	29.2	62.7	33.5	0.0004
Distance activities	32.2	61.2	29.0	<0.0001
Social functioning	42.0	69.3	27.3	0.0003
Mental health	37.2	65.1	27.8	<0.0001
Role difficulties	34.1	59.1	25.0	0.005
Dependency	40.9	64.8	23.9	0.005
Driving	35.8	45.8	10.0	0.11
Colour vision	60.7	90.5	29.8	0.0002
Peripheral vision	35.7	71.4	35.7	<0.0001

Postoperative NEI VFQ-25 and vision-related quality of life outcomes (baseline versus mean average follow-up)

VFQ-25 (n=24)	Baseline	Average follow-up 16 months	Mean change	p value
Overall score	44.6	72.2	27.6	<0.0001
General health	54.5	57.2	3.0	0.44
General vision	32.8	69.3	36.5	<0.0001
Ocular pain	75.5	82.8	7.3	0.10
Near activities	31.5	66.3	34.8	<0.0001
Distance activities	33.0	61.0	28.0	<0.0001
Social functioning	44.8	73.2	28.4	<0.0001
Mental health	38.5	67.9	29.3	<0.0001
Role difficulties	35.4	66.2	30.7	0.0001
Dependency	42.0	70.7	28.7	0.0003
Driving	44.6	54.5	9.9	0.2368
Colour vision	64.6	87.5	22.9	0.0004
Peripheral vision	34.4	70.7	36.3	<0.0001

Visual acuity of contralateral eye (baseline versus average follow-up)

A change in scores was observed in patients who had poor vision in the contralateral eye. Patients with vision better than 20/200 in the contralateral eye showed statistically significant improvement in overall scores (0.0013) and subscale scores compared with baseline.

Abbreviations used: NEI VFQ, National Eye Institute Visual Function Questionnaire.

Study 7 Munoz-Gutierrez G (2013)

Details

Study type	**Retrospective case series**
Country	Spain (single centre)
Recruitment period	2006–11
Study population and number	n=**37 (41 eyes)** Indications for surgery: 7 with ampullous keratopathy, 5 mucosynechiae syndromes, 4 aniridic keratopathy, 3 corneal ulcer, 2 caustication, 2 leukoma, 2 herpetic keratitis, 2 ocular trauma, 2 keratoconus, 1 calcium keratopathy, 1 immunotactoid keratopathy, 1 Terrien marginal degeneration, 1 limbal insufficiency, 1 sclerocornea, 1 neurotrophic keratitis, 1 ectodermic syndrome, 1 congenital glaucoma. Concomitant surgical procedures: 8 vitrectomies, 8 cataract removals, 4 intraocular lens insertions, 3 intraocular lens explants, 1 Ahmed valve insertion. Prior surgeries: penetrating keratoplasties: mean 2.36 (0–8); non-penetrating keratoplasties: mean 1.58 (0–9).
Age and sex	Mean 56.4 years; 59.5%(22/37) male
Patient selection criteria	Inclusion criteria: patients with a visual acuity of 20/200 with the best or worst eye but maintaining acceptable visual function (demonstrated by means of visual acuity measurement or supplementary evaluations).
Technique	Boston keratoprosthesis type I implanted by 3 surgeons. If the patient was phakic, cataract was extracted and rendered aphakic prior to aphakic prosthesis implantation. If the patient had an intraocular lens, a pseudophakic prosthesis was placed. In 10% (4/37) patients, bilateral procedures were performed. Patients were followed-up weekly for the first few months and subsequently between every 6 and 12 weeks. 5% povidone iodine washes were added at each check-up for patients with a high risk or previous history of endophthalmitis, autoimmune diseases or those with only 1 seeing eye.
Follow-up	**Mean 22.17 months (range 3–46 months)**
Conflict of interest/source of funding	No conflicts of interest.

Analysis

Study design issues: Small sample size, patients' clinical records were analysed and those who did not have a follow-up of at least 3 months were excluded from the analysis. Visual acuity was measured in decimal scale and converted to logMAR. Conversion scales by Schulze–Bonsel for visual acuities between no perception of light (0.001) and finger counting (0.015) were used.

One patient who had a bilateral procedure had a contralateral osteo-odonto-keratoprosthesis.

All extraocular complications which did not affect vision (for example palpebral ptosis) and were not secondary to keratoprosthesis type I were excluded from the study.

Study population issues: Patients had a variety of diseases and received multiple surgeries and prolonged topical treatments.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **37 (41 eyes)**

Mean best corrected visual acuity (BCVA) (in the logMAR scale)

	logMAR
Baseline	2.05 (range 1.10-2.52)
After surgery	1.16 (range 0.08-2.70)
Last follow-up*	1.47 (range 0.08-3)

*mean 22.17 months.

82.9% (32/37) patients maintained or improved vision

Retention rate: 95.12% (39/41)

Safety

Post-surgery complications	**% (n=41)**
Retroprosthetic membranes (14 needed treatment [24 laser YAG and 3 additional surgical membranectomy done]; 8 did not need treatment; 6 were secondary due to concomitant surgical procedures)	53.65 (22/41)
Chorioretinal adhesion problems (retinal detachment and/or choroidal detachment/retinoschisis) (6 needed surgery: 5 had vitrectomy, 1 had TSCPC)	26.82 (11/41)
Infection (2 infectious keratitis, 5 endophthalmitis; corneal graft substituted in 3 and vitrectomy performed in all and antibiotics given)	17.07 (7/41)
Stromal necrosis	4.87 (2/41)
Device extrusion (in patients with Lyell syndrome)	4.87 (2/41)
Hypertensive crises	4.87 (2/41)
Occlusive vasculopathy (peripheral occlusive vasculitis and ischaemia of the entire retina)	4.87 (2/41)
Non-infectious vitritis	2.44 (1/41)
Pre-retinal membrane	2.44 (1/41)
Vitreous haemorrhage	2.44 (1/41)
Hypotony/pseudopapilloedema	2.44 (1/41)
Acute glaucoma (resolved with application of TSCPC, IOP under control; 1 had choroidal detachment after surgery)	4.87 (2/41)

Abbreviations used: BCVA, best corrected visual acuity; IOP intraocular pressure; logMAR, logarithm of the minimum angle of resolution; TSCPC, trans-scleral cyclophotocoagulation; YAG, yttrium-aluminium-garnet.

Study 8 Ang AY (2012)

Details

Study type	**Retrospective case series**
Country	USA (single centre)
Recruitment period	2004–11
Study population and number	**n=122 (136 eyes)**
Age and sex	Average 50.7 years; 50% male
Patient selection criteria	Not reported.
Technique	Boston keratoprosthesis type I devices (with 8.5 mm diameter, polymethyl methacrylate (PMMA) back plates) were implanted.
Follow-up	**Mean 23.5 months (range 2–77 months)**
Conflict of interest/source of funding	No conflicts of interest.

Analysis

Study design issues: Patient medical records were reviewed and cases of traumatic rupture were identified.

Key efficacy and safety findings

Safety
Number of patients analysed: **122 (136 eyes)**
Incidence of traumatic wound rupture: 2.9% (4/136; average age 39 years)
Indications: congenital aniridia, 2, Stevens–Johnson syndrome, 1, scarred vascularised cornea after traumatic global rupture, 1.
Average time to injury: 4.2 months (1.0–9.0 months) after implantation.
Site of rupture: All ruptures occurred at the graft–host junction.
Cause of injury: accidental blunt eye injuries by various objects (2 were minor trauma).
2 eyes had complete keratoprosthesis extrusion (one at 4 days after injury; another at 9 months after injury) and vitreous prolapse to the wound. These patients underwent therapeutic PK and after 2 months, vision deteriorated due to retinal detachment. In 1 patient it decreased from hand motion to no light perception and in another from 20/300 CDVA to counting fingers vision, respectively.
One eye that had 4-clock hours of superior wound rupture recovered vision from light perception to 20/40 at 8 months post-trauma. Patient underwent suturing to the dehisced area with a 10–0 nylon interrupted suture.
One eye that had 2-clock hours wound rupture maintained a stable vision of 20/125 after repair.
Abbreviations used: CDVA, corrected distance visual acuity; PK, penetrating keratoplasty; PMMA, polymethyl methacrylate.

Study 9 Dokey A (2012)

Details

Study type	**Retrospective case series**
Country	USA (single centre)
Recruitment period	2004–10
Study population and number	**n=68 (68 eyes)**
Age and sex	Range 32–69 years
Patient selection criteria	Patients with corneal opacity or disease secondary to previous multiple donor graft failures (average 1.7); acquired or congenital limbal stem cell deficiency, other conditions with poor donor corneal graft survival who underwent Boston keratoprosthesis type I implantation between 2004–10 were included. Paediatric patients were excluded.
Technique	Boston keratoprosthesis type I devices with perforated back plates were implanted by a single surgeon.
Follow-up	**Median 16.9 months (range 6.9–26.7months)**
Conflict of interest/source of funding	No conflicts of interest.

Analysis

Follow-up issues: 1 patient was lost to follow-up.

Study design issues: Retrospective study, small sample size, patient medical records were reviewed and cases of chronic hypotony were identified.

Key efficacy and safety findings

Safety
Number of patients analysed: **67 (67 eyes)**
Chronic hypotony not related to anatomic problems (e.g. retinal detachment, over filtering glaucoma tube shunts, tissue necrosis with aqueous leak): **9% (6/67)** at a median of 18.5 months after implantation.
Hypotony was identified when a lower than usual eye pressure was detected at more than 1 visit by digital palpation.
5 eyes had device implantation for corneal graft failure (median 2) and 1 eye had primary device implantation for severe corneal scarring from trachoma. All eyes had decreased visual acuity and retroprosthetic membranes; 5 had previous history of glaucoma or ocular hypertension, but only 3 had a glaucoma drainage implant.
Treatment and outcome: 4 patients had pars plana vitrectomy and silicone oil injection. All had increased vision ranging from hand motion to 20/400, 1 patient with 1 affected eye deferred treatment and progressed to phthisis bulbi requiring enucleation and 1 eye had pre-phthisis and no surgery was offered.
Acute hypotony was reported in 1 patient after application of a laser in 1 eye with glaucoma tube shunts.
Incidence of chronic hypotony: at 1 year 3.7% (95% CI 0.9 to 14%); at 2 years13.3% (95% CI 5.5 to 30.0%) and at 3 years 20%.
Risk factors for hypotony: Cox regression analysis demonstrated an increased risk of chronic hypotony in eyes with retroprosthetic membranes ($p<0.01$) but no increase in risk for older patients ($p>0.1$), eyes with glaucoma drainage implants ($p>0.5$) or multiple prior donor corneal transplants ($p>0.5$).
Abbreviations used: CI, confidence interval.

Study 10 Philips DL (2014)

Details

Study type	**Retrospective case series**
Country	USA (single centre)
Recruitment period	2008–13
Study population and number	**n=9 (9 eyes) with failed interventions for severe chemical and thermal injury.** Indications: 7 alkali burns, 1 with acid burn and 1 with a thermal burn. 6 bilateral injuries, 3 unilateral injuries. Previous surgeries: limbal stem cell transplants and subsequent penetrating keratoplasty Concomitant surgical procedures: glaucoma procedures in all, anterior vitrectomy in 6, tarsorrhaphy in 1.
Age and sex	Mean 55.4 years; 89% (8/8) male.
Patient selection criteria	Not reported
Technique	Boston keratoprosthesis type I implanted by 2 surgeons. Patients were examined at day 1, 1 week, 2 weeks, 1 month and quarterly thereafter. Postoperative bandage lens was exchanged every 1 to 3 months. All eyes received standard antibacterial prophylaxis.
Follow-up	**Mean 40.7 months (range 29–60 months)**
Conflict of interest/source of funding	No conflicts of interest.

Analysis

Study design issues: Retrospective chart review was performed. Patients who had the surgery for chemical or thermal injuries were included.

Key efficacy and safety findings

Safety

Number of patients analysed: **9 eyes**

Visual outcomes at mean follow-up of 40.7 months

The median BCVA was 20/60 (range, 20/15 to no light perception) (p=0.02). One eye was >20/20, 3 eyes were >20/40, and 6 eyes were >20/70.

Prosthesis retention rate (defined as in situ maintenance of the initial KPro-1 until the most recent follow-up, irrespective of the functional outcome): 77.8% (7/9).

Failure rate: 21% (2/9), (**in 2 patients with sterile corneal ulceration at the graft–optic junction**: 1 occurred after 52 months and 1 at 10 months, both successfully removed and replaced, 1 of the eyes also had a concomitant retinal detachment repair and 1 developed endophthalmitis and became blind and was enucleated).

Complications

Postoperative complications*	**100% eyes**
Serious complications^	**66.7% (6/9) eyes**
Sterile corneal ulceration (with prosthesis extrusion)	22 (2/9)
Microbial keratitis (1 fungal, 1 bacterial)	22 (2/9)
Endophthalmitis (bacterial)	22 (2/9)
Retinal detachments	22 (2/9)
Infections (in those with microbial keratitis, endophthalmitis)	44 (4/9)
Cystoid macular oedema (treated with intravitreal injections)	33 (3/9)
Epiretinal membranes (not surgically removed)	22 (2/9)

*more than 1 complication occurred in 2 eyes.

^ these complications contributed to visual outcomes of hand motion in 2 eyes and no light perception in 1 eye.

Abbreviations used: BCVA, best corrected visual acuity; KPro, keratoprosthesis.

Case reports on adverse events (11, 12, 13)

Safety

Knaoff JM (2010)

Case report - adverse event

USA

n=1

Pigmented deposits on the keratoprosthesis associated with the use of topical ibopamine as a treatment for hypotony

A 56-year-old man with a history of multiple corneal and cataract surgeries developed chronic hypotony (treated with topical ibopamine), chronic corneal oedema, neovascularisation and scarring. Due to the neurotrophic corneal bed, Boston keratoprosthesis type I was implanted and patient continued treatment for hypotony. After surgery his vision improved to 20/200, but 3 months after surgery his vision dropped to counting fingers and a large central black deposit on the bandage lens on the front plate of the keratoprosthesis was noted. This resulted in deterioration of best corrected visual acuity. This was treated by removing the bandage contact lens and changing to a daily disposable contact lens and regular cleaning of the front plate with diluted baby shampoo and surgical sponges.

Najem K (2014)

Retrospective case series - adverse event

Canada

n=3 (mean age 62.3 years) 2 Aniridia, 1 failed PKs secondary to keratitis.

Device leak

All three patients (3 eyes) developed several postoperative complications. Device leaks at the keratoprosthesis stem were reported in all leading to hypotony (at a mean of 13.7 months) after Boston keratoprosthesis type-1 implantation surgery. All patients had uveitis and vitritis preceding choroidal and retinal detachments, and required vitreoretinal surgeries (pars plana vitrectomy) for repair. An objective leak through the cornea-anterior front plate interface of the keratoprosthesis was seen intraoperatively by the vitreoretinal surgeon. In 1 patient the leak was no longer evident, in the second patient, a repeat KPro was needed to stop the persistent leak, in the third patient the persistent leak was repaired with glue. Mean best corrected visual acuity stabilised at 20/300 after the complication resolved, with a mean intraocular pressure of 10 mmHg.

Chen JL (2012)

Case report-adverse event

USA

n=1

Diplopia

A 33-year-old woman with a history of penetrating trauma to the left eye at age 13 years with traumatic cataract and corneal scarring, had a series of failed corneal transplants resulting in counting fingers vision and sensory exotropia. After successful implantation of the Boston keratoprosthesis type 1, her vision improved but she developed horizontal diplopia.

Patient underwent strabismus surgery. This restored binocular vision.

Abbreviations used: BCVA, best-corrected visual acuity; IOP intraocular pressure; PK, penetrating keratoplasty.

Efficacy

Visual acuity

A case series of 150 patients (158 eyes) who had type I corneal graft–keratoprosthesis implantation reported that preoperatively only 9% of eyes had best corrected visual acuity (BCVA) of 20/200 or better. Postoperatively, 70% (97/138) of eyes had achieved BCVA of 20/200 or better at a median follow-up of 6.3 months; 30% (41/138) of eyes did not achieve BCVA of 20/200 or better because of pre-existing posterior segment conditions. The probability of maintaining the same vision at 7 years (n=97 eyes; estimated with Kaplan–Meier survival curves) was 50%[3].

A case series of 40 patients (42 eyes) who had type I corneal graft–keratoprosthesis implantation reported that at 1 week 90% (38/42) of eyes had an improvement in best spectacle corrected visual acuity (BSCVA) by 2 or more lines compared with preoperative BSCVA. Best ever vision was reached by 6 months in 100% of eyes with improved BSCVA (n=38) but 39% (15/38) of eyes did not maintain the improved vision. At last follow-up (at a mean of 64 months), 55% (23/42) of eyes had an improvement in BSCVA by 2 lines or more[5].

Retention (survival) rate

The case series of 150 patients (158 eyes) reported an overall device retention rate of 84% at 2 years and 67% (89/133) at 7-year follow-up[3].

The case series of 40 patients (42 eyes) reported that the overall keratoprosthesis survival rate (defined as anatomical retention at last follow-up) was 81% (34/42) during an average follow-up of 64.9 months[5].

A case series of 300 patients (300 eyes) who had type I corneal graft–keratoprosthesis implantation reported an overall retention rate (defined as anatomical retention at the last follow-up date) of 93% at an average follow-up of 17.1 months. The mean survival time was 3.8 years (standard error±0.09). The probability of retention after 1 and 2 years was 94% and 89%, respectively[1].

Device failure

The case series of 150 patients (158 eyes) reported device removal in 33.2% (44/133) of patients at 7-year follow-up[3]. In 25% (35/139) of eyes, the device was removed (30/139) or the eye was enucleated (5/139) as a result of device-related complications during follow-up[3].

The case series of 40 patients reported keratoprosthesis failure (defined as lack of retention because of extrusion or removal) in 19% (8/42) of eyes corresponding to a failure rate of 4 per 100 eye years or 0.04/eye year[5]. Two devices were explanted as a result of early and late postoperative endophthalmitis, 6 had device extrusion from severe corneal melting. Multivariate

analysis showed that autoimmune disease was the only independent risk factor for keratoprosthesis failure (hazard ratio [HR], 5.68; 95% confidence interval [CI] 1.41 to 22.85, p=0.014)[5]. The retention rate in 8 eyes with an autoimmune disease was 50% (4/8), corresponding to a failure rate of 0.14 eye years, whereas it was 88% (30/34) in eyes with non-autoimmune aetiology, resulting in a significantly lower failure rate of 0.02/eye year (log rank test p=0.006)[5].

The case series of 300 patients (300 eyes) reported device failure (defined as a lack of anatomical retention, which includes removal, extrusion or loss of the eye) in 7% (21/300) patients. The reasons for loss include sterile keratolysis (n=9), fungal infections (n=8), retroprosthetic membranes (n=3), and bacterial endophthalmitis (n=1). Sixteen patients received a replacement keratoprosthesis, 2 had standard penetrating keratoplasty without a keratoprosthesis, 1 developed a self-sealing membrane and 2 eyes were enucleated. Multivariate analysis demonstrated 3 independent risk factors for keratoprosthesis loss: autoimmune aetiology such as Stevens–Johnson syndrome, ocular cicatricial pemphigoid (HR 11.94; 95% CI 3.31 to 43.11, p=0.0002), ocular surface exposure needing a concomitant tarsorrhaphy (HR 3.43; 95% CI 1.05 to 11.22, p=0.042) and a number of prior failed penetrating keratoplasties (HR 1.64; 95% CI 1.18 to 2.28, p=0.003)[1].

Repeat keratoprosthesis implantation

The case series of 150 patients (158 eyes) reported that 12% (5/42) of eyes had repeated keratoprosthesis implantation because of recurrent corneal melts with device extrusion[3].

Vision related quality of life

A case series of 24 patients who had corneal graft–keratoprosthesis implantation (type I in 23 patients and type II in 1 patient) reported significant improvement in the postoperative vision-related quality of life (assessed using the National Eye Institute Visual Functioning Questionnaire [NEI VFQ-25]) at 3-month follow-up when compared with baseline scores (patient-reported visual function overall score: 43.1 versus 70.0 at 3 months [p<0.001]). Subscale scores within NEI VFQ-25 showed significant improvement in general vision, near and distance activities, social functioning, mental health, role difficulties, dependency, colour vision and peripheral vision (p<0.05). The improvement was also seen when comparing baseline scores with postoperative scores at an average follow-up of 16 months[6].

Safety

Retroprosthetic membrane

Retroprosthetic membrane formation was reported in 54% (22/41) of eyes in a case series of 37 patients who had type-I corneal graft–keratoprosthesis

implantation at a mean follow-up of 22 months. Fourteen patients needed treatment with yttrium-aluminium-garnet (YAG) laser (3 of them needed additional surgical membranectomy) and 8 patients did not need any treatment. In 6 patients, retroprosthetic membrane formation was secondary to concomitant surgical procedures[7].

Retroprosthetic membrane formation was reported in 52% (22/42) of eyes in a case series of 40 patients (42 eyes implanted with type I corneal graft–keratoprosthesis) at a mean follow-up of 64 months (further details were not reported)[5].

Retroprosthetic membrane formation was reported in 50% (66/133) of patients in a case series of 150 patients (158 eyes) at 7-year follow-up. The incidence seemed to plateau after the first 3 years; 33% of these patients underwent a YAG laser membranectomy and 18.6% needed a surgical membranectomy[3].

Corneal melting

Corneal melting was reported in 24% (10/42) of eyes in the case series of 40 patients at a mean follow-up of 64 months[5]. This occurred in patients with Stevens–Johnson syndrome and the melt led to further morbidity, infection and implant extrusion[5].

Retinal detachment

Chorioretinal adhesion problems (retinal detachment with or without choroidal detachment or retinoschisis) were reported in 27% (11/41) of eyes in the case series of 37 patients at a mean follow-up of 22 months. Six patients needed surgery: 5 had vitrectomy and 1 had trans-scleral cyclophotocoagulation[7].

Retinal detachment was reported in 19% (25/133) of patients in the case series of 150 patients (158 eyes) at 7-year follow-up (further details were not reported)[3].

Glaucoma

Glaucoma or increased intraocular pressure was reported in 81% (34/42) of eyes (in 5 eyes of people with, and 29 eyes of people without, Stevens–Johnson syndrome) in the case series of 40 patients at a mean follow-up of 64 months. Increased intraocular pressure was noted in 19% (8/42) of eyes, glaucoma was newly diagnosed in 30% (13/42) of eyes and 30% (13/42) of eyes with preoperative glaucoma had disease progression. All were treated with anti-glaucoma drugs, but 12 needed surgical interventions at mean follow-up of 22.1 months, corresponding to a glaucoma surgery rate of 0.062/eye year[5].

Glaucoma needing additional surgery for management (that is, tube shunt surgery or diode ciliary body ablation) was reported in 22% (29/133) of patients in the case series of 150 patients (158 eyes) at 7-year follow-up. The need for glaucoma surgery did not differ when comparing eyes with and without glaucoma

(21% versus 17%, p=0.99).There was an increased need for glaucoma surgery postoperatively in eyes without glaucoma compared with prior or concurrent glaucoma surgery (31.4% versus 18.9%, p=0.10)[3].

Endophthalmitis

Infectious endophthalmitis was reported in 16% (20/133) of patients in the case series of 150 patients (158 eyes) at 7-year follow-up (further details were not reported)[3].

Infectious endophthalmitis (that occurred from days to years after surgery) was reported in 12% (5/42) of eyes in the case series of 40 patients at a mean follow-up of 64 months (further details were not reported)[5].

Infectious keratitis

Infectious keratitis was reported in 21% (9/42) of eyes (3 eyes of people with autoimmune disease and 6 eyes of people with non-autoimmune disease) in the case series of 40 patients at a mean follow-up of 64 months (further details were not reported)[5].

Infections (infectious keratitis in 2 and endophthalmitis in 5) were reported in 17% (7/41) of eyes in the case series of 37 patients at a mean follow-up of 22 months. Corneal graft was substituted in 3 patients and vitrectomy was performed in all. Topical treatments were provided for all[7].

Sterile corneal stromal necrosis

Sterile necrosis was reported in 20% (26/133) of patients in the case series of 150 patients (158 eyes) at 7-year follow-up (further details were not reported)[3].

Stromal necrosis was reported in 5% (2/41) of eyes in the case series of 37 patients at a mean follow-up of 22 months (further details were not reported)[7].

Sterile vitritis

Sterile vitritis was reported in 4% (4/101) of eyes in an international series compared with 11% (10/94) of eyes in a US series (p=0.096) in a retrospective case series of 194 patients at a mean follow-up of 14.2 and 24.1 months (further details were not reported)[2].

Cystoid macular oedema

Cystoid macular oedema was reported in 10% (13/133) of patients in the case series of 150 patients (158 eyes) at 7-year follow-up (further details were not reported)[3].

Persistent epithelial defects

Persistent epithelial defects were reported in 8% (11/133) of patients in the case series of 150 patients (158 eyes) at 7-year follow-up (further details were not reported)[3].

Persistent epithelial defects were reported in 10% (10/101) of eyes in the international series compared with 36% (34/94) of eyes in the US series ($p<0.0001$) in the retrospective case series of 194 patients at a mean follow-up of 14.2 and 24.1 months (further details were not reported)[2].

Vitreous haemorrhage

Vitreous haemorrhage was reported in 10% (4/42) of eyes in the case series of 40 patients at 1-year follow-up (further details were not reported)[5].

Epiretinal membrane

Epiretinal membrane formation was reported in 1 patient in the case series of 40 patients (42 eyes) at 1-year follow-up (further details were not reported)[5].

Pre-retinal membrane was reported in 1 patient in the case series of 37 patients (40 eyes) at a mean follow-up of 22 months (further details were not reported)[7].

Device leak

Device leaks at the keratoprosthesis stem (through the cornea–anterior front plate interface of the device) were reported in 3 eyes (at a mean of 13.7 months) after type I corneal graft–keratoprosthesis implantation in a case report of 3 patients. In 1 patient, the leak was not evident; in the second patient, a repeat keratoprosthesis implantation was needed to stop the persistent leak; in the third patient the persistent leak was repaired with glue. Mean best corrected visual acuity stabilised at 20/300 after the complication resolved[12].

Traumatic wound rupture

Traumatic wound rupture (at the graft–host junction) at an average of 4.2 months after type 1 corneal graft–keratoprosthesis implantation was reported in 3% (4/136) of eyes in a case series of 122 patients. In 2 eyes, the device was extruded and therapeutic penetrating keratoplasties were performed, but vision deteriorated. In 2 eyes with wound rupture, suturing of the wound was done. Vision improved in 1 eye and in the other it was stable[8].

Occlusive vasculopathy

Occlusive vasculopathy (peripheral occlusive vasculitis and ischaemia of the entire retina) was reported 5% (2/41) of eyes in the case series of 37 patients at a mean follow-up of 22 months (further details were not reported)[7].

Corneal infiltrate

Corneal infiltrate was reported in 12% (12/101) of eyes in the international series compared with 10% (9/94) of eyes in the US series in the retrospective case series of 194 patients at a mean follow-up of 14.2 and 24.1 months (further details were not reported)[2].

Scleritis

Scleritis was reported in 1 patient in a case series of 122 patients (126 eyes) at 6-month follow-up (further details were not reported)[4].

Choroidal haemorrhage

Choroidal haemorrhage was reported in 3% (4/122) of patients in the case series of 122 patients (126 eyes) at 6-month follow-up (further details were not reported)[4].

Hypotony

Chronic hypotony was reported in 9% (6/67) of patients in a case series of 68 patients at a median follow-up of 18.5 months after type I corneal graft–keratoprosthesis implantation. The incidence of chronic hypotony was 3.7% at 1 year (95% confidence interval [CI] 0.9% to 14%) and 13.3% at 2 years (95% CI 5.5% to 30%). All eyes had retroprosthetic membranes and decreased visual acuity and 5 eyes had previous history of glaucoma or ocular hypertension. Four patients had pars plana vitrectomy and silicone oil injection and reported increased vision ranging from 'hand motion' to 20/400. One patient with 1 affected eye deferred treatment and the eye progressed to phthisis bulbi needing enucleation. One eye had pre-phthisis and no surgery was needed[9].

Hypotony/pseudopapilloedema was reported in 1 patient in the case series of 37 patients at a mean follow-up of 22 months (further details were not reported)[7].

Posterior capsular tear

Posterior capsular tear was reported in 1 patient during the surgery in the case series of 40 patients (further details were not reported)[5].

Corneal ulceration

Sterile corneal ulceration at the graft–optic junction was reported in 22% (2/9) of eyes (1 after 52 months and 1 at 10 months), in a case series of 9 patients (9 eyes) with failed interventions for chemical and thermal injury. Both devices were removed and replaced, 1 also had a concomitant retinal detachment repair. Vision deteriorated in 1 eye and the other eye developed endophthalmitis and became blind and painful, and was enucleated[10].

Diplopia

Horizontal diplopia after type I keratoprosthesis implantation was reported in a patient with a history of trauma and a series of failed corneal transplants. Strabismus surgery restored binocular vision[13].

Pigmented deposits on the device

Pigmented deposit on the keratoprosthesis (a large central black deposit on the bandage contact lens on the front plate of the device) associated with the use of topical ibopamine as a treatment for chronic hypotony was reported in a patient implanted with a type I device. Postoperatively, vision improved to a BCVA of 20/200, but after 3 months, vision deteriorated because of the pigmented deposit. This was treated by removing the bandage contact lens and changing to a daily disposable contact lens and regular cleaning of the front plate with diluted baby shampoo and surgical sponges[11].

Validity and generalisability of the studies

- There are no randomised controlled trials comparing implantation of a type I corneal graft–keratoprosthesis with repeat donor corneal transplantation.
- Most of the studies were retrospective case series mainly from centres in the USA. One study compared the results of implantations at 1 centre in the USA with an international case series.
- The main indication for type I corneal graft–keratoprosthesis implantation was repeated standard corneal transplantation failure. Some studies also included patients who had it as a primary procedure in eyes that were at high risk of failure with standard transplantation (for example, Stevens–Johnson syndrome, mucous membrane pemphigoid).
- There is considerable variability in indications for surgery and the number of previous graft failures across studies.
- Data on visual acuity were missing beyond 1-year follow-up in most of the studies.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

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

- Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus and keratectasia. NICE interventional procedure guidance 466 (2013). Available from http://www.nice.org.uk/guidance/IPG466
- Corneal inlay implantation for correction of presbyopia. NICE interventional procedure guidance 455 (2013). Available from http://www.nice.org.uk/guidance/IPG455
- Corneal endothelial transplantation. NICE interventional procedure guidance 304 (2009). Available from http://www.nice.org.uk/guidance/IPG304
- Implantation of miniature lens systems for advanced age-related macular degeneration. NICE interventional procedure guidance 272 (2008). Available from http://www.nice.org.uk/guidance/IPG272
- Corneal implants for keratoconus. NICE interventional procedure guidance 227 (2007). Available from http://www.nice.org.uk/guidance/ipg227
- Corneal implants for correction of refractive error. NICE interventional procedure guidance 225 (2007). Available from http://www.nice.org.uk/guidance/ipg225
- Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium NICE interventional procedure guidance 216 (2007). Available from http://www.nice.org.uk/guidance/IPG216
- Insertion of hydrogel keratoprosthesis. NICE interventional procedure guidance 69 (2004). Available from http://www.nice.org.uk/guidance/IPG69

NICE guidelines

- Glaucoma: Diagnosis and management of chronic open angle glaucoma and ocular hypertension. NICE clinical guideline 85 (2009). Available from http://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. 2 Specialist Advisor Questionnaires for Implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes were submitted and can be found on the NICE website https://www.nice.org.uk/guidance/indevelopment/GID-IP1160

Patient commentators' opinions

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

Issues for consideration by IPAC

- Ongoing trials
  - JPRN-UMIN000007063 Exploratory clinical trial of artificial cornea Boston keratoprosthesis in eyes with refractory corneal opacity after unsuccessful corneal transplantation. Study type: non-randomised study; sample size: n=6; primary outcomes: visual acuity, ratio of KPro survival; Location: Japan.
  - NCT02084745: Timing of glaucoma drainage device with Boston Keratoprosthesis surgery. Study type: randomised study; (simultaneous implantation of glaucoma drainage device at time of type 2 surgery versus implantation of a glaucoma drainage device 6 months after type 2 surgery) estimated enrolment: n=60; primary outcomes: visual field mean deviation, Humphrey visual field 24-2; study start date: March 2014; completion date: March 2017; Location: Canada.

References

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3. Srikumaran D, Munoz B et al (2014). Long-term outcomes of Boston type 1 keratoprosthesis implantation: A retrospective multicenter cohort. Ophthalmology 121:2159-2164
4. Dunlap K., Chak G et al (2010). Short-term visual outcomes of Boston type 1 keratoprosthesis implantation. Ophthalmology 117: 687-692
5. Lekhanont K., Thaweesit P et al (2014). Medium-term outcomes of boston type 1 keratoprosthesis implantation in Bangkok, Thailand. Cornea 33: 1312-1319
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12. Najem K, Sebag M, and Harissi-Dagher M (2014). Boston keratoprosthesis type 1 device leak. Canadian Journal of Ophthalmology 49: 106-108.
13. Chen JL, Shen TT et al (2012). Strabismus surgery in a patient with a Boston K-pro keratoprosthesis. Journal of Aapos: American Association for Pediatric Ophthalmology & Strabismus 16: 476-477.

Appendix A: Additional papers on implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes

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
Al Afraj K et al (2012). Short term visual outcomes of Boston keratoprosthesis type I in Saudi Arabia. Middle East Afr J Ophthalmology. 19:88-92.	Retrospective case series n=4 eyes (4 cases) 2 post-trachoma dense vascularized corneal scarring, 1 corneal alkali burn and 1 repeated failed corneal grafts Median follow-up: 11 months.	All patients demonstrated significant improvement in vision; with pre-operative visual acuity of hand movements (HM), counting fingers and HM improved to best corrected visual acuity (BCVA) of 20/200, 20/60, 20/50 and 20/30 on their last follow-up visits respectively. None of the patients developed glaucoma. No retro-prosthetic membrane developed till the last follow-up visit. One of the four patients had a corneal melt (due to severe dryness associated with trachoma) 6 months after the KPro implantation and underwent a successful KPro revision. Despite the relatively poor prognosis expected in alkali burn eye, the patient attained the maximum BCVA (20/30) of the four eye series on the last follow-up visit at six months.	Larger studies with longer follow-up included in table 2.
Aldave AJ et al (2009). The Boston type I keratoprosthesis: improving outcomes and expanding indications. Ophthalmology 116: 640-651.	Retrospective case series n=49 (50 eyes, 57 procedures) Repeat corneal transplantation failure (68%) BKPro type 1 2004-8 Follow-up: mean 17.3 months	Visual acuity of 20/100 or better was 67% at 6 months (n = 45), 75% at 1 year (n = 28), 69% at 2 years (n = 13), and 100% at 3 years (n = 7). Keratoprosthesis retention rate was 84% at an average follow-up of 17 months (79 person-years of follow-up), with 100% retention in 8 eyes with no history of prior corneal transplantation (14.8 person-years of follow-up). The most common postoperative complications were retroprosthetic membrane formation (22 eyes) and persistent epithelial defects (19 eyes). No cases of infectious endophthalmitis were encountered, and only 1 patient required glaucoma surgery.	Additional study related to Aldave 2012, included in table 2.
Ahmad S et al (2014). Predictors of Visual Outcomes Following Boston Type 1 Keratoprosthesis Implantation. Am J Ophthalmol.	Retrospective case series n=59 (59 eyes) KPro type 1 Follow-up: mean 37.8 months	88% (52/59) eyes achieved improved vision post implantation, with 7 eyes failing to gain vision as a result of pre-existing glaucoma (n=4) or retino-choroidal disease (n=3). 40% (21/52) maintained their best ever visual acuity at last visit. The likelihood of maintaining best ever vision was 71% at 1 year, 59% at 2 years and 48% at 3 years. Primary KPro implantation was associated with a higher likelihood of losing best ever	Factors associated with all cause and glaucoma related loss of visual acuity.

		vision as compared to KPro implantation as a repeat corneal procedure (Hazard Ratio [HR]=3.06; p=.006).	
Akpek EK et al (2007). Outcomes of Boston keratoprosthesis in aniridia: a retrospective multicenter study. American Journal of Ophthalmology 144: 227-231.	Retrospective case series n=15 (16 eyes) Follow-up: median 17 months Indication: Aniridia	All devices remained in situ throughout the follow-up period. The visual acuity improved in all but 1 patient from a median of counting fingers (light perception to 20/300) to 20/200 (hand motions to 20/60). Comorbid conditions particularly optic nerve and foveal hypoplasia limited the final postoperative vision. No endophthalmitis or extrusion of the device occurred. One device required repair procedure without necessitating a removal.	Additional study related to Dunlap 2010, included in table 2.
Aquavella JV et al (2006). Keratoprosthesis: current techniques. McCormick, G. J., and Palakuru, J. R. Cornea 25: 656-662.	Retrospective comparative case series n=32 Cardona KPro versus 25 Dohlman Doane type 1 KPro Eyes with poor prognosis for penetrating keratoplasty. 2003-5 USA	In Cardona cases, 39% (12/31) achieved a visual acuity of 20/40 or better postoperatively, degrading to 16% (5/31) at the end. 50% (15/31) required surgical revision. 16% (5/31) developed endophthalmitis, and 58% (18/31) developed retroprosthetic membranes. 5 dislocations of the prosthesis and an additional 3 frank extrusions (26%) reported. In the Dohlman-Doane cases, no reoperations, endophthalmitis, dislocations, or extrusions reported. 48% (12/25) achieved 20/200 acuity or better, and 12% (3/25) achieved 20/40 or better. Retroprosthetic membranes formed in 3 cases.	Early model of the Boston KPro device (Dohlman Doane KPro device).
Aquavella JV et al (2005). Keratoprosthesis: the Dohlman-Doane device. American Journal of Ophthalmology 140: 1032-1038.	Retrospective case series n=25 patients multiple graft failure or otherwise deemed poor for conventional keratoplasty 88% (22/25) repeat PK eyes 2003-5, USA Follow-up: 12 months	All devices were retained without dislocation or extrusion, no instances of endophthalmitis or surface infection. Patients achieved best acuity in an average of 2 months (range, 1 to 180 days). Improvement in acuity was observed in an average of 13 days. Retroprosthetic membranes occurred in 3 cases, with multiple recurrences in one instance. Visual acuity ranged from no light perception to 20/25. This prosthesis can be implanted routinely and maintained with minimal complications in poor prognosis keratoplasty, which presents the potential for visual rehabilitation.	Early model of the Boston KPro device (Dohlman Doane KPro device).
Aquavella JV et al (2007). Pediatric keratoprosthesis. Ophthalmology 114: 989-994.	Retrospective case series n=17 (22 eyes) children with primary congenital disease and previous failed keratoplasty. Follow-up: 220 patient months (mean, 9.7 months). 2 Aplha cor, and 20 BKpro type 1 implanted.	In all 21 Boston cases, the prosthesis was retained without dislocation or extrusion. Visual axis clear in 100%, retroprosthetic membranes were removed in 5 eyes. Reoperation was necessitated for management of concurrent glaucoma (n = 3) or retinopathy (n = 2). No surface infection or endophthalmitis. In 7 instances where patient age was 4 years or more, visual acuity ranged from counting fingers to 20/30. In the remaining cases, all infants were able to follow light, fingers, and objects. The device is retained without extrusion or rejection.	Paediatric patients. Larger studies with longer follow-up included in table 2.
Bakhtiari, P et al	Retrospective	At a mean final follow-up of 26.1 months	Fewer than

(2012). Surgical and visual outcomes of the type I Boston Keratoprosthesis for the management of aniridic fibrosis syndrome in congenital aniridia. American Journal of Ophthalmology 153: 967-971.	case series n=9 (9 eyes) patients with congenital aniridia that developed aniridic fibrosis syndrome. Follow-up: mean 26.1 months	(range 6 to 48 months), vision remained improved in all patients. No patient had recurrence of the fibrotic membrane after KPro implantation. Type I Boston KPro may be considered in the surgical treatment of this condition.	10 patients undergoing repeat corneal transplantation.
BarnesSD et al (2007). Fungal colonization and infection in Boston keratoprosthesis. Cornea 26: 9-15.	Retrospective case series n=182 patients (202 eyes) B-KPro type 1 (148 eyes), type II (54 eyes) 1990-2004 Follow-up: mean 2.84 years.	4 definite and 1 probable fungal infections in 6893 patient-months of follow-up, or 0.009 fungal infections per patient-year reported. The rate was higher in eyes receiving a vancomycin-containing topical prophylactic regimen than those with on a non-vancomycin regimen (5 cases/2774 person-months vs. 0 cases/4119 person-months; P = 0.011). In eyes with type 1 KPro, the rate was higher with therapeutic contact lens wear than without (4/1682 vs. 0/3115 person-months; P = 0.015).	Adverse event already reported in table 2.
Boutin T, Jabbour S et al (2015). Improving management and outcomes of the Boston type 1 keratoprosthesis: Lessons learned from available evidence. Expert Review of Ophthalmology 10, 3, 1023294	Review evidence about management and outcomes of the Boston KPro type I	Boston Keratoprosthesis type I (KPro) surgery is a novel treatment for severe corneal blindness for recurrent graft failure and high-risk conditions such as cicatrizing disease, aniridia, herpetic keratitis or chemical burns. Recently, modifications in design, surgical techniques and postoperative management have increased the success rate of the Boston KPro. Complication rates have decreased substantially in the last decade making the Boston KPro a safe therapeutic alternative to certain corneal pathologies. However, certain comorbidities such as glaucoma and late-onset fungal infections remain a problem.	Narrative review
Bradley JC et al (2009). Boston type 1 keratoprosthesis: the university of California Davis experience. Cornea 28: 321-327.	Retrospective case series 2004-8 n=28 (30 eyes) KPro type 1 Follow-up: mean 19 months.	At an average follow-up of 19 months (range, 1-48; SD, 13.8; and median, 13), postoperative vision improved to >or=20/200 in 77% of eyes. Among eyes at least 1 year after the operation (16 eyes), vision was >or=20/200 in 75% of eyes and >or=20/40 in 25% of eyes. At an average follow-up of 19 months, retention of the initial keratoprosthesis was 83.3%.	Additional study related to Greiner 2011.
Brown CR et al (2014).Boston keratoprosthesis type 1 for herpes simplex and herpes zoster keratopathy. Cornea 33: 801-805.	Retrospective case series n=9 eyes with visual loss due to herpes simplex virus (HSV, n=5) and herpes zoster virus (HZV, n=4) keratopathy. BKPro type 1. Follow-up: mean 48.4 months (8/9) with previous	Graft retention rate was 100% in the HSV group, compared with 25% in the HZV group after 50.5 months (P = 0.048). 3 cases of microbial keratitis, 2 endophthalmitis, in the HZV group, compared with no cases in the HSV group (P = 0.048). There was significantly better best-corrected visual acuity in the HSV group than in the HZV group (P = 0.019). All 5 HSV eyes had improved best-corrected visual acuity compared with preoperative acuity, whereas only 1 HZV eye experienced a similar result (P = 0.048).	Fewer than 10 patients undergoing Repeat corneal transplantation.

	keratoplasty/keratoprosthesis.		
Cade F et al (2011). Glaucoma in eyes with severe chemical burn, before and after keratoprosthesis. Cornea 30:1322-1327.	Retrospective case series n=23 (28 eyes) patients with severe ocular chemical burns 1999-2010 B-KPro Follow-up: 57 months	21 eyes had preoperative, 9 had glaucoma progression after BKPro implantation. 2 more eyes developed glaucoma. Preoperative vision was counting fingers or worse in all eyes. Best-corrected postoperative VA ranged from no light perception to 20/20. 17 eyes (61%) achieved 20/60 or better VA at some point during their follow-up, but only 9 (32%) maintained 20/60 at the last follow-up. Of the 28 eyes, 6 had the BKPro replaced once and 1 had it replaced twice. 8 patients developed retinal detachment.	Adverse event already reported in table 2.
Chan CC et al (2012). Infectious endophthalmitis after Boston type 1 keratoprosthesis implantation. Cornea 31: 346-349.	n=3/105 eyes (2004-10) Follow-up: mean 25 months after Boston KPro implantation	3 cases had infectious endophthalmitis. The incidence of endophthalmitis was 2.4%. All patients wore a contact lens and were on vancomycin and a fourth-generation fluoroquinolone (moxifloxacin). One patient required KPro removal and therapeutic penetrating keratoplasty. Vision did not recover for 2 patients who presented with vision decreased to light perception. One patient, who presented with decreased vision of 20/400, recovered to 20/60.	Adverse event already reported in table 2.
Chan CC and Holland EJ (2012). Infectious keratitis after Boston type 1 keratoprosthesis implantation. Cornea 31: 1128-1134.	Retrospective case series n=10/126 eyes (2004-10) Follow-up: mean 25 months after Boston KPro implantation.	Incidence of infectious keratitis after KPro was 7.9%. Occurred even when patients were on vancomycin and fluoroquinolone for prophylaxis. Four patients had Kpro removal with therapeutic penetrating keratoplasty and 1 had Kpro replacement. At final follow-up, only 2 patients retained their preinfection best vision. Risk factors for infectious keratitis included a diagnosis of cicatrizing conjunctivitis (Stevens-Johnson syndrome, ocular cicatricial pemphigoid, or chemical injury) and a history of persistent epithelial defect (P = 0.0003 and 0.0142, respectively).	Adverse event already reported in table 2.
Chang H-Y, Luo Z K et al (2015). Primary implantation of type i Boston keratoprosthesis in nonautoimmune corneal diseases. Cornea.34, 64-270.	Retrospective case series 43 eyes (37 patients) Follow up: average of 39 months (1-6 years) Primary implantation of type I BKPro	Preoperative best-corrected visual acuity ranged from 20/60 to light perception, with vision of 20/200 or worse in 88%. Vision was >20/200 at 1 year in 77% of eyes (P < 0.0001). Complications included retroprosthetic membrane formation (51%), glaucoma progression (47%), corneal melt (19%), and sterile vitritis (14%). In a large series with long follow-up, primary Boston KPro effectively restored vision. Close follow-up is needed to manage the known complications after Boston KPro	Primary procedure.
Chhablani J et al (2015). Erratum to: Endophthalmitis in Boston keratoprosthesis: case series and review of literature. Int Ophthalmol.	Retrospective case series n=45 B-KPro type 1 (2009-2012)	The incidence of endophthalmitis was 11.1 % (5/45) and average time to develop endophthalmitis was 5.62 months (range 2 days to 8 months). Post-Boston K-Pro, the visual acuity ranged from light perception (LP) to 20/50. K-pro was explanted in 4 patients. There was bacterial and fungal growth in two patients each and one vitreous	Adverse event already reported in table 2.

		did not grow anything. All the eyes were phthisic at last visit.	
Chew HF et al (2009). Boston keratoprosthesis outcomes and complications. P., and Cohen, E. J. Cornea 28: 989-996.	Retrospective case series 2005-7 USA, 1 site n=37 Follow-up: mean 16 months type 1-36, type II-1; 78% (29/37) eyes repeat PK.	No intraoperative complications occurred. Postoperative complications included retroprosthetic membrane [24 (65%)], increased intraocular pressure [14 (38%)], glaucoma progression [5 (13.5%)], and endophthalmitis [4 (11%). 36 KPros (97%) were retained-1 type 2 KPro (3%) extruded and was replaced. Mean best-corrected visual acuities were 20/90 at last follow-up. 31 patients (84%) improved 2 lines or greater-3 patients (8%) had worse vision.	Adverse events already reported in table 2.
Cortina MS et al (2012). Boston type I keratoprosthesis for visual rehabilitation in a patient with gelatinous drop-like corneal dystrophy. Cornea 31: 844-845.	Case report n=1 gelatinous drop-like corneal dystrophy (GDLD) in both eyes in a 49 year old, Boston type I keratoprosthesis	The surgery was uneventful and one month after surgery, best corrected vision improved to 20/20 and has been maintained for a period of more than 14 months. No post-operative complications were observed. Histopathology of the corneal specimen is presented.	Rare disorder; fewer than 10 patients undergoing repeat corneal transplantation.
Crnej A et al (2014). Glaucoma progression and role of glaucoma surgery in patients with boston keratoprosthesis. Cornea.33:349-354.	Retrospective case series n=87 (168 eyes) 2004-2009 B-KPro Follow-up : 3.3 years.	66% eyes had glaucoma preoperatively, and 26% developed de novo glaucoma. The mean intraocular pressure (by finger palpation) was 16.5 +/- 5.7 mm Hg. In B-KPro-implanted eyes with glaucoma, 65% had undergone glaucoma surgery at some point, and 30% did not show progression. 31% of the total cohort had disc pallor with a cup-to-disc ratio of <0.8.	Adverse event already reported in table 2.
Cruzat A et al (2013). Wound anatomy after type 1 Boston KPro using oversized back plates. Cornea 32:1531-1536.	Retrospective case series n=16 patients B-Kpro using oversized back plates Follow-up: 6-12 months	None of the patients with larger back plates developed a significant RPM during a 12-month follow-up period. One patient with a larger back plate developed a corneal melt at the KPro stem as a result of chronic exposure	Adverse event already reported in table 2.
de Oliveira LA et al (2014). Experience with Boston keratoprosthesis type 1 in the developing world. Canadian Journal of Ophthalmology 49: 351-357.	Prospective case series n=30 (30 eyes) 2008-12 KPro type 1 Brazil Follow-up: average 32 months (1-55 months)	Postoperative VA statistically improved during all postoperative follow-ups. Retention of the keratoprosthesis was 93.3%. The incidence of retroprosthetic membrane was 26.66%. Progression of glaucoma occurred in 7/16 eyes (43%). 3 patients developed glaucoma,1 eye had infectious keratitis, and 2 eyes had retinal detachment.	Adverse event already reported in table 2.
de laPaz MF, et al (2014). Anatomical survival and visual prognosis of Boston type 1 keratoprosthesis in challenging cases. Graefes Arch Clin Exp	Retrospective case series n=67 BKPro type I , 52 previous graft failure, 11 primary procedure.	Retention of the prosthesis was achieved in 95 % at 1 year and 78 % at 4.5 years. Two eyes suffered extrusion of the KPro, six underwent successful exchange of the prosthesis either due to infection, necrosis or extrusion, three KPro's had to be explantated, and two eyes ended	Adverse event already reported in table 2.

Opthalmol 252:83-90.	Follow-up mean 26 months	up in enucleation due to panophthalmitis. The most frequent complication was development of a retroprosthetic membrane in 21 eyes (34 %).	
de Rezende Couto Nascimento V et al (2014). Influence of primary diagnosis and complications on visual outcome in patients receiving a Boston type 1 keratoprosthesis. Ophthalmic Research 52: 9-16.	Retrospective case series n=57 (59 eyes) KPro type 1 Follow-up: at least 3 months	The number of graft failures before Kpro implantation did not influence VA outcome. Except for the relatively good VA outcome in chemical burn and radiation injury patients, there seems to be no association between primary diagnosis and positive or negative VA outcome.	Studies with longer follow-up included in table 2.
Fadlallah A et al (2013). Boston Type I Keratoprosthesis for Treatment of Gelatinous Drop-Like Corneal Dystrophy After Repeated Graft Failure. Semin Ophthalmol	Case report n=1 gelatinous drop-like corneal dystrophy (GDLD) in both eyes in a 43 year old, Boston type I keratoprosthesis in left eye implanted after graft failure.	The surgery was uneventful and 1 month after surgery, BCVA improved to 20/30, which has been maintained for a period of more than nine months. At the 12-month visit, her vision was noted to be diminished to 20/200 due to a retroprosthetic membrane and improved to 20/25 two weeks after a Yag capsulotomy. Histopathologic examination of the corneal specimen disclosed predominantly subepithelial amyloid deposition.	Rare disorder; fewer than 10 patients undergoing repeat corneal transplantation.
Fadlallah A et al (2014). Gamma-irradiated corneas as carriers for the Boston type 1 keratoprosthesis: advantages and outcomes in a surgical mission setting. Cornea 33: 235-239.	Retrospective case series n=17 eyes (16 patients) 2010-12 Boston KPro type 1 implantation	16 eyes (94.1%) improved in corrected visual acuity over the course of follow-up. Overall, 13 eyes (76.4%) developed at least 1 complication after surgery. Retroprosthetic membrane formation was the common complication, in 10 eyes (58.8%). Neither infectious keratitis nor corneal stromal necrosis was noted during the follow-up period. The retention percentage was 94.1%.	KPro using gamma-irradiated carrier corneas. Adverse events already reported in table 2.
Fadous R, Levallois-Gignac S et al (2015). The Boston Keratoprosthesis type 1 as primary penetrating corneal procedure. Br J Ophthalmol .	Retrospective comparative case series Patients with corneal blindness and poor prognosis for PK. n=30 patients with KPro as a primary procedure (group 1) compared with 40 patients who had PK prior to KPro (group 2).	Preoperative BCVA was 20/200 or better in 10% of eyes in group 1 (range 20/150 light perception (LP)), and in 5% of eyes in group 2 (range 20/100 LP; p=0.42). BCVA was significantly better in group 1 throughout the follow-up ($p<0.05$). At 12 months, 87% and 63% of eyes achieved a BCVA better than 20/200 in groups 1 and 2, respectively ($p<0.05$). The complication rates and retention rate were similar in the two groups. This study demonstrates that the Boston KPro implantation may be successful as a primary procedure in patients at high risk of failure with traditional PK. Further, there appears to be a visual benefit to primary KPro surgery	Primary procedure.
Goldman DR et al (2013). Postoperative posterior segment complications in eyes treated with the Boston type I keratoprosthesis. Retina 33: 532-541.	Retrospective case series n=94 (98 eyes, 110 implantations) Follow-up: mean 28.2 months BKPro type 1	The mean time posterior segment complication was 5.6 months. 38 eyes (40.9%) experienced at least 1 postoperative posterior segment complication, the most common of which were retinal detachment (16.9%, 14 of 83), choroidal detachment (16.9%, 14 of 83), and sterile vitritis (14.5%, 12 of 83). CDVA was worse among eyes that	Additional study related to Aldave 2012, included in table 2.

		experienced posterior segment complications compared with eyes that did not at multiple postoperative follow-up intervals.	
Grassi CM et al (2015). Idiopathic vitritis in the setting of Boston keratoprosthesis. Cornea 34: 165-170.	Retrospective case series n=23 eyes of 346 patients 2000-13 Boston Kpro	23/346 eyes developed idiopathic vitreous inflammation. 6/23 patients had symptoms similar to endophthalmitis but were culture negative. Sterile vitritis was 4/23. Vision decline and time to recovery of vision was variable (median, 9 lines on Snellen chart), (median, 8.9 weeks). 9 eyes had repeat bouts (43 episodes in 23 patients). 17/23 eyes with idiopathic vitritis after keratoprosthesis later developed other complications.	Safety issue already covered in table 2.
Greiner MA et al (2011). Longer-term vision outcomes and complications with the Boston type 1 keratoprosthesis at the University of California, Davis. Ophthalmology 118: 1543-1550.	Cohort study USA, 2004-10 BKPro type 1 n=35 (40 eyes) Follow-up: mean 33.6 months	19/32 eyes (59%) retained BCVA >20/200 at 1 year; 16/27 eyes (59%) at 2 years; 7/14 eyes (50%) at 3 years; and 2/7 eyes (29%) at 4 years. Glaucoma in 11 eyes (27.5%); progression in 9 (22.5%). RPM in 22 (55%), 5 (12.5%) had endophthalmitis, 6 (15%) had corneal melt, 7 (17.5%) had keratoprosthesis replacement, and 23 (57.5%) had surgery. Keratoprosthesis retained in 32 eyes (80%).	Safety outcomes already reported in table 2.
Guell JL et al (2011). Outcomes with the Boston Type 1 Keratoprosthesis at Instituto de Microcirugia Ocular IMO. Saudi Journal of Ophthalmology 25: 281-284.	Retrospective case series 2006-11 BKPro type 1 n=53 (54 eyes) 90.7% (49/54) eyes repeat PK. Follow-up: average 20 months	Preoperative BCVA ranged from 20/200 to light perception. At an average follow-up of 20.15 months +/- 12.7 (range, 1-56), postoperative vision improved to 20/200 in 18 eyes (33.3%) and 20/50 in 4 eyes (7.4%). The graft retention was 96%.	Larger studies with longer follow-up included in table 2.
Hager JL, Phillips DL et al (2015). Boston type 1 keratoprosthesis for failed keratoplasty. Int Ophthalmol.	Retrospective case series n-24 eyes with a failed keratoplasty (13 corneal odema, 8 with trauma, 3 with keratoconus) KpRO-1 Mean follow-up: 28.9 months (range 7-63 months)	The median best corrected visual acuity (BCVA) was 20/125. The BCVA was >/=20/40 in 4 (16.7 %) eyes, >/=20/70 in 9 (37.5 %) eyes, and >/=20/200 in 14 (58.3 %) eyes. Overall, the postoperative BCVA improved in 17 (70.9 %) eyes, was unchanged in 3 (12.5 %) eyes, and was worse in 4 (16.7 %) eyes. The initial Kpro-1 was retained in 22 (91.7 %) eyes, and was successfully repeated in the other 2 eyes. One or more serious prosthesis- or sight-threatening complications occurred in 8 (33.3 %) eyes. These included 1 case of wound dehiscence leading to prosthesis extrusion, 1 case of fungal keratitis leading to prosthesis extrusion, 4 cases of endophthalmitis, and 5 retinal detachments.	Larger and longer follow-up studies included in table 2.
Hassanaly SI et al (2014). Outcomes following Boston type 1 keratoprosthesis implantation in aniridia patients at the	Retrospective case series n=19 (26 eyes) Type 1 Follow-up: mean	No intraoperative complications. After a mean follow-up, BCVA was 20/200 or better in 14 eyes. Visual potential was limited by pre-existing terminal glaucoma (n=2), phthisis after retinal detachment (n=4), and suprachoroidal hemorrhage (n=2). Other	Larger studies with longer follow-up included in table 2.

University of Montreal. American Journal of Ophthalmology 158: 270-276.	28.7 months	complications included retroprosthetic membrane formation (n=15), infectious keratitis (n=1), extrusion (n=2), and corneal melt (n=4). Uncomplicated vitritis in 6 eyes. No endophthalmitis. Most eyes have glaucoma. The retention rate was 77%.	
Harissi-Dagher M and Dohlman CH (2008). The Boston Keratoprosthesis in severe ocular trauma. Canadian Journal of Ophthalmology 43:165-169.	Retrospective case series n=30 (30 eyes) with ocular trauma USA Type 1 Follow-up: not reported.	Best-corrected postoperative visual acuity ranged from 20/20 to no light perception (median: 20/80). The incidence of postoperative complications was greater in the chemical burn group than in either the mechanical trauma or the thermal burn group.	Larger studies with longer follow-up included in table 2.
Harissi-Dagher M et al (2007). Importance of nutrition to corneal grafts when used as a carrier of the Boston Keratoprosthesis. Cornea 26: 564-568.	Retrospective comparative case series n=128 (157 eyes) Mean follow-up: 35 months 100% repeat PK Dohlman Doane KPro (79 eyes with 8, 1.3-mm diameter holes in the back plate, and 78 eyes with solid back plate).	48/157 eyes (31%) developed some degree of tissue melt around the stem, including 8/79 eyes (10%) in the back plate with holes group and 40/78 eyes (51%) in the solid back plate group (P < 0.0001). Among the melts in the back plate with holes group, 4/8 (50%) suffered from an underlying autoimmune disease such as SJS or OCP. The Boston KPro design with a back plate containing holes protects the overlying corneal tissue from necrosis and melts.	Early model of the Boston KPro device (Dohlman Doane KPro device).
Harissi-Dagher, M et al (2013). Pars plana vitrectomy through the Boston Keratoprosthesis type 1. Eye (Basingstoke) 27: 767-769.	Retrospective case series n=70 B-KPro type 1 + PPV 2008-11	7% (5/70) patients required PPV for vitreoretinal complications post-KPro surgery. Repeat PPV was necessary in some cases. Although anatomical repair of the vitreoretinal complications was achieved in most cases, post PPV visual acuity remained poor in the majority.	Combined procedure.
Hou JH et al (2012). Outcomes of boston keratoprosthesis implantation for failed keratoplasty after keratolimbal allograft. Cornea.31: 1432-1435.	Retrospective case series n=7 (7 eyes) with ocular surface disease and limbal stem cell deficiency treated with BKPro type 1 after failed keratoplasty (after keratolimbal allograft) at an average of 9.9 months. Follow-up: average 19.5 months	BCVA improved from a median of counting fingers CFto a median of 20/400 (range, CF@3ft to 20/25). 85.7% (6 of 7) retention of implanted devices at the last follow-up, with 1 eye requiring repeat KPro for corneal melt and implant extrusion after abrupt cessation of immunosuppression.	Fewer than 10 patients undergoing repeat corneal transplantation.
Huh ES et al (2014). Outcomes of pars plana glaucoma drainage implant in Boston type 1	Retrospective case series n=20 patients (20 eyes)	Two eyes required glaucoma drainage implant explantation: one eye due to endophthalmitis from a nonhealing corneal ulcer and the other eye due to corneal melt. No patients' experienced conjunctival	Combined procedure.

keratoprosthesis surgery. Journal of Glaucoma.23: e39-e4	B-KPro type 1 + PPV +GDD with graft Average follow-up: 31.6 months	erosion over a pars plana positioned glaucoma drainage implant or tube.	
Jain V et al (2012). Fungal keratitis with the type 1 Boston keratoprosthesis: early Indian experience. Cornea 31: 841-843.	Case report n=2 type 1 Boston KPro	Uneventful intraoperative and postoperative courses. Patients presented with keratitis and endophthalmitis within few months. Culture was positive for fungus in both the cases. Despite aggressive antifungal medical therapy and surgical management, one patient's eye was eviscerated and the other lost the potential for any useful vision.	Larger and longer follow-up studies included in table 2.
Jasinskas V et al (2013). Keratoprosthesis surgery as an alternative to keratoplasty. Medicina (Kaunas) 49:6: 291-9.	Case series n=5 patients with corneas inappropriate for standard transplantation. Boston type I keratoprosthesis Mean follow-up: 26.4 months.	The mean follow-up was 26.4 months (range, 12 to 36 months; SD, 13.1). The main measures of outcomes were visual acuity and keratoprosthesis stability. At least 1 year after the operation (5 eyes), vision acuity was >0.1 in 100% of the eyes and >0.4 in 50% of the eyes. Retention of the initial keratoprosthesis was 100%. The results of this study seem to be similar to those reported internationally.	Larger studies with longer follow-up included in table 2.
Iyer G et al (2011). Boston keratoprosthesis for keratopathy in eyes with retained silicone oil: a new indication. Cornea 30:1083-1087.	Retrospective case series n=8 eyes 2008-10, India BKPro type 1 primary procedure or after a failed PK.	Anatomic retention and visual improvement were noted in (87.5%, 7/8). Visual acuity improved to 20/200 or better in 6 eyes (66.67%). Repeated corneal melt necessitated the removal of the prosthesis with corneal transplant in 1 eye. Membranectomy was performed twice for retroprosthetic membrane in 1 eye.	Fewer than 10 patients undergoing repeat corneal transplantation.
Kamyar R et al (2012). Glaucoma associated with Boston type I keratoprosthesis. Cornea 31:134-139.	Retrospective cohort study n=29 (30 eyes) 76.7% (23/30) eyes with repeat PK. BKPro type 1 Follow-up: mean 17 months	BCVA improvement to 20/330 at 9 months; mean BCVA was 20/600 at the last follow-up. Postoperative increased IOP (22 mm Hg or higher) was noted in 15 eyes (50%), glaucoma development or progression was noted in 7/15 (23% of total eyes). Six patients (20%) required repeat KPro implantation, and retroprosthetic membranes developed in 23 eyes (77%). No patient had vitritis or infectious endophthalmitis.	Larger and longer follow-up studies included in table 2.
Kang JJ et al (2012). Visual outcomes of Boston keratoprosthesis implantation as the primary penetrating corneal procedure. Cornea 31:1436-1440.	Retrospective case series n=19 (21 eyes) Type 1-19. Type II-2 for chemical or thermal injury, aniridia, and Stevens-Johnson syndrome. 2007-11 Follow-up: mean 14.6 months	At last follow-up for all eyes, 15 eyes (71.4%) achieved BCVA>20/200 and 4 eyes (19%) improved to BCVA>20/50. No intraoperative complications. Postoperative complications include retroprosthetic membrane formation (47.6%), cystoid macular edema (33.3%), elevated intraocular pressure (23.8%), glaucoma progression (14.3%), and endophthalmitis (4.8%). The initial keratoprosthesis was retained in 19 eyes (90.5%).	Primary procedure.
Kim MJ et al (2013). Microbial keratitis after Boston type I keratoprosthesis	Retrospective case series n=105 (110 eyes)	20 infectious infiltrates in 15 eyes (13.6%) of 15 patients (14.3%), a rate of 0.073 infections per eye-year. The rate of culture-positive bacterial keratitis was 0.022	Safety already reported in

implantation: incidence, organisms, risk factors, and outcomes. Ophthalmology 120: 2209-2216.	2004-12 KPro type 1	infections per eye-year, and the rate of culture-positive fungal keratitis was 0.015 infections per eye-year. Prolonged vancomycin use, persistent corneal epithelial defect were associated with an increased risk for fungal keratitis and infectious keratitis overall. There were no cases of endophthalmitis.	table 2.
Khalid Al Arfaj 2015. Boston Keratoprosthesis – Clinical Outcomes with Wider Geographic Use and Expanding Indications – A Systematic Review. Saudi Journal of Ophthalmology.	Systematic review 2005-14) Boston keratoprosthesis (B-KPro)	While most of the studies report smaller datasets (typically <50 eyes), some of the recent multicenter studies have reported large datasets (up to 300 eyes). Most of the literature is published from the US; however, last few years have witnessed some papers reporting the successful use of B-Kpro from developing countries or arid climatic conditions (such as the Kingdom of Saudi Arabia). Due to differences in the causes of corneal blindness in different geographic regions, newer indications for B-Kpro are emerging (e.g. trachoma). Additionally, improving clinical outcomes and increasing surgeon confidence have also expanded indications to include cases of unilateral visual impairment and paediatric age. We observed that there is growing body of evidence of successful clinical use of B-KPro; however, financial challenges, lack of trained surgeons, shortage of donor corneas must be overcome to improve accessibility of B-KPro.	Narrative synthesis of evidence. Large studies included in the review are already included in table 2 in the overview.
Khan BF et al (2007). The Boston keratoprosthesis in herpetic keratitis. Archives of Ophthalmology 125: 745-749.	Retrospective case series n=14 (17 eyes) BKPro type 1 Follow-up: median 14 months	94% (16/17) eyes had visual acuity improvement within 1 week. 88% (15/17)) achieved a best visual acuity of 20/25 to 20/70 and, at the last examination. 4 patients with prolonged preoperative inflammation and ulceration had resolution. The KPro had no extrusions. Complications included retroprosthesis membrane in 3 eyes and 1 tissue melt in an early case.	Additional study related to Dunlap 2010, included in table 2.
Lee SH et al (2013). Evaluation of microbial flora in eyes with a Boston type 1 Keratoprosthesis. Cornea 32:1537-1539.	Prospective case series n=15 (17 eyes) B-KPro+ topical antibiotics for failed corneal grafts, limbal stem cell deficiency, chemical burns, and SJS.	Nine of the 17 eyes implanted with the K-Pro (53%) had positive cultures. Two of the 13 (15%) of the control swabs exhibited bacterial growth. Eight percent (1/12) of the sonicated lenses were positive on culture, whereas 4/12 (33%) of the lenses placed in thioglycolate broth were positive for organisms	Safety already covered in table 2.

Lee WB, Shtein RM et al (2015). Boston Keratoprosthesis: Outcomes and Complications: A Report by the American Academy of Ophthalmology. Ophthalmology Apr 28. pii: S0161-6420(15)00306-1. doi: 10.1016/j.ophtha.2015.03.025. [Epub ahead of print]	Review Boston type I keratoprosthesis (BI-KPro) surgery in eyes with severe opacification not amenable to corneal transplantation.	In 9 articles, a best-corrected Snellen visual acuity (BCSVA) of 20/200 or better occurred in 45% to 89% of eyes. Five articles described a BCSVA of 20/50 or better in 43% to 69% of eyes, and 4 articles found a BCSVA of 20/40 or better in 11% to 39% of eyes. Retention rates of the BI-KPro ranged from 65% to 100%. Reasons for loss of vision after BI-KPro implantation most commonly included corneal melts resulting from exposure keratopathy, endophthalmitis, and infectious keratitis or corneal ulceration. The 2 most common complications after surgery were retroprosthetic membrane formation (range, 1.0%-65.0%; mean +/- standard deviation [SD], 30.0+/-19.0%) and elevated intraocular pressure (range, 2.4%-64.0%; mean +/- SD, 27.5+/-18.1%). The 2 most common posterior segment complications were endophthalmitis (range, 0%-12.5%; mean +/- SD, 4.6+/-4.6%) and vitritis (range, 0%-14.5%; mean +/- SD, 5.6+/-4.7%).	Narrative synthesis of evidence. Abstract only available, full paper ordered.
Li JY, Greiner MA et al (2011). Long-term complications associated with glaucoma drainage devices and Boston keratoprosthesis. American Journal of Ophthalmology 152 (2) 209-218.	Retrospective case series Patients who had Boston type 1 keratoprosthesis n=40 eyes (35 patients) and concurrent treatment for glaucoma. Average follow-up: 33.6 months	Conjunctival breakdown occurred in association with 10 glaucoma drainage device implants in 9 eyes. 11 had glaucoma drainage device before surgery, 3 at surgery, 2 after surgery. All but one of the eroded glaucoma drainage devices were placed before surgery. Associated complications included endophthalmitis, hypotony, and keratoprosthesis extrusion, with 6 glaucoma drainage devices requiring removal. Long-term beset-corrected visual acuity was maintained better in eyes in which glaucoma drainage device erosions did not develop.	Complications already reported in table 2.
Modjtahedi S and Eliott Dean (2014). Vitreoretinal complications of the Boston keratoprosthesis. Seminars in Ophthalmology 29: 338-349.	Review	Vitreoretinal complications remain a significant cause of ocular morbidity. Retroprosthetic membranes, infectious endophthalmitis, sterile vitritis, vitreous hemorrhage, vitreous opacities, retinal detachment, cystoid macular edema, choroidal detachments, retinal vascular occlusion, and epiretinal membrane have been described, may require the intervention of a vitreoretinal specialist.	General review of safety outcomes.
Palioura S et al (2013).The Boston keratoprosthesis type I in mucous membrane pemphigoid. Cornea 32: 956-961.	Retrospective case series n=8 (8 eyes) patients with MMP. 4 had previous PK. BKPro type 1 implanted Follow-up: mean 3.2 years.	Visual acuity improved to 20/200 or better in 6 eyes (75%) and to 20/40 or better in 3 eyes (37.5%). Only 1 of 6 eyes (16.7%) was able to maintain visual acuity of 20/200 or better. (62.5%, 5/8) extruded or had to be replaced during a mean follow-up time of 1.7 +/- 1.7 years. Loss of vision occurred because of keratoprosthesis type I extrusion, end-stage glaucoma, and retinal or choroidal detachment.	Fewer than 10 patients undergoing repeat corneal transplantation.
Patel AP et al (2012). Boston type 1 keratoprosthesis: the	Retrospective case series	At last follow-up, 43.1% of eyes had a BCVA of 20/200. Retention rate was 87.9% over an average follow-up of 21.5+/-11.4 months	Larger and longer follow-up

New York Eye and Ear experience. Eye 26: 418-425.	n=51 (58 eyes) 2006-10, USA type 1 Follow-up: average 21.5 months 81% (47/58) eyes repeat PK.	(median 22 months, range 3-47 months). Complications increased with time, with 65.5% of eyes experiencing at least one event by 6 months and 75.9% by 1 year. The most common post-operative complication was retroprosthetic membrane formation (50.0%)	studies included in table 2.
Pavan-Langston D and Dohlman CH (2008). Boston keratoprosthesis treatment of herpes zoster neurotrophic keratopathy. Ophthalmology 115 (2: Suppl) Suppl-3.	Case report n=1 B-KPro in a severely inflamed ulcer in herpes zoster neurotrophic keratopathy and extracapsular cataract extraction of a mature cataract.	One week after surgery, the inflammation was almost entirely resolved, and cultures of the host button were negative for any organisms. Vision gradually increased from LP to 20/60 over the ensuing 4 months. The Boston keratoprosthesis procedure successfully salvaged and restored vision in this high-risk herpes zoster eye in which standard keratoplasty would almost certainly have failed.	Fewer than 10 patients undergoing repeat corneal transplantation.
Peggy Chang HY et al (2015). Primary Implantation of Type I Boston Keratoprosthesis in Nonautoimmune Corneal Diseases. Cornea	Retrospective case series n=37 (43 eyes) KPro type 1 Indication: non-autoimmune corneal diseases Follow-up: average 39 months.	Preoperative best-corrected visual acuity ranged from 20/60 to light perception, with vision of 20/200 or worse in 88%. Vision was >/=20/200 at 1 year in 77% of eyes (P < 0.0001). Complications included retroprosthetic membrane formation (51%), glaucoma progression (47%), corneal melt (19%), and sterile vitritis (14%).	Primary procedure.
Pineles SL et al (2010). Binocular visual function in patients with Boston type I keratoprostheses. Cornea 29:1397-1400.	Prospective case series n=17 Indication; unilateral visual impairment. KPro type 1 follow-up: mean 21 months	94% (16/17) demonstrated binocular function. Second-degree fusion at near was demonstrated via the Worth-4-dot test in 13/17 (76%); third-degree fusion in 7/17 (41%) patients. Patients with better binocular function tended to be of younger (P = 0.05) and have better visual acuity (P = 0.006). 5 had some degree of ocular misalignment. Overall, patients with strabismus had worse binocularity (P = 0.04).	Study reports binocular vision outcomes.
Qian CX et al (2015). Anterior Segment Optical Coherence Tomography in the Long-Term Follow-up and Detection of Glaucoma in Boston Type I Keratoprosthesis. Ophthalmology 122: 317-325.	Prospective case series n=20 K-Pro in 1 eye and OCT imaging before and after implantation. Follow-up: mean 18.8 months	Anterior segment OCT can be used to observe anatomic changes after KPro implantation that cannot be detected otherwise. We were unable to demonstrate a correlation between anatomic features and clinical progression	Role of OCT for diagnosis of glaucoma.
Ramchandran RS et al (2012). Infectious endophthalmitis in adult eyes receiving Boston type I keratoprosthesis.	Retrospective case series n=130 patients (141 eyes) Boston KPro	7% (10/141) eyes treated for bacterial endophthalmitis. Average time to endophthalmitis developing was 9.8 months. Coagulase-negative staphylococci were identified in 7 eyes. In 7/10 eyes, recurrent endophthalmitis occurred at a mean of 4	Safety issue already covered in table 2.

Ophthalmology 119: 674-681.	2004-2008	months after resolution of the initial episode. At each episode of endophthalmitis, most eyes were receiving only fluoroquinolone ophthalmic drops for prophylaxis.	
Rixen JJ et al (2013). Treatment of aniridia with Boston type I keratoprosthesis. Cornea 32: 947-950.	Retrospective case series n=7 (7 eyes) patients with congenital aniridia BKPro type 1 2009-11 Follow-up: median 18 months.	After a median follow-up period of 18 months compared with the preoperative visual acuity, the final vision was improved in 6 eyes (85.7%) and worse in 1 eye (14.3%). The K-pro graft was retained in all 7 eyes (100%). The most common complication was the formation of a retroprosthetic membrane in 3 eyes (42.9%), none of which required either a YAG capsulotomy or a vitrectomy. One eye (14.3%) developed a wound dehiscence that required surgical repair.	Fewer than 10 patients undergoing repeat corneal transplantation.
Robert MC et al (2013). Microbial colonization and antibacterial resistance patterns after boston type 1 keratoprosthesis. Ophthalmology.120: 1521-1528.	Cross sectional, case control study n=75 patients (75 eyes) (25 B-KPro eyes, 25 PKP eyes, 25 control eyes)	Culture positivity rates and bacterial species composition were similar in KPro, PKP, and control eyes. Eyes with KPro were more likely to be colonized with FQ-resistant bacteria. Chronic prophylaxis with low-dose FQ is likely responsible for this increased antibiotic resistance.	Safety issue already covered in table 2.
Robert MC et al (2012). Boston keratoprosthesis type 1 surgery: use of frozen versus fresh corneal donor carriers. Cornea 31:339-345.	Prospective case series n=37 Follow-up: mean 9.6 months Type 1 BKpro Fresh corneal graft versus frozen corneal graft (19 vs 18)	Surgery was uneventful in all cases. Mean follow-up was 9.65 months. Median postoperative VA were 20/150 (range, 20/30 to hand motions) and 20/150 (range, 20/40 to counting fingers) in the fresh and frozen cornea groups, respectively. Inflammation and retroprosthetic membrane formation were the most common complications with similar rates between the 2 groups. The device retention rate was 100%.	Related to Talagic 2012.
Robert MC. and Harissi-Dagher M (2011). Boston type 1 keratoprosthesis: the CHUM experience. Canadian Journal of Ophthalmology 46: 164-168.	Retrospective case series n=43 (46 eyes) 2008-10 Type 1 Follow-up: mean 10 months	Median BCVA at last follow-up was 20/150 (range, 20/30 to no light perception). The device retention rate was 100% at the end of the follow-up period. Postoperative complications included retroprosthetic membrane in 12 eyes (26%) and glaucoma progression in 11 eyes (23%).	Related to Talagic 2012.
Robert, MC and Dohlman, CH (2014). A review of corneal melting after Boston Keratoprosthesis. [Review]. Seminars in Ophthalmology 29 (5-6) 349-357.	Review of corneal melting after BKPro and postoperative care that has halted the occurrence of melting.	Eyes with autoimmune diseases such as Stevens-Johnson syndrome, toxic epidermal necrolysis syndrome, and mucous membrane pemphigoid remain vulnerable to corneal melt, leak, and extrusion. The development of new strategies to prevent melting in eyes with autoimmune disease is crucial to improve the outcomes of this group of patients, as they are often those with the most desperate need for visual rehabilitation with B-KPro.	Narrative review
Rootman DB et al (2015). Ocular surface, fornix, and eyelid rehabilitation in Boston type I keratoprosthesis patients with mucous	Retrospective case series n=9 (9 eyes) patients with MMP.	Free grafting and simple advancement flaps do not appear to be effective for rehabilitation in these eyes. However, even vascularized pedicle and bucket handle flaps retracted 50% of the time. Individuals with SJS were more likely to both require	Fewer than 10 patients undergoing repeat corneal transplantati

membrane disease. Ophthalmic Plastic & Reconstructive Surgery 31: 43-49.	BKPro type 1 Ocular surface reconstructive surgery after or at the time of implantation.	conjunctival rehabilitation after keratoprosthesis surgery and develop graft retraction in the course of management	on.
Rudnisky CJ et al (2012). Risk factors for the development of retroprosthetic membranes with Boston keratoprosthesis type 1: multicenter study results. Ophthalmology 119: 951-955.	Cohort study n=265 (265 eyes) BKPro type 1 2003-8, 18 sites, USA Follow-up: mean 17.8 months	The overall RPM formation rate was 31.7% (n = 84). The most significant risk factor for RPM development was infectious keratitis, resulting in 70.6% RPM. The hazard ratio (HR) of RPM development in these eyes was 3.20 (95% confidence interval, 1.66-6.17). Aniridia was also an independent risk factor for RPM development (HR, 3.13; 95% confidence interval, 1.10-8.89).	Additional study related to Ciolino 2013, included in table 2.
Sayegh RR et al (2008). The Boston keratoprosthesis in Stevens-Johnson syndrome. American Journal of Ophthalmology 145: 438-444.	Retrospective case series n=15 (16 eyes) 200-5 Type 1 in10, type II-6 Follow-up: mean 3.6 years (42 months)	75% (12/15) eyes had visual acuity of 20/200 or better, 8 eyes (50%) had vision of 20/40 or better. Visual acuity was maintained at 20/200 or better over a mean period of 2.5+/-2.0 years. Preexisting glaucoma was found to be a significant risk factor for visual loss. There were no cases of KPro extrusion or endophthalmitis.	Additional study related to Harrisi-Dagher 2008.
Sejpal K et al (2011). The Boston keratoprosthesis in the management of corneal limbal stem cell deficiency. Cornea 30 1187-1194.	Retrospective case series n=22 (23 eyes) 2004-10 Follow-up: 3 years Indication: corneal limbal stem cell deficiency. KPro type 1	CDVA was 20/50 in 69%, 88%, and 67% of eyes with LSCD at 1, 2, and 3 years. It is higher in eyes with LSCD. Retention failure rate in eyes with LSCD (0.148/eye-year) was higher than the eyes without LSCD (0.114/eye-year), The most common complications in eyes with LSCD were persistent corneal epithelial defect (PED) formation (56.5% of eyes) and sterile corneal necrosis (30%), whereas retroprosthetic membrane formation (46%), PED formation (23%) more common in eyes without LSCD.	Additional study related to Aldave 2012.
Shapiro, B. L et al (2013). High-resolution spectral domain anterior segment optical coherence tomography in type 1 Boston keratoprosthesis. Cornea 32: 951-955.	n=23 (26 eyes) Follow-up: 35.8 months BKPro type 1	Retroprosthetic membrane formation, found in 77% of KPro eyes. In 65% of KPro eyes, we identified epithelium behind the front plate, and in 54%, we identified an epithelial lip over the anterior surface of the KPro front plate. In 31% of KPro eyes, we identified periprosthetic cysts, gaps or spaces, and thinning in the corneal carrier graft.	Additional study related to Grenier 2011.
Shihadeh WA and Mohidat HM (2012). Outcomes of the Boston keratoprosthesis in Jordan. Middle East African journal of ophthalmology 19:97-100.	Retrospective case series 2007-10 n=19 (20 eyes) type 1 Follow-up: mean 18.1 months 95% (19/20) repeat PK	Best corrected visual acuity (BCVA) improved significantly in 85% of eyes; 65% had a BCVA of 20/200 or better and 25% had a BCVA of 20/50 or better. The most frequent complication was retroprosthesis membrane (RPM) formation, which occurred in 45% of eyes. Two eyes (10%) had implant extrusion and required further surgery.	Larger and longer follow-up studies included in table 2.
Sivaraman KR et al (2013). Retroprosthetic	Retrospective case series	AS OCT evidence of a retro-backplate membrane was observed in 100% of eyes	Anterior segment

membrane and risk of sterile keratolysis in patients with type I Boston Keratoprosthesis. American Journal of Ophthalmology 155:814-822.	n=47 (50 eyes) B-KPro type 1+ anterior segment OCT	that melted and in 34.1% of eyes that did not (P = .0034; risk ratio, 2.9; 95% confidence interval, 1.9 to 4.4). Retro-backplate membrane thickness in the melt group was 278 mum versus 193 mum in the nonmelt group (P = .025)	OCT measurements of retro-backplate membranes.
Talajic JC et al (2012). Prevalence, progression, and impact of glaucoma on vision after Boston type 1 keratoprosthesis surgery. American Journal of Ophthalmology 153 267-274.	Retrospective case series n=38 (38 eyes) KPro type 1 Follow-up: mean 16.5 months Glaucoma in 29 patients before and 34 after implantation.	Patients taking IOP lowering medications increased from 19 (50%) to 28 (76%) after surgery (P = .017). 8 (21%) had glaucoma progression. 15 (40%) had a cup-to-disc ratio of 0.85 or more. 5 required glaucoma surgery. VA was limited by glaucoma in 14 patients (37%), 11 of whom had a VA of 20/200 or worse. Visual fields were limited by glaucoma in 25 patients.	Reports only glaucoma outcomes.
Todani A et al (2011). Titanium back plate for a PMMA keratoprosthesis: clinical outcomes. Graefes Archive for Clinical & Experimental Ophthalmology 249 1515-1518.	Retrospective case series n=78 55 PMMA versus 23 titanium back plates Follow-up: minimum 6 months	Titanium seems to be associated with less RPM formation than PMMA when used as a material for the BKPro back plate	Study comparing outcomes based on 2 types of backplates.
Utine, CA et al (2011). Clinical features and prognosis of Boston type I keratoprosthesis-associated corneal melt. Ocular Immunology & Inflammation 19 413-418.	Retrospective case series n=66 patients 2004-2010 B-KPro	6 patients had an underlying inflammatory ocular surface disorder. Four experienced corneal melt (6.1%) 5-42 months after the initial surgery. One patient was diagnosed with Sjogren's syndrome as a result of diagnostic workup following melt. 3 patients were treated with systemic immunomodulatory therapy; 2 experienced fungal keratitis and subsequent endophthalmitis. KPro had to be explanted and replaced with donor cornea in all cases.	Safety issue covered in table 2.
Utine CA et al (2011). Visual and clinical outcomes of explantation versus preservation of the intraocular lens during keratoprosthesis implantation. Journal of Cataract & Refractive Surgery 37 1615-1622.	Comparative case series n=15 IOL aphakic KPro versus 10 pseudophakic KPro follow-up: 1 year	Refractive outcomes were better in aphakic patients than in patients who were left pseudophakic. Although not frequent, posterior segment complications after IOL explantation might necessitate further surgeries and cause decreased visual acuity during long-term follow-up in the aphakic group.	Larger and longer follow-up studies included in table2.
Verdejo-Gomez L et al (2011). The Boston Type I keratoprosthesis: an assessment of its efficacy and safety. Ophthalmic Surgery, Lasers & Imaging 42: 446-452.	Retrospective case series n=12 BKPro type 1 Follow-up: mean 23 months.	BCVA improved in 83.3% patients, and 16.7% maintained their previous vision. Patients with glaucoma comorbidity had the most limited final postoperative vision. 4 eyes presented limited corneal melt. In 2 eyes, corneal stromal bleeding led to a vitreous hemorrhage that was completely resolved after some weeks. No endophthalmitis or extrusion of the device occurred.	Additional study related to Guell 2011.

Wang Q and Harissi-Dagher M (2014). Characteristics and management of patients with Boston type 1 keratoprosthesis explantation--the University of Montreal Hospital Center experience. American Journal of Ophthalmology 158:1297-1304.	Retrospective observational study n=110 eyes 2008-12 KPro type 1 Explantation versus retention (11 vs 99) Follow-up: mean 19.7 +/- 10.5 (4-40) months	11 eyes had KPro explantation, failure rate of 0.03/life-year. Explanted at 19.7 months for sterile keratolysis (n = 7), infection (n = 2), and hypotony and painful blind eye (1 each). Compared to patients with KPro retention, those requiring KPro explantation were associated with aniridia (P = .0038), sterile keratolysis (P < .001), retroprosthesis membrane (P = .02), and intraocular inflammation (P = .04). Posterior segment complications (n = 5, 62.5%) were the most common cause of permanent vision loss.	Factors associated with explantation.
Yildiz EH et al (2010). The Boston keratoprosthesis in 2 patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Cornea 29: 354-356.	Case report n=2 B-KPro in patients with ocular history of corneal ulcers in 1 and keratitis, recurrent corneal erosions, and scarring in both eyes in 1. Lens extraction, IOL implanted.	The surgeries were uneventful. On postoperative day 1, visual acuity of 20/40 was achieved in both patients and it remained stable during the 2-year follow-up period. There were no postoperative complications seen in either patient.	Fewer than 10 patients undergoing repeat corneal transplantation.
Zerbe BL et al (2006). Results from the multicenter Boston Type 1 Keratoprosthesis Study. Ophthalmology 113:1779-7	Prospective case series n=141 2003-9 BKPro Type 1 Follow-up: average 8.5 months (0-24)	Postoperative vision improved to 20/200 in 57%. Among eyes at least 1 year after the operation (62 eyes), vision was 20/200 in 56% and 20/40 in 23%. graft retention was 95%. Severe visual loss or failure to improve from keratoprosthesis was usually secondary to comorbidities such as advanced glaucoma, macular degeneration, or retinal detachment.	Additional study related to Ciolino 2013, included in table 2.

Appendix B: Related NICE guidance for implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes

Guidance	Recommendations
Interventional procedures	**Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus and keratectasia. NICE interventional procedure guidance 466 (2013)** Most of the published evidence on photochemical corneal collagen cross-linkage (CXL) using riboflavin and ultraviolet A (UVA) for keratoconus and keratectasia relates to the technique known as 'epithelium-off' CXL'. 'Epithelium-on (transepithelial) CXL' is a more recent technique and less evidence is available on its safety and efficacy. Either procedure (epithelium-off or epithelium-on CXL) can be combined with other interventions, and the evidence base for these combination procedures (known as 'CXL-plus') is also limited. Therefore, different recommendations apply to the variants of this procedure, as follows. 1.1 Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia is adequate in quality and quantity. Therefore, this procedure can be used provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Current evidence on the safety and efficacy of epithelium-on (transepithelial) CXL, and the combination (CXL-plus) procedures for keratoconus and keratectasia is inadequate in quantity and quality. Therefore, these procedures should only be used with special arrangements for clinical governance, consent and audit or research. 1.3 Clinicians wishing to undertake epithelium-on (transepithelial) CXL, or the combination (CXL-plus) procedures should take the following actions: • Inform the clinical governance leads in their NHS trusts. • Ensure that patients and their parents or carers understand the uncertainty about the efficacy and safety of the procedures in the long term and provide them with clear information. In addition, the use of NICE's information for the public is recommended. • Audit and review clinical outcomes of all patients having these procedures for keratoconus and keratectasia. 1.4 Patient selection for these procedures should include assessment of corneal thickness and consideration of the likelihood of disease progression. 1.5 The procedures should only be carried out by ophthalmologists with expertise in managing corneal disease and specific training in the use of ultraviolet light or by appropriately trained staff under their supervision. 1.6 NICE encourages further research into CXL using riboflavin and UVA for keratoconus and keratectasia, especially epithelium-on (transepithelial) CXL and the combination (CXL-plus) procedures. Details of the techniques used should be clearly described. Reported outcomes should include visual acuity, corneal topography and quality of life. Data on long-term outcomes for all types of CXL using riboflavin and UVA for keratoconus and keratectasia would be useful – specifically data about prevention of progression to corneal transplantation and about repeat procedures and their efficacy.

	Corneal inlay implantation for correction of presbyopia. NICE interventional procedure guidance 455 (2013) 1.1 The evidence for corneal inlay implantation for correction of presbyopia is limited in quantity and quality and comes predominantly from case series; there is some evidence of efficacy in the short term. In addition, there are reports that adverse effects occur frequently. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake corneal inlay implantation for correction of presbyopia should take the following actions: • Inform the clinical governance leads in their Trusts. • Ensure that patients understand that this is principally a cosmetic procedure that may reduce their need to wear spectacles or contact lenses. They should be made aware of other management options for presbyopia. They should be informed about the possible adverse events associated with the procedure and encouraged to balance these carefully against the expected benefits. Patients should be provided with clear written information. In addition, the use of NICE's information for the public is recommended. • Audit and review clinical outcomes of all patients having corneal inlay implantation for the correction of presbyopia (see section 3.1). 1.3 Both clinicians and manufacturers are encouraged to collect details of complications and long-term outcomes following corneal inlay implantation for correction of presbyopia, and to publish their findings. NICE may review the procedure on publication of further evidence. **Corneal endothelial transplantation. NICE interventional procedure guidance 304 (2009)** 1.1 Current evidence on the safety and efficacy of corneal endothelial transplantation (also known as endothelial keratoplasty [EK]) is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance and consent. 1.2 NHS Blood and Transplant (formerly UK Transplant) runs a corneal transplant register, and clinicians should submit details about all patients undergoing corneal endothelial transplantation to this register. 1.3 The procedure should only be carried out by surgeons with specific training in this technique. 1.4 NICE encourages publication of long-term outcomes from register or research data. **Implantation of miniature lens systems for advanced age-related macular degeneration. NICE interventional procedure guidance 272 (2008)** 1.1 Evidence on the efficacy of implantation of miniature lens systems for advanced age-related macular degeneration (AMD) shows that the procedure can improve both vision and quality of life in the short term. Short-term safety data are available for limited numbers of patients. There is currently insufficient

	long-term evidence on both efficacy and safety. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake implantation of miniature lens systems for advanced AMD should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the need to adapt to having a lens system implanted into one eye, the risk of early complications and the uncertainties about long-term efficacy and safety. They should provide clear information. In addition, the use of the Institute's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having implantation of miniature lens systems for advanced AMD. 1.3 Patient selection is crucial and should include detailed assessment to predict the patient's ability to process visual stimuli following the operation. 1.4 Further publication of safety and efficacy outcomes would be useful, specifically with regard to longer term follow-up. The Institute may review the procedure upon publication of further evidence. **Corneal implants for keratoconus. NICE interventional procedure guidance 227 (2007)** 1.1 Current evidence on the safety and efficacy of corneal implants for keratoconus appears adequate to support the use of this procedure provided that normal arrangements are in place for consent, audit and clinical governance. **Corneal implants for correction of refractive error. NICE interventional procedure guidance 225 (2007)** 1.1 Current evidence on the efficacy of corneal implants for the correction of refractive error shows limited and unpredictable benefit. In addition, there are concerns about the safety of the procedure for patients with refractive error which can be corrected by other means, such as spectacles, contact lenses, or laser refractive surgery. Therefore, corneal implants should not be used for the treatment of refractive error in the absence of other ocular pathology such as keratoconus. **Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium. NICE interventional procedure guidance 216 (2007)** 1.1 Current evidence on the safety and efficacy of tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to use tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium should take the following actions.

	• Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy, and provide them with clear written information. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium (see section 3.1). 1.3 Further research on long-term outcomes and the risks and benefits of long-term systemic immunosuppressant regimes would be useful. The Institute may review the procedure upon publication of further evidence. **Insertion of hydrogel keratoprosthesis. NICE interventional procedure guidance 69 (2004)** 1.1 Current evidence on the safety and efficacy of insertion of hydrogel keratoprosthesis does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake insertion of hydrogel keratoprosthesis should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. Use of the Institute's information for the public is recommended. • Audit and review clinical outcomes of all patients having insertion of hydrogel keratoprosthesis. 1.3 Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. 1.4 The manufacturer of the synthetic hydrogel cornea implant used in this procedure maintains a registry. The Institute may review the procedure upon publication of further evidence.

NICE guidelines	**Glaucoma: Diagnosis and management of chronic open angle glaucoma and ocular hypertension. NICE clinical guideline 85 (2009). Available from** 1.4 Treatment for people with chronic open angle glaucoma (COAG) 1.4.1 Check that there are no relevant comorbidities or potential drug interactions before offering medication. 1.4.2 Offer people newly diagnosed with early or moderate COAG, and at risk of significant visual loss in their lifetime, treatment with a prostaglandin analogue. 1.4.3 Offer people with advanced COAG surgery with pharmacological augmentation (MMC or 5-FU) as indicated. Offer them information on the risks and benefits associated with surgery. 1.4.4 Offer people who present with advanced COAG and who are listed for surgery interim treatment with a prostaglandin analogue. 1.4.5 Encourage people using the prescribed pharmacological treatment to continue with the same treatment unless: • their IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss • there is progression of optic nerve head damage • there is progression of visual field defect • they are intolerant to the drug. 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-FU) as indicated. If the pharmacological treatment option is chosen, after trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5-FU) as indicated or laser trabeculoplasty. 1.4.7 Offer surgery with pharmacological augmentation (MMC or 5-FU) 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. 1.4.8 Consider offering people with COAG who are intolerant to a prescribed medication: • alternative pharmacological treatment (a prostaglandin

	analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) **or** • a preservative-free preparation if there is evidence that the person is allergic to the preservative. After trying two alternative pharmacological treatments consider offering surgery with pharmacological augmentation (MMC or 5-FU) as indicated or laser trabeculoplasty. 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 implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	11/06/2015	Issue 6 of 12, June 2015
HTA database (Cochrane Library)	11/06/2015	Issue 2 of 4, April 2015
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	11/06/2015	Issue 5 of 12, May 2015
MEDLINE (Ovid)	11/06/2015	1946 to June Week 1 2015
MEDLINE In-Process (Ovid)	11/06/2015	June 10, 2015
EMBASE (Ovid)	11/06/2015	1974 to 2015 Week 23
CINAHL (NLH Search 2.0)	11/06/2015	n/a
PubMed	11/06/2015	n/a
JournalTOCS	11/06/2015	n/a

Trial sources searched on 10 December 2014

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- WHO International Clinical Trials Registry

Websites searched on 10 December 2014

- 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 Corneal Transplantation/

2 keratoprosthes*.tw.

3 (cornea* adj4 (transplant* or synthetic or artificial or prosthes* or prosthetic or donor or implant*)).tw.

4 Prosthokeratoplasty.tw.

5 or/1-4

6 (boston adj4 (kpro or keratoprosthes*)).tw.

7 (dohlman-doane adj4 (kpro or keratoprosthes*)).tw.

8 6 or 7

9 5 and 8

10 corneal opacity/

11 (cornea* adj4 (opac* or opaq* or edema or oedema)).tw.

12 exp Corneal Diseases/

13 (cornea* adj4 (diseas* or injur* or disorder* or infect* or neovasculari* or dystroph* or ulcer* or hypoxi* or inflamm*)).tw.

14 Graft Rejection/

15 (graft adj4 (fail* or reject* or disease*)).tw.

16 Steven-Johnson.tw.

17 Aniridia.tw.

18 (Peter* adj4 anomal*).tw.

19 Eye Burns/

20 ((ocular or eye*) adj4 (burn* or chemical* or thermal or herpes)).tw.

21 photokeratitis.tw.

22 (Cicatrizing adj4 (condition* or disorder* or conjunctivitis)).tw.

23 (Ocular adj4 cicatricial adj4 pemphigoid).tw.

24 (Suboptimal adj4 vision).tw.

25 keratoconus.tw.

26 keratitis*.tw.

27 (dystroph* adj4 (meesman or epithelial or endothelial or reis-buckler or stromal or granular or macular or lattice)).tw.

28 keratoconjunctivitis.tw.

29 Keratoconjunctivitis/

30 Keratopathy.tw.

31 (acute adj4 red adj4 eye*).tw.

32 myop*.tw.

33 Nearsighted*.tw.

34 shortsighted*.tw.

35 Astigmatism/

36 astigmatism.tw.

37 ((refractive or refraction) adj4 (error* or defect* or disorder*)).tw.

38 Refractive Errors/

39 ((cone or conical or curv*) adj4 (ectasia or cornea*)).tw.

40 keratitides.tw.

41 or/10-40

42 9 and 41

43 animals/ not humans/

44 42 not 43