NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of corneal inlay implantation for correction of presbyopia

Treating presbyopia by inserting an artificial disc into the cornea

Age-related long-sightedness (presbyopia) develops as the lens in the eye becomes stiffer, making it difficult to focus on close objects. It is usually corrected with reading glasses or contact lenses. Surgery such as lens replacement may be offered. Corneal inlay implantation is a surgical treatment in which a disc is placed inside a flap or pocket made in the cornea (the transparent layer at the front of the eye). This improves near vision by changing the way in which light passes through the eye.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this 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 overview was prepared in December 2012.

Procedure name

Corneal inlay implantation for correction of presbyopia

Specialist societies

Royal College of Ophthalmologists

Description

Indications and current treatment

Presbyopia results from age-related deterioration of the lens in the eye and usually begins to develop at around 40 years of age. The lens deterioration causes difficulty with accommodation (focusing on near objects).

Standard treatment for presbyopia is corrective glasses or contact lenses. Surgery (monovision or blended vision laser in situ keratomileusis [LASIK], or refractive lens exchange or replacement) may be considered in some patients.

What the procedure involves

Corneal inlay implantation is a procedure that aims to improve near visual acuity and increase depth of focus. It may particularly benefit people who find it difficult to use glasses or contact lenses, for instance those with limited dexterity.

The procedure is usually performed on the non-dominant eye, under topical anaesthesia. The patient fixates their eye on a light source on a surgical microscope so that the surgeon can identify the target position on the centre of the visual axis. Laser or microkeratome techniques are used to create either a lamellar corneal flap or a pocket within the corneal stroma. The flap or pocket is separated with a spatula and a special insertion tool is used to position the inlay within it at the marked centre of the axis. The flap or pocket self-seals, holding the inlay in place. Patients are normally prescribed corticosteroids and antibiotic eye drops in the short term and artificial tears for as long as needed. The inlay can be removed or replaced if needed.

A number of different inlays are available. They are made of different materials but are all sufficiently permeable to allow nutrients to pass through the small holes in the inlay to the cornea. They work on different optical principles; examples include:

- KAMRA Inlay/ACI 7000PDT (previous version ACI-7000) (AcuFocus Inc) inlay, an opaque disc with a narrow aperture that uses the pinhole effect to increase the depth of focus
- InVue/Icolens (Neoptics AG) and Flexivue Microlens (Presbia), transparent discs where the prescribed thicknesses give the required correction in the annular zone, and the central zone has no correction
- Vue+/PresbyLens (Revision Optics), a transparent disc with similar properties to the cornea. Implantation causes a change in the effective corneal curvature.

Outcome measures

Visual acuity

Visual acuity is the minimal angle (or size) that a letter projected at a given distance must have for the retina to be able to discriminate the letter. Intermediate and distant visual acuity are typically measured using a Snellen or ETDRS chart with letters ranging from large to small sizes, and measured at a range of distances. Measurements may be uncorrected, corrected by glasses or contact lenses, measured using the surgical eye only, or measured using binocular vision. The first figure represents the test distance (20 feet for the Snellen acuity method or 6 metres for the metric equivalent). The second figure represents the distance at which a person with normal vision can see a particular letter. A visual acuity of 20/20 (6/6 metric) means that if you and a person with 'normal' eyesight both stand 20 feet (6 metres) away from an object, you would see the same thing. If you have a visual acuity of 20/40 (6/12 metric), then if you stood 20 feet (6 metres) away from an object and the 'normally-sighted' person stood 40 feet away, you would both see the same thing: this suggests that you have worse eyesight than normal. It is possible to have vision superior to 20/20: the maximum acuity of the human eye is generally thought to be around 20/15 (6/4.5 metric).

For near visual acuity, different reading charts are used. Results are often reported using the Jaeger scale or a logMAR scale and can be converted back to the Snellen scale as shown below.

Vision	logMAR	Snellen	Jaeger
	–0.3	20/10	
	–0.2	20/12.5	
Superior vision	–0.1	20/16	
Normal vision	0.0	20/20	J1+
Worse than normal	0.1	20/25	J1
		20/30	J2
	0.2	20/32	
	0.3	20/40	J3
	0.4	20/50	J5
	0.5	20/63	
		20/70	J7
	0.6	20/80	
	0.7	20/100	J10

The loss of lines from the reading charts is reported in addition to the numerical scores.

Contrast sensitivity

Contrast sensitivity measures the ability to detect different levels of contrast under different light conditions. Sensitivities are reported as photopic (under

bright light where the eye detects light using cones), scotopic (under very low light levels where the eye detects light using rods) and mesopic (under intermediate/medium light levels where both rods and cones are used).

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to corneal inlay implantation for correction of presbyopia. Searches were conducted of the following databases, covering the period from their commencement to 21 May 2012: 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, an 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 presbyopia
Intervention/test	Corneal inlay implantation
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 overview

This overview is based on 624 patients from 5 case series[1,2,3,4,5,6,7,8,9].

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 corneal inlay implantation for the correction of presbyopia

Abbreviations used: CCT, central corneal thickness; CDVA, corrected distance visual acuity; CIVA, corrected intermediate visual acuity; CNVA, corrected near visual acuity; cpd, cycles per degree; D, dioptres; DNVA, distance-corrected near vision; ECC, endothelial cell count; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; FACT, Functional Acuity Contrast Test; IVA, intermediate visual acuity; J, Jaeger; NVA, near visual acuity; preop: preoperative; SE, spherical equivalent; UDVA, uncorrected distance visual acuity; UIVA, uncorrected intermediate visual acuity; UNVA, uncorrected near visual acuity; wpm, words per minute.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Waring G (2011)[1]
Prospective case series
Multicentre, 24 sites in USA, Europe, Asia.
Recruitment period: Not reported
Study population: naturally emmetropic presbyopes.
n = 508 (507 eyes implanted)
Age: mean 53 years
Sex: not reported
Patient selection criteria: 45–60 years of age, SE between +0.5 and –0.75D with cylinder ≤0.75D. UNVA 20/40 to 20/100, CDVA at least 20/20 in both eyes.
Technique: Flap or pocket created using femtosecond laser or microkeratome, at least 180µm deep. KAMRA corneal inlay (. 5 µm thick, 3.8mm outer diameter, 1.6mm inner diameter, 8400 porosity holes) implanted in non-dominant eye, unless psychological testing indicated otherwise.
Follow up: 18 months
Conflict of interest/source of funding: The author has a financial interest and serves as World Surgical Monitor for AcuFocus Inc.</td>
<td>Number of patients analysed: 507 eyes

Visual acuity
<table>
<tr><th>Mean</th><th>Pre (n=507)</th><th>18 months (n=99)</th><th>p value</th></tr>
<tr><td>UNVA</td><td>J8
0.482±0.925 logMAR</td><td>between J2 and J3
0.139±0.851 logMAR</td><td>p<0.0001</td></tr>
<tr><td>UIVA</td><td>20/35
0.239±0.837 logMAR</td><td>20/26
0.139±0.853 logMAR</td><td>p<0.0001</td></tr>
<tr><td>UDVA</td><td>Shown graphically only, between 20/20 and 20/16</td><td>20/20
0.011±0.890 logMAR</td><td>p<0.0001</td></tr>
</table>
</td>
<td>Loss of contrast sensitivity

There was a significant decrease in photopic (p<0.001) and mesopic (p<0.0001) contrast sensitivity at all spatial frequencies. They were within the range of the normal population at 1 year.</td>
<td>Follow-up issues:
1 patient had a thinner than planned flap and the inlay was not implanted. 507 patients had the inlay implanted.
1, 5, 15 and 84 patients were lost to follow-up at 1, 6, 9 and 12 months. Only 99 patients were available at 18 months follow-up.
No explanation is given for patients lost to follow-up
Study design issues:
Results are reported graphically for a range of months, but numerical results were given for 18 months follow-up.
Visual acuity measured with ETDRS and Optec6500. Contrast sensitivity measured using Optec and FACT
Study population issues:
24 of the patients are reported in more detail in Dexl (2012)[2]</td>
</tr>
</table>

Abbreviations used: CCT, central corneal thickness; CDVA, corrected distance visual acuity; CIVA, corrected intermediate visual acuity; CNVA, corrected near visual acuity; cpd, cycles per degree; D, dioptres; DNVA, distance-corrected near vision; ECC, endothelial cell count; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; FACT, Functional Acuity Contrast Test; IVA, intermediate visual acuity; J, Jaeger; NVA, near visual acuity; preop: preoperative; SE, spherical equivalent; UDVA, uncorrected distance visual acuity; UIVA, uncorrected intermediate visual acuity; UNVA, uncorrected near visual acuity; wpm, words per minute.

Study details	Key efficacy findings	Key safety findings	Comments

Study details

Dexl A (2012)[2], (2011)[3]

Prospective case series

Austria

Recruitment period: 2009

Study population: Naturally emmetropic patients with presbyopia

n = **24**

Age: mean 52 years

Sex: 50% female

Patient selection criteria: naturally emmetropic presbyopia, 45–60 years, preoperative SE of plano (+0.5 to –0.75D with ≤0.75D refractive cylinder), UDVA at least 20/20 in both eyes, UNVA between 20/40 and 20/100 in inlay eye, corneal power >41D and <47D, minimum CCT ≥500µm, ECC≥2000 cells/mm^2 in the surgical eye. Corneal power higher than 41D but less than 47D in all meridians.

Technique: Pocket created using femtosecond laser. Three different femtosecond lasers were used with pocket depths of 200–260µm.

ACI 7000PDT KAMRA corneal inlay. 5 µm thick, 3.8mm outer diameter, 1.6mm inner diameter, 8400 porosity holes.

Key efficacy findings

Number of patients analysed: **24**

Visual acuity *(p values not reported if not stated)*

	Pre operative (n=24) Mean	**1 month (n=24) Mean**	**12 months (n=24) Mean**
UNVA (lines) in surgical eyes	J7/8, 20/63	J3	J2
			J3 or better in 92% (22/24) eyes
			J1 in 12% (3/24) eyes
binocular UNVA (lines)	J6, 20/50		J2
			J1 in 21% (5/24) eyes (p<0.001)
UIVA(lines) in surgical eyes	20/32	20/25	20/25 (p<.001)
binocular UIVA (lines)	20/25	20/20	20/20 (p<.001)
			20/20 or better in 38% (9/24) eyes
UDVA (lines) in surgical eyes	20/16		20/20 (at 24 months)
binocular UDVA (lines)	20/16		20/16 (p=0.3) (at 24 months)

Stability of SE refraction (n=24)

	Pre-operative	**12 months**	**24 months**
Mean SE refraction (D)	0.06±0.26	0.27±0.37 (p=0.06)	-0.11±0.53 (p=.17)

Key safety findings

Loss of lines

2 patients lost more than 2 lines of UDVA from preoperative (decrease from 20/16 to 20/25 in 1 patient and 20/32 in the other patient).

3 patients lost 1 line of CDVA in the surgical eye; 1 patient lost 3 lines (change from 20/16 to 20/32).23 patients had CDVA of 20/20 in surgical eye at 24 months and all patients had 20/16 mean binocular CDVA during follow-up.

Hyperopic shift

Hyperopic refractive shift >0.5D in 2 eyes from 3 months to 12 months follow-up.

Epithelial ingrowth

1 patient had small amount of epithelial ingrowth at pocket entrance 1 month after implantation (a complication of the femtosecond laser assisted pocket creation and unrelated to the inlay). Ingrowth was stable over time and required no treatment

Negative safety findings

No inlays explanted or recentred.

No irritation or inflammatory reaction or changes in corneal appearance by slit lamp exam at 12 months.

No evidence of deposits along the interface or on the surface of the inlay.

Mean ECC remained stable in surgical eye (preoperative 2417± 255 cells/mm^2; 2392±258 cells/mm^2 at 12 months; p=0.74).

No significant change in mean CCT

Comments

Study design issues:

Same surgeon for all implants and a third generation KAMRA inlay was used.

There are differences in the pocket depth stated (200–260µm)Part of FDA clinical trial 'Safety and Effectiveness of the AcuFocus Corneal Inlay ACI7000PDT in Presbyopes' NCT0085031, with participating clinics in the USA, Asia and Europe.

Patient satisfaction measured using a self-rated questionnaire about preoperative and postoperative (3,6, and 12 months) symptoms and subjective scores for problems with vision at distance, intermediate and near on a scale 1–7; higher score indicating very easy.

Postoperative refraction measured subjectively.

Visual acuity tested with Optec6500P vision tester and ETDRS charts.

In an additional study[3], outcomes were measured using the Salzburg Reading Desk technology allowing continuous reading distance measurements with video-stereo photogrammetry.

Abbreviations used: CCT, central corneal thickness; CDVA, corrected distance visual acuity; CIVA, corrected intermediate visual acuity; CNVA, corrected near visual acuity; cpd, cycles per degree; D, dioptres; DNVA, distance-corrected near vision; ECC, endothelial cell count; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; FACT, Functional Acuity Contrast Test; IVA, intermediate visual acuity; J, Jaeger; NVA, near visual acuity; preop: preoperative; SE, spherical equivalent; UDVA, uncorrected distance visual acuity; UIVA, uncorrected intermediate visual acuity; UNVA, uncorrected near visual acuity; wpm, words per minute.

Study details	Key efficacy findings	Key safety findings	Comments
Follow-up: **24 months** Conflict of interest/source of funding: Dr Riha is a surgical advisor to Acufocus, Inc. no other author has a financial or proprietary interest in any material or method mentioned. For Dexl A (2012): Publication was supported by the Fuchs-Foundation for the promotion of Ophthalmology, which is financially supported by AcuFocus, and Adele-Rabensteiner-Foundation of the Austrian Ophthalmologic Society. Dexl and Grabner are patent owners of the Salzburg-Reading-Desk. Grabner has received travel expenses from AcuFocus. Riha works as a clinical application specialist for AcuFocus Inc.	**Patient reported satisfaction at 24 months** **Reduced use of reading glasses** (mean score± SD) 12 months / 24 months Under bright light: 5.0±1.7 / 5.3±1.4 Under dim light: 3.1±1.6 / 3.1±1.6 **Overall satisfaction with procedure**: 4.9±1.6 / 5.0±1.7 75% (18/24) said they would have the procedure again,21% (5/24) were undecided and 1 patient said they wouldn't have the procedure again. Reported graphically: Increased score for near tasks (eg reading newspapers) and intermediate tasks (eg reading computer screens), significantly greater in bright light than in dim light. Decrease in need for reading glasses was statistically significant (p<.001). Change for distance tasks (eg watching a movie or driving a car) was very small. **Reading performance** Mean±SD **Pre-operative** / **1 month** / **12 months** / **24 months** Mean reading speed (wpm): 141±20 / 150±26 / 156±26 (p<0.003) / 146±20 (p=.261) Max reading speed (wpm): 171±28 / 188±35 / 196±38 (p=0.001) / 180±22 (p=.110) Mean reading acuity* logRAD): 0.33±0.13 / 0.27±0.12 / 0.24±–0.10 (p<0.005) / 0.23±0.11 (p=.004) Smallest print size** (mean, mm): 1.5±0.42 / 1.2±0.29 / 1.12±0.22 (p<0.001) / 1.01±0.22 (p<.001)	(preoperative 558 ±31 µm; 565 ±34 µm at 12 months; p=0.46).	Bilateral uncorrected reading acuity, mean and maximum reading speed and smallest log scale print size were assessed with the standardised Radner Reading Charts. **Study population issues:** These patients are also reported in less detail in the larger study by Waring (2011)[1] **Other issues**: Paper to be published on changes observed using confocal microscopy. Authors report that there is a potential learning curve with the pocket technique.

Abbreviations used: CCT, central corneal thickness; CDVA, corrected distance visual acuity; CIVA, corrected intermediate visual acuity; CNVA, corrected near visual acuity; cpd, cycles per degree; D, dioptres; DNVA, distance-corrected near vision; ECC, endothelial cell count; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; FACT, Functional Acuity Contrast Test; IVA, intermediate visual acuity; J, Jaeger; NVA, near visual acuity; preop: preoperative; SE, spherical equivalent; UDVA, uncorrected distance visual acuity; UIVA, uncorrected intermediate visual acuity; UNVA, uncorrected near visual acuity; wpm, words per minute.

Study details	Key efficacy findings	Key safety findings	Comments

Mean reading distance (cm)	46.7±6.3	44.6±6.2	42.8±5.8 (p<0.004)	39.5± 6.4 (p<.001)

* At patient-defined ‘best distance’,
** Size of a lower case letter that can be read effectively.

A mean improvement in smallest log scaled reading sentences of 1.58 ±1.50 lines, 21% (5/24) had no gain, 4.2% (1 patient) had lost a line and 75% (19/24) had improvement of up to 5 lines from baseline.

Abbreviations used: CCT, central corneal thickness; CDVA, corrected distance visual acuity; CIVA, corrected intermediate visual acuity; CNVA, corrected near visual acuity; cpd, cycles per degree; D, dioptres; DNVA, distance-corrected near vision; ECC, endothelial cell count; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; FACT, Functional Acuity Contrast Test; IVA, intermediate visual acuity; J, Jaeger; NVA, near visual acuity; preop: preoperative; SE, spherical equivalent; UDVA, uncorrected distance visual acuity; UIVA, uncorrected intermediate visual acuity; UNVA, uncorrected near visual acuity; wpm, words per minute.

Study details

Bouzoukis MD (2012)[4]

Prospective case series

Greece

Recruitment period: Not reported

Study population**:** Naturally emmetropic presbyopes

n = 45 patients

Age: mean 52 years

Sex: 42% female

Patient selection criteria:

Age 45–60 years, 12 month postoperative follow-up, UNVA 20/50 or worse, UDVA 20/30 or better, CNVA and CDVA 20/20, SE refraction for distance between –0.75 and +0.75 D, reading glasses for at least 1 year, CCT>500µm, ECD >2000 cells/mm^2.

Technique: Intracorneal pocket created using mechanical microkeratome. Pocket depth was 3/5 of total cornea.

Invue Lens, 3-mm diameter, 15–20µm thickness depending on add power. 0.15-mm hole in centre of disc for nutrient exchange. Inlay selected by calculating the total power needed for a reading distance of 33cm.

Follow-up: **12 months**

Conflict of interest/source of funding: Authors have no financial or proprietary interests in this material.

Key efficacy findings

Number of patients analysed: **45**

Accuracy

After treatment the add power for CNVA was within ±0.5D in 98% of operated eyes.

Visual acuity

	Pre operative	12 months% of eyes
UNVA surgical and binocular	20/50 or worse	20/20 in 29%
		20/25 or better in 76%
		20/32 or better in 98%
		20/40 or better in 100%
CNVA surgical)	20/25 or better	±0.5D in 98% of eyes
UDVA surgical	20/25 or better	20/20 in 7%
		20/25 or better in 36%
		20/32 or better in 82%
		20/40 or better in 93%
		20/50 or better in 100%
UDVA binocular		20/20 or better in 20% 20/25 or better in 100%
CDVA	20/20 or better	3 patients lost 1 line of CDVA in operated eye, binocular unchanged.
Near SE (D)	2.1±0.3	not reported
Distance SE (D)	0.27±0.33	–1.2±0.28

Patient-rated vision performance (assessed by patient satisfaction questionnaire) (n=45)

	Pre operative	3 months	6 months	12 months
Binocular UNVA*	1.00	3.82	3.80	3.73
Binocular UDVA#	4.00	3.76	3.76	3.67
Use of reading glasses##	4.00	1.18	1.20	1.24

*1=bad, 2=unchanged, 3=good, 4=excellent

#1=decreased, 2=slightly decreased, 3=almost unchanged, 4=unchanged

4=always, 3=more than 50% of my activities, 2= less than half of my activities, 1=never

Key safety findings

Loss of lines

3 patients lost 1 line of CDVA in operated eye (inlay not removed as they were satisfied with binocular UNVA and UDVA)

Patient reported outcomes

	No	Yes
Glare or halos?	82%	18%

Loss of contrast sensitivity (measured using FACT)

Operated eye: Significant decrease (p<0.5) found at 6, 12, 18 cpd for both mesopic and photopic conditions at all spatial frequencies (1, 3 and 12 months). No absolute numbers given.

Binocular: Mesopic or photopic not reported

cpd	Pre-operative	12 month	p value
12	30.53±19.26	15.25±12.25	p<0.05
18	9.90±8.04	4.00±3.58	p<0.05

Negative safety findings

No intra- or postoperative complications noted,

No corneal haze around the inlay found using slit lamp microscopy**.**

Endothelial cell density

2485±237 cells/mm^2 preoperatively, 2365±333 cells/mm^2 12 months postoperatively (p<0.1)

Corneal topographic astigmatism (measured by topographic analysis)

–0.64±0.37D preoperatively, –1.11±0.28D at 12 months postoperatively. Mean surgically induced astigmatism was –0.44±0.19D at a mean axis of 169.46°±21.72°

Comments

Follow-up issues:

12 month post operative follow-up is an inclusion criteria. This implies that patients that did not attend follow-up were not included in the study, historically.

Study design issues:

45 patients from a consecutive series of 446

Visual acuity measured using ETDRS visual charts at 4m for distance vision, modified ETDRS at 33cm for near vision

Visual quality measured by wavefront analysis and corneal topography. Contrast sensitivity measured using FACT.

Conofocal microscopy performed to assess endothelial cell density and depth of inlay in the cornea.

Patient reported outcomes were assessed by asking patients to grade the 4 questions preoperatively and at 3, 6 and 12 months on a scale of 1 to 4.

Abbreviations used: CCT, central corneal thickness; CDVA, corrected distance visual acuity; CIVA, corrected intermediate visual acuity; CNVA, corrected near visual acuity; cpd, cycles per degree; D, dioptres; DNVA, distance-corrected near vision; ECC, endothelial cell count; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; FACT, Functional Acuity Contrast Test; IVA, intermediate visual acuity; J, Jaeger; NVA, near visual acuity; preop: preoperative; SE, spherical equivalent; UDVA, uncorrected distance visual acuity; UIVA, uncorrected intermediate visual acuity; UNVA, uncorrected near visual acuity; wpm, words per minute.

Study details

Seyeddain O (2012)[5,10], Dexl A (2011a)[7] Dexl A (2011b)[6]

Prospective case series

Austria

Recruitment period: 2006–2007

Study population naturally emmetropic presbyopic patients

n = **32**

Age: mean 52 years

Sex: 78.1% female

Patient selection criteria: 45–55 years of age[10], preoperative UNVA between 20/40 (J5) and 20/100 (J10/J11) in the surgical eye, UDVA at least 20/20 in both eyes, cycloplegic refraction of ±0.5D, CCT ≥500µm, ECD in surgical eye ≥2000 cells/mm^2 if 45 to 49 years or 1800cells/mm^2 if over 50 years of age. Corneal power 41 – 47 D in all meridians, stable refraction 12 months before implantation.

Technique: All procedures performed by same surgeon In non-dominant eye.

Superior hinged flap created using femtosecond laser at depth of 170µm.

ACI7000 Inlay Acufocus corneal inlay. 10 µm thick, 3.8mm outer diameter, 1.6mm inner diameter, 1600 porosity holes. Average light

Key efficacy findings

Number of patients analysed: **32**

Refraction and Visual Acuity (p values not reported unless stated)

Mean±SD	**Pre operative**	**24 months**	**36 months**
SE refractive error (D)	0.19±0.22[10]	–0.13 ±0.83 [10]	0.08 ±0.68
Cycloplegic refraction (D)	0.06 ±0.16	–0.16 ±0.81	0.03 ±1.02
UNVA surgical	J7/8	J2	J1
UNVA binocular	J6	J1 [10] (p<0.001)	J1 (p<0.00001)
UIVA surgical	20/40	20/25 (p<0.00001)	20/25 (p<0.00001)
UIVA binocular	20/32 [10]	20/20 [10]	20/20 (p<0.001)
UDVA surgical	20/16	20/20	20/20
UDVA binocular	not stated	20/16'	20/16 (p=0.77)
CDVA surgical	NR	NR	20/20 or better in 88% (28/32) 1 line gained by 9% (3/32)
CDVA binocular			20/16

Dependence on reading glasses for near visual acuity tasks (assessed by patient satisfaction questionnaire)

Spectacle use	**Pre-operative %**	**24 month %**	**36 month %**
Never	0.0	12.5	12.5
Occasionally	0.0	75.0	43.7
Some of the time	12.5	3.1	37.5
Most of the time	59.4	9.4	6.3
Always	28.1	0.0	0.0

Key safety findings

Event	**% (n)**
Loss of visual acuity: • 2 lines of UDVA • 1 line of CDVA • 3.8 lines of CDVA (reported as 2.2 lines at 24 months[10])	 12.5 (4/32) 28.3 (9/32) 3.1 (1/32)
Misplacement of inlay resulting in low increase in NVA and IVA and reduction in UVDA (3 and 6 months). Implants recentred at 6 months leading to significant increase in visual acuity.	6.3 (2/32)
Refractive error decreased slightly post implantation, but with a wider ranges of values (p<0.003, 36 months): • –1.25 D • –1.50 D • +1.25 D • +2.25 D	 9.4 (3/32) 3.1 (1/32) 3.1 (1/32) 3.1 (1/32)
Pattern SD increased indicating non-uniform loss of visual field (p=0.0003, 36 months). Changes are not clinically significant. Mean values are reported but what is being measured is unclear.	All
Flap striae at 1 month treated by lifting and smoothing the flap. Epithelial ingrowth at 3 months similarly treated. Repeated ingrowth resolved using nylon sutures at the flap margin, removed after 2 months.	3.1 (1/32)

Comments

Follow-up issues:

All patients attended all booked follow-up sessions, with the exception of 1 patient at 30 months.

Study design issues:

Patient satisfaction questionnaire designed by AcuFocus.

Improving surgical technique and technology

Authors note that ECD loss was due to surgical manipulation. It was higher in first 11 patients (–7.2%) than 20 patients (–4.9%) who had later.

Authors note inlay technology evolving to improve CDVA outcomes.

Other issues

4 patients had a hyperopic shift >+0.5 D, and tomography in these patients showed central corneal flattening from 6 to 36 months. Authors hypothesise that this could be the result of surgical technique or natural trend for this age group.

Corneal epithelial deposits were noted in 18 eyes. Authors speculate that the new karma inlay design (ACI 7000PDT) avoids this by

Abbreviations used: CCT, central corneal thickness; CDVA, corrected distance visual acuity; CIVA, corrected intermediate visual acuity; CNVA, corrected near visual acuity; cpd, cycles per degree; D, dioptres; DNVA, distance-corrected near vision; ECC, endothelial cell count; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; FACT, Functional Acuity Contrast Test; IVA, intermediate visual acuity; J, Jaeger; NVA, near visual acuity; preop: preoperative; SE, spherical equivalent; UDVA, uncorrected distance visual acuity; UIVA, uncorrected intermediate visual acuity; UNVA, uncorrected near visual acuity; wpm, words per minute.

Study details

transmission through the annulus of the inlay is 7.5%

Follow-up: **33.8 months**

Conflict of interest/source of funding: AcuFocus financially supports the Research Foundation for Promoting Ophthalmology. Dr Grabner received travel expenses from AcuFocus. Dr Riha works as a clinical application specialist for AcuFocus

Drs Dexl and Grabner own the patents on the Salzburg Reading Desk Technology

Key efficacy findings

Patient-rated vision performance (assessed by patient satisfaction questionnaire) (n=32)

Mean ±SD	Pre-operative	36 months
Near vision		
Reading small text	9.4±1.0	3.0±2.3
Reading newspaper	8.8±1.5	1.8±1.8
Labels on medicine bottles	8.8±1.7	3.2±2.6
Fine handwork (sewing)	9.3±1.0	3.7±2.5
Intermediate vision		
Reading computer screen	4.9±2.5	2.0±2.2
Viewing car dashboard	1.7±2.5	0.5±1.1
Distance vision		
Watch movie	0.1±0.4	0.2±0.6
Night time driving	0.6±0.8	2.1±3.0

*0=no problem; 10=severe problem

Overall satisfaction with procedure:

Would have procedure again %	Undecided %	Would not have procedure again %
85 (27/32)	13 (4/32)	3 (1/32)

Reading performance

Mean results	Preoperative	1 month	24 month
reading speed (wpm)	142±13	146±15	149±17 (p=0.029)
reading acuity*(logRAD)	0.38±0.14	0.27±0.13	0.24±0.11 (p<0.000001)
Smallest log scaled sentence* (1–14)	7.4±01.3	9.2±1.3	9.9±1.5 (p<0.00001)
Reading distance	48.1±5.4	40.6±4.3	38.9±6.3 (p<0.0001)

*94% (30/32) patients gained up to 6 lines, 1 patient had no gain,1 patient lost 1line in log scaled sentences

Key safety findings

Corneal epithelial iron deposits (36 months). Median interval to diagnosis 18 months. • Central spot • 'Half-moon' in inferior cornea or complete ring • Both spot and ring deposits (Deposit location associated with corneal flattening.)	56.3 (18/32) 5.5 (1/18) 55.5 (10/18) 38.9 (7/32)
ECD reduced by 6% (6 months). No significant loss at further follow-up.	All

Contrast sensitivity

A small decrease in contrast sensitivity was reported (graphically) in the surgical eye, (particularly in glare and mesopic light).

Patient-reported visual symptoms (assessed by patient questionnaire, absolute numbers not reported)

Symptoms %		Night vision	halo	blurry vision	dryness
none	preop	43.8	90.6	81.3	84.4
	3 yr	37.5	37.5	71.9	40.6
mild	preop	43.8	6.3	18.7	12.5
	3 yr	40.6	34.4	25.0	50.0
moderate	preop	12.4	3.1	0.0	3.1
	3 yr	6.3	25.0	3.1	9.4
severe	preop	0.0	0.0	0.0	0.0
	3 yr	15.6	3.1	0.0	0.0

Comments

having thinner inlay and more holes..

Measurement techniques

Visual acuity measured using Optec 6500P vision tester and logarithmic ETDRS deriving Snellen equivalent.

Patient-reported outcomes include a satisfaction questionnaire and another questionnaire designed by AcuFocus[10].

Diagnostic tools for investigation of retinal disease and glaucoma were: Digital Wide Field Lens, 3-mirror Goldmann Contact Lens 903, FF450 plus IR fundus camera, Spectralis HRA optical coherence tomographer. Glaucoma diagnostics tools were: 2-mirror contact lens 905, GDx VCC, Heidelberg retina tomography. Images were reviewed independently by two specialists.

Reading performance measured using the Salzburg Reading Desk technology allowing continuous reading distance measurements with video-stereo photogrammetry.

Abbreviations used: CCT, central corneal thickness; CDVA, corrected distance visual acuity; CIVA, corrected intermediate visual acuity; CNVA, corrected near visual acuity; cpd, cycles per degree; D, dioptres; DNVA, distance-corrected near vision; ECC, endothelial cell count; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; FACT, Functional Acuity Contrast Test; IVA, intermediate visual acuity; J, Jaeger; NVA, near visual acuity; preop: preoperative; SE, spherical equivalent; UDVA, uncorrected distance visual acuity; UIVA, uncorrected intermediate visual acuity; UNVA, uncorrected near visual acuity; wpm, words per minute.

Study details

Yilmaz O (2011)[8] ,Yilmaz O (2008)[9]

Prospective case series

Turkey

Recruitment period: 2005

Study population: Emmetropic patients with presbyopia (natural and post LASIK)

n = **39 patients,**

Age: mean 52 years

Sex: 56% female (Yilmaz 2008[11] reports 64% female)

Patient selection criteria: naturally emmetropic presbyopia, or post LASIK presbyopia, 45–60 years, UNVA of 20/40 or worse correctable to 20/25 or better at distance. At least 3 weeks post LASIK

Technique: a superior hinged lamellar flap created using mechanical microkeratome, or relifting previous LASIK flap. Inlay in non-dominant eye. Right eye: 4/39; left eye: 35/39

ACI-7000 Acufocus corneal inlay 10 µm thick, 3.8mm outer diameter, 1.6mm inner diameter, 1600 porosity holes of 25µm diameter. Average light transmission through the annulus of the inlay is 7.5%

Key efficacy findings

Number of patients analysed: **39**

Visual Acuity

Mean	Preoperative n=39	Year 1 n=34	Year 4 n=22
UNVA	J7 20/50	J1+ 20/16 (p<0.001)	J1 20/20(p<0.001)
UIVA	20/32[9]	20/20 (p<0.05)[9]	not reported
UDVA	20/20	20/20, or 20/16 binocular	20/25(p<0.107)
CDVA	20/20		20/20

Change in refractive error

Manifest spherical equivalence (MSE)	Preoperative n=39	Year 4 n=22
Mean MSE, all eyes (D)	0.06 (±0.29)	–0.28 (±0.87) (p=0.054)
Mean MSE, excluding cataracts (D)	0.02 (±0.29)	–0.13 (±0.79) (p=0.218)

Patient-rated vision performance[9] (n=34)

Mean ±SD	Pre operative	Year 1
Near vision		
Threading needle	8.9±1.0	3.6±2.3
Reading newspaper	7.9±1.4	1.7±1.8
Reading phone book	5.9±1.5	0.9±1.7
Distance vision		
Watch movie	0.3±0.6	0.4±1.6
Daytime driving	0.2±0.5	0.2±0.6
Night time driving	0.6±0.8	1.1±1.4

0=no problem, 10=severe problem

Key safety findings

Explanted inlays = 10% (4/39)

1 explant at 6 weeks due to buttonhole flap, UNVA and UDVA returned to previous, or better, state and SE was ±1.00 D.

2 explantations at 3 months, due to refractive shifts (1 myopic and 1 hyperopic affected uncorrected visual acuity). Returned to within ±1.00 D of the preoperative refraction, with no loss of CDVA.

1 explant at 17 months due to thin flap (58µm), measured following patient complaints. After explantation eye returned to preoperative refractive state with no loss of CDVA, CNVA or UNVA.

Change in refractive error < ±1.0 D

1 Myopic –2.0 D

1 Hyperopic +3.0 D, both reported discomfort from glare and halos. After explantation eyes returned to within ±1.0 D of preop state.

Loss of lines CDVA

lines lost	1 month %(n) [9]	1 year %(n)[9]	4 years %(n)
>1	13 (5/39)	1 (1/34)	27 (6/22)
=2	0		5 (1/22)

There was no mean difference in mean CDVA between preoperatively and the last follow-up (both 20/20).

Corneal complications related to LASIK (inlay eye, fellow eye):

Dry eye (treated by artificial tears) 4/39, 4/27

Epithelial ingrowth (not onto visual axis) 5/39, 3/27

Comments

Follow-up issues: In year 1, five patients were lost to follow-up: 3 were explanted, 2 did not present for follow-up[9]. Reasons for other patients not followed up are not given.

Time	Patient (n).
Preoperative	39
1 year	34
2 year	28
3 year	27
4 year	22

Study design issues: Mix of patients that are naturally emmetropic (12) and those that are emmetropic post LASIK (27) for hyperopia.

Same surgeon performed all procedures, including previous LASIK. Inlay inserted at least 3 weeks after emmetropia established post LASIK

Subjective assessments of symptoms and patient satisfaction were evaluated using a questionnaire.

Other issues

Authors report that there were some improvements in design of inlay and implantation technique (creation of a

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<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Follow-up: mean 52.2 months

Conflict of interest/source of funding: no author has a financial or proprietary interest in any material or method mentioned. Dr Yilmaz is a paid consultant to AcuFocus Inc.</td>
<td>Dependence on reading glasses
The use of glasses for near vision was reported to have decreased significantly, however numerical results are not given.</td>
<td>Cataracts
5 eyes with the inlay developed cataract that affected visual function. Two patients had small incision cataract extractions, 1 after the 3-year examination and 1 after the 4-year examination; the remaining 3 were scheduled for extraction. If these 3 are excluded, UDVA at 4 years is 20/20 (p=0.513)
<table>
<tr><td></td><td colspan="4">Post-cataract surgery</td></tr>
<tr><td></td><td>Refractive error</td><td>CDVA</td><td>UNVA</td><td>UDVA</td></tr>
<tr><td>3 year</td><td>–0.75 D</td><td>no loss</td><td>20/20</td><td></td></tr>
<tr><td>4 year</td><td>None</td><td>not reported</td><td>20/16</td><td>20/20</td></tr>
</table>
Negative safety findings
No inlay complications (decentration or dislocation, corneal vascularisation, or corneal haze).</td>
<td>deeper flap, centration of inlay on visual axis, no need for interface irrigation at completion, reduction in inlay light transmission to less than 10%)</td>
</tr>
</table>

Abbreviations used: CCT, central corneal thickness; CDVA, corrected distance visual acuity; CIVA, corrected intermediate visual acuity; CNVA, corrected near visual acuity; cpd, cycles per degree; D, dioptres; DNVA, distance-corrected near vision; ECC, endothelial cell count; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; FACT, Functional Acuity Contrast Test; IVA, intermediate visual acuity; J, Jaeger; NVA, near visual acuity; preop: preoperative; SE, spherical equivalent; UDVA, uncorrected distance visual acuity; UIVA, uncorrected intermediate visual acuity; UNVA, uncorrected near visual acuity; wpm, words per minute.

Study details	Key efficacy findings	Key safety findings	Comments
Sharma (2010)[11] Conference Abstract Case series Mexico Recruitment period: not reported Study population: emmetropic presbyopes (mean preoperative SE +0.31D, mean near add +2.03 D. n=8 Age: 52 years (mean) Technique: implanted with a 1.5 mm diameter PresbyLens corneal hydrogel inlay under standard LASIK-flaps for improvement of near and intermediate vision. Follow-up: 2 years Conflict of interest/source of funding: not reported.		The slit lamp examination revealed clear corneas with very mild edge haze. The mesopic UCDVA was minimally affected with a maximum of 3 lines lost in the surgical eye.	

Efficacy

Visual acuity

Uncorrected near visual acuity (UNVA)

A case series of 508 patients reported an improvement from preoperative mean monocular UNVA of J8 (0.482±0.925 logMAR) to between J2 and J3 (0.139±0.851 logMAR) at 18 months follow-up (n=99, p<0.0001)[1].

A case series of 45 patients showed an improvement in UNVA from 20/50 or worse preoperatively to 20/25 or better in 76% of operated eyes and binocularly at 1 year after treatment[4].

A case series of 32 patients reported that mean UNVA in the treated eye improved from J7/8 preoperatively to J2 at 1 year after treatment and J1 at 3 years after treatment[5]. Binocular UNVA also improved from J6 to J1 at 3 years after treatment (p<0.00001)[5].

A case series of 39 patients reported an improvement in mean UNVA in the treated eye from 20/50 preoperatively to 20/20 in the 22 reported patients followed up for 4 years (p<0.001)[8]. Binocular UNVA also improved from a preoperative mean of J6 to J1 in 34 patients at 1 year after treatment (p<0.001)[9].

Uncorrected intermediate visual acuity (UIVA)

The case series of 508 patients reported an improvement in mean monocular UIVA from 20/35 (0.239±0.837 logMAR) preoperatively to 20/26 (0.139±0.853 logMAR) at 18 months follow-up (n=99, p<0.0001)[1].

The case series of 32 patients reported that mean UIVA in the treated eye improved from 20/40 preoperatively to 20/25 at 3 years after treatment (p<0.00001)[5]. Binocular UIVA also improved from 20/32 to 20/20 at 3 years after treatment (p<0.001)[5].

The case series of 39 patients showed an improvement in mean monocular UIVA from 20/32 preoperatively to 20/20 in the 34 reported patients after 1 year (p<0.05). Binocular UIVA also improved from a preoperative mean of 20/25 to 20/20 at 1 year (p<0.05)[9].

Uncorrected distance visual acuity (UDVA)

The case series of 508 patients reported a deterioration in mean monocular UDVA (reported graphically) from between 20/20 and 20/16 preoperatively to 20/20 (0.011±0.890 logMAR) at 18 months follow-up (n=99, p<0.0001)[1].

In a case series of 24 patients (from the case series of 508 patients[1]), there was a change in mean monocular UDVA from 20/16 preoperatively to 20/20 at 1 year, while the mean binocular UDVA remained constant at 20/16 (p=0.3)[2].

In a case series of 45 patients, there was a change from preoperative monocular UDVA of 20/25 or better to 20/25 or better in 36%, 20/40 or better in 93% and 20/50 or better in 100% of operated eyes. Binocular UDVA was 20/20 in 20% and 20/25 or better in 100% of patients at 1 year after treatment (absolute numbers not given)[4].

The case series of 32 patients reported that mean UDVA in the treated eye decreased slightly from 20/16 to 20/20 at 3 years (p<0.001). Binocular UDVA was reported as not significantly different between preoperative (unstated) and 20/16 at 3 years after treatment (p=0.77)[5].

The case series of 39 patients reported preoperative mean UDVA in the treated eye changed from 20/20 to 20/25 in the 22 reported patients after 4 years (p=0.107)[8].

Reading performance

A case series of 32 patients reported an increase in mean reading speed per minute from 142 words before treatment to 149 words after a mean follow-up of 2 years (p=0.029). Mean reading distance decreased from 48.1 cm to 38.9 cm at 2 years after treatment (p<0.0001)[6].

A case series of 24 patients reported an increase in mean reading speed from 141 words per minute to 146 words per minute at 2 years after treatment (p=.261). Mean reading distance decreased from 46.7 cm to 39.5 cm at 2 years after treatment (p<.001)[3].

Dependence on reading glasses for near tasks

The case series of 32 patients reported that the percentage of patients using glasses all or most of the time decreased from 88% to 6% at 3 years (absolute numbers not given). This was a patient-reported outcome on a 5-point scale from never to always[5].

A case series of 39 patients reported that the use of glasses for near vision decreased significantly after inlay implantation (numbers not reported)[9].

Patient satisfaction

A case series of 24 patients reported a mean satisfaction with the procedure of 5.0 (on a scale of 1–7 where high scores showed more satisfaction) at 2 years after treatment. Mean satisfaction with reduction in reading glasses was 5.3 in bright light and 3.1 in dim light, using the same scale. It was reported that 75% (18/24) of patients said they would have the procedure again, 21% (5/24) were

undecided and 1 patient said he would not have the procedure again (exact question not reported)[2].

The case series of 32 patients reported that 85% would have the procedure again, 13% were undecided and 1 patient would not have the procedure again (absolute numbers not given; exact question and scale not reported)[5].

Patient scores for vision

The case series of 32 patients reported that patient scores for near tasks of 'reading small text (map)', 'reading a book or newspaper', 'reading labels on medicine bottles' and 'doing fine handwork (sewing)' improved from 9.4 to 3.0, from 8.8 to 1.8, from 8.8 to 3.2 and from 9.3 to 3.7 at 3-year follow-up (assessed subjectively on a scale where 0 is no problem and 10 is a severe problem). Scores for intermediate tasks of 'reading computer screen' and 'viewing car dashboard' improved from 4.9 to 2.0 and from 1.7 to 0.5 at 3-year follow-up. Scores for distance tasks of 'watching movie' and 'driving at night' deteriorated from 0.1 to 0.2 and from 0.6 to 2.1 at 3 years[5].

The case series of 39 patients (34 patients at 1-year follow-up) reported that patient scores for near tasks of 'reading a newspaper', 'threading a needle' or 'reading telephone book' improved from 7.9 to 1.7, from 8.9 to 3.6, and from 5.9 to 0.9 at 1-year follow-up (assessed subjectively on a scale of 0 to 10 where a higher score indicates a more severe problem). Scores for distance tasks of 'watching a movie' or 'driving during the day' remained low with changes from 0.3 to 0.4 and 0.2 constant at 1 year. The score for 'driving at night' was not significantly different from baseline changing from 0.6 to 1.1 at 1 year[9].

Safety

Inlay explantation

Removal of the inlay was reported in 4 patients in the case series of 39 patients because of a buttonhole flap (in 1 patient at 6 weeks), refractive shifts and reported glare and halos (in 2 patients after 3 months) and a thin corneal flap causing symptoms (in 1 patient after 17 months). Following removal of the inlay, visual acuity returned its pretreatment value in all 4 patients[9].

Inlay recentration

Inlays were recentred after 6 months because of initial misplacement in 2 patients in the case series of 32 patients. Both patients' visual acuity for near, intermediate and distance improved after recentration (reported graphically)[5].

Corneal flap-related problems

A thinner than planned flap was created in 1 patient in the case series of 508 patients, resulting in no inlay being implanted[1], and in 1 patient in the case

series of 39 patients, resulting in the inlay being explanted (also reported under inlay explantation)[8].

Flap striae developed in 1 patient after 1 month in the case series of 32 patients, resulting in epithelial ingrowth that needed repeated flap lift and debridement and was resolved by suturing after 2 months. At 3 years, the acuity of the treated eye was J1 UNVA, 20/32 UIVA, 20/20 UDVA[5].

Corneal epithelial iron deposits were observed in 18 patients at 36 months in the case series of 32 patients[5]. The authors stated that the deposits had no noticeable influence on distance, near, corrected or uncorrected visual acuity[7].

A buttonhole flap requiring inlay explantation developed in 1 patient at 6 weeks in the case series of 39 patients (also reported under inlay explantation)[8].

Epithelial ingrowth was reported in 1 patient at 6 months in a case series of 24 patients. Ingrowth was stable over time and no treatment was required[2].

In the case series of 39 patients, epithelial ingrowth was observed in the treated eye in 5 out of 27 patients who had previously been treated with LASIK for hyperopia. Ingrowth was also seen in 3 of the non-treated eyes in these 27 patients. No ingrowth was considered clinically significant or required surgical intervention[8].

Lost lines of vision

More than 2 lines of UDVA were lost by 2 patients at 2 years in a case series of 24 patients. In the same case series, 1 or more lines of CDVA were lost by 4 patients[2].

In the case series of 45 patients, 1 line of CDVA was lost by 3 patients at 1 year[4].

Loss of visual acuity at 3 years was reported in 14 patients in the case series of 32 patients (2 lines of UDVA were lost by 4 patients, 1 line of CDVA was lost by 9 patients, and 3.8 lines of CDVA were lost by 1 patient)[5]. In the case series of 39 patients, 1 or more lines of CDVA were lost by 6 patients at 4 years and 2 lines of CDVA were lost by 1 patient[8].

Contrast sensitivity and night vision problems

A significant decrease in photopic ($p<0.001$) and mesopic ($p<0.0001$) contrast sensitivity at all spatial frequencies was reported in the case series of 508 patients at 1 year after treatment. These decreases were within the range of the normal population[1].

A statistically significant ($p<0.5$) decrease in contrast sensitivity in photopic and mesopic conditions was reported at 6, 12 and 18 cycles per degree in the case series of 45 patients at 1 year after treatment[4].

A small decrease in contrast sensitivity was reported (graphically) in the treated eye (particularly in glare and mesopic light) in the case series of 32 patients[5].

Severe problems with night vision were reported by 5 patients in the case series of 32 patients, using a patient-reported 4-point score ranging from no symptoms to severe symptoms[5].

Glare, halo and blurred vision

Severe, moderate and mild halo was reported by 1, 8 and 11 patients respectively in the case series of 32 patients at 3 years using a patient-reported 4-point score ranging from no symptoms to severe symptoms. Mild or moderate halo had been reported by 3 patients before treatment. Five patients in the same study reported severe problems with night vision[5].

Moderate and mild blurred vision was reported by 1 and 8 patients in the case series of 32 patients at 3 years, using the same patient-reported measure. Mild blurred vision was also reported by 6 patients preoperatively[5].

Glare or halos were reported by 18% of patients in the case series of 45 patients at 1 year using a patient-reported measure (yes/no)[4].

Dry eye

Moderate eye dryness was reported by 3 patients at 3 years in a case series of 32 patients, compared with 1 patient preoperatively. Mild eye dryness was reported by 16 patients, compared with 4 preoperatively[5].

In the case series of 39 patients, eye dryness was reported in the treated eye of 4 out of 27 patients who had previously been treated with LASIK for hyperopia. Dryness was also reported in 4 of the non-treated eyes in these 27 patients[8].

Refractive shift

Hyperopic refractive shift was reported in 2 eyes at 3 months in the case series of 24 patients[2].

Hyperopic shifts of +2.25 D in 1 patient and +1.25 D in 1 patient were measured at 3 years in the case series of 32 patients. In total, a hyperopic shift greater than +0.5 D was measured in 4 patients in the same series[5].

Myopic refractive shifts of −1.5 D in 1 patient, and −1.25 D in 3 patients were measured at 3 years in the case series of 32 patients[5].

A hyperopic shift of +3.0 D in 1 patient, and a myopic shift of −2.0 D in 1 patient were measured in the case series of 39 patients. In both cases, the inlay was explanted and the eyes returned to within ±1.0 D of their preoperative state[8].

Visual field

Mean deviation decreased significantly in treated eyes ($p<0.0001$) and non-treated eyes ($p=0.001$) between preoperative state and follow-up at 3 years in the case series of 32 patients. Pattern standard deviation increased significantly ($p=0.0003$) in treated eyes at 3 years. None of the changes were clinically significant[5].

Cataracts

Cataracts affecting visual function and needing surgical treatment developed in 5 treated eyes after 3–4 years in the case series of 39 patients[8].

Endothelial cell density

Endothelial cell density reduced from a mean of 2485±237 cells/mm^2 preoperatively to 2365±333 cells/mm^2 12 months postoperatively ($p<0.1$) in the case series of 45 patients[4].

Mean endothelial cell density reduced by 6% over 6 months in the case series of 32 patients. Follow-up showed a stabilised loss of less than 1% per year[5].

Haze

Very mild edge haze around the corneas was reported at 2 years follow-up in all the patients in a case series of 8 patients[10].

Validity and generalisability of the studies

- Trials were not included if they were primarily a treatment for conditions other than presbyopia.
- All but 1 of the studies in table 2 are for a single type of device. The design of this device has changed over time, so 2 different versions are considered. The occurrence of iron deposits in the cornea was noted for the earlier device (ACI-7000), but has not been reported for the newer modified version (ACI-7000PDT).
- Other devices have been studied, but only conference abstracts were found. These did not report any additional adverse events, and are therefore listed in Appendix A.
- Reporting of results is not standard between studies and in some cases is incomplete.

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

- Intraocular lens insertion for correction of refractive error, with preservation of the natural lens. NICE interventional procedure guidance 289 (2009). Available from http://guidance.nice.org.uk/IPG289
- Corneal implants for the correction of refractive error. NICE interventional procedures guidance 225 (2007). Available from http://guidance.nice.org.uk/IPG225
- Photorefractive (laser) surgery for the correction of refractive error. NICE interventional procedure guidance 164 (2006). Available from http://guidance.nice.org.uk/IPG164
- Scleral expansion surgery for presbyopia. NICE interventional procedure guidance 70 (2004). Available from http://guidance.nice.org.uk/IPG70

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 does not represent the view of the society.

Mr Bruce Allan, Mr Jean-Pierre Danjoux, Mr Francisco C Figueiredo, Mr David O'Brart (Royal College of Ophthalmologists).

- None of the Specialist Advisers have performed or taken part in the selection or referral of a patient for this procedure. Two advisers stated that they have undertaken bibliographic research.
- Three Advisers stated that this procedure could be considered to be novel and of uncertain safety and efficacy. One Adviser stated that is a minor variation of an existing procedure which is unlikely to alter the procedure's safety and efficacy. He also stated that various inlays for presbyopia are available and some have a very poor safety record.
- Three Advisers agreed that less than 10% of specialists are engaged in this work.
- All Advisers considered comparators as spectacles (varifocal or reading glasses), monovision or multifocal contact lenses, surgical procedures such

as refractive lens exchange with multifocal intraocular lenses, excimer laser refractive surgery and scleral implants. One Adviser stated that the current evidence is from non-comparative case series.

- The Advisers considered the key efficacy outcomes as improved unaided near or reading vision with maintained distance vision, uncorrected reading and distance visual acuity, mean gain in uncorrected visual acuity, corrected distance visual acuity, distance-corrected near visual acuity, refractive error, critical reading speed, defocus curve, dysphotopsia, contrast sensitivity and quality of life. Two Advisers noted that long-term (more than 5 years) efficacy is unknown. Another Adviser noted that all patients may not achieve their desired result. The same Adviser stated that although unaided near vision may be improved, it may not be to the level needed for the patient to be independent of near-vision spectacles.
- Specialist Advisers listed theoretical adverse events as malplacement, decentration, infectious keratitis, corneal scarring or opacification, corneal thinning and melting, reduction in best spectacle-corrected distance visual acuity, reduction in unaided distance vision, reduced or loss of contrast sensitivity, glare and halos, flap-related complications, refractive shift, light sensitivity, failure to achieve desired improvement in unaided near vision, loss of intermediate vision, failure to adapt to near monovision, difficulty measuring intraocular pressure accurately, severe night vision problems, mesopic contrast sensitivity and explantation. The other Adviser considered that early postoperative complications are similar to those for laser refractive surgery.
- The Specialist Advisers stated that anecdotal events included postoperative corneal infection, patient dissatisfaction with results and reduced best spectacle-corrected distance vision. One Adviser stated that the long-term safety of the procedure is unknown.
- All Advisers stated that training and experience in corneal and refractive surgery, including training in the creation of lamellar corneal flaps or pockets (for example, LASIK and femtosecond laser or microkeratome procedures) is needed and that centres with facilities to perform these procedures are

required. Two Advisers stated that full certification and wet lab facilities for training are typically provided by manufacturers.

- One Adviser stated that this procedure is likely to remain within the private sector, because it is directed to treating physiology and contact lenses and glasses can address this problem. Two Advisers stated that the procedure is likely to have a slow to moderate speed uptake in refractive surgery practices in private sector mainly due to safety issues and lack of long-term evidence. One Adviser stated that the speed of diffusion is likely to be slow because good conventional monovision strategies are currently available.
- All Advisers stated that a minority of hospitals but at least 10 in the UK are likely to undertake this procedure and it could have only a minor impact on the NHS.
- Three Advisers stated that it is unlikely that this procedure would be undertaken as an NHS procedure and it would only be done in private clinics and hospitals on a fee-paying basis.

Patient Commentators' opinions

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

Issues for consideration by IPAC

Ongoing trials

- NCT00850031: Prospective multicentre clinical trial to evaluate safety and effectiveness of the AcuFocus KAMRA inlay ACI-7000PDT in presbyopia patients. Study type: single arm non-randomised study, estimated enrolment: 400 patients, estimated primary completion date: February 2012, study completion date: February 2012, Locations: Australia, Austria, Germany, New Zealand, Singapore, UK.
- NCT01352442: Prospective multicentre trial to evaluate safety and effectiveness of the AcuFocus KAMRA inlay ACI-7000PDT implanted

intrastromally for modified monovision in presbyopic subjects. Study type: single arm non-randomised study, estimated enrolment: 150 patients, estimated primary completion date: August 2012, study completion date: September 2012, Location: Austria.

- NCT01373580: Prospective multicentre trial to evaluate safety and effectiveness of the Revision Optics Inc PresbyLens corneal inlay for the improvement of near vision in presbyopic patients with MRSE from −0.50 to +1.00. Study type: prospective observational study, Estimated enrolment: 400 patients, Study start date: April 2010, Location: USA.

Current publications

- Presentation to be given at European Society of Cataract and Refractive Surgeons (ESCRS) meeting in September 2012 reporting results of a prospective case series with Vue+ in Ultralase Eye clinics in the UK with 45 patients and a 6-month follow-up (Gupta V et al.).
- Poster at European Society of Cataract and Refractive Surgeons (ESCRS) meeting in September 2012 summarising initial results of a prospective case series with IcoLens in Dublin with 36 patients treated to date, and a total of 45 planned (Bailey C et al.).

Other issues

- None of the devices included have yet been given FDA approval.
- Technology for both devices and implantation technique is evolving.
- There have been several changes of device names and manufacturing companies during the development of this technology.

References

1. Waring GO. (2011) Correction of presbyopia with a small aperture corneal inlay. Journal of Refractive Surgery 27 (11): 842–845

2. Dexl AK, Seyeddain O, Riha W et al. (2012) One-year visual outcomes and patient satisfaction after surgical correction of presbyopia with an intracorneal inlay of a new design. Journal of Cataract & Refractive Surgery 38 (2): 262–269

3. Dexl AK, Seyeddain O, Riha W et al. (2012) Reading Performance and patient satisfaction after corneal inlay implantation for presbyopia correction: Two-year follow-up. Journal of Cataract & Refractive Surgery 38: 1808–1816

4. Bouzoukis DI, Kymionis GD, Panagopoulou SI et al. (2012) Visual outcomes and safety of a small diameter intrastromal refractive inlay for the corneal compensation of presbyopia. Journal of Refractive Surgery 28 (3): 168–173

5. Seyeddain O, Hohensinn M, Riha W et al. (2012) Small-aperture corneal inlay for the correction of presbyopia: 3-year follow-up. Journal of Cataract & Refractive Surgery 38 (1): 35–45

6. Dexl AK, Seyeddain O, Riha W et al. (2011) Reading performance after implantation of a small-aperture corneal inlay for the surgical correction of presbyopia: Two-year follow-up. Journal of Cataract & Refractive Surgery 37 (3): 525–531

7. Dexl AK, Ruckhofer J, Riha W et al. (2011) Central and peripheral corneal iron deposits after implantation of a small-aperture corneal inlay for correction of presbyopia. Journal of Refractive Surgery 27 (12): 876–880

8. Yilmaz OF, Alagoz N, Pekel G et al. (2011) Intracorneal inlay to correct presbyopia: long-term results. Journal of Cataract & Refractive Surgery 37 (7): 1275–1281

9. Yilmaz OF, Bayraktar S, Agca A et al. (2008) Intracorneal inlay for the surgical correction of presbyopia. Journal of Cataract & Refractive Surgery 34 (11): 1921–1927

10. Seyeddain O, Riha W, Hohensinn M et al. (2010) Refractive surgical correction of presbyopia with the AcuFocus small aperture corneal inlay: 2-year follow-up. Journal of Refractive Surgery 26 (10): 707–715

11. Sharma GD, Porter T, Holliday K et al. (2010) Sustainability and biocompatability of the PresbyLens corneal inlay for the corrrection of presbyopia. ARVO 2010 for sight: the future of eye and vision research.

Appendix A: Additional papers on corneal inlay implantation for correction of presbyopia

The following table outlines the studies that are considered potentially relevant to the 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
Casas-Llera P, Ruiz-Moreno JM.; Alio JL. Retinal imaging after corneal inlay implantation. Journal of Cataract and Refractive Surgery 2011; 37(9):1729-31,	= 2 emmetropic presbyopes FU= 10 days	KAMRA inlay. Imaging was carried out largely without problems.	Similar data are already reported in Table 2 for a group of 10 patients.
Dexl AK, Ruckhofer J, Riha W. Central and peripheral corneal iron deposits after implantation of a small-aperture corneal inlay for correction of presbyopia. Journal of Refractive Surgery 2011; 27(12): 876-880	n=32 emmetropic presbyopes FU=3 years	ACI7000 inlay. 18 eyes developed corneal iron deposits. Median interval between implantation and diagnosis was 18±9 months. Report no noticeable influence on any visual acuity measure.	3-year follow-up of same case series in table 2.
Dexl AK, Seyeddain O, Grabner G. (2011) Follow-up to "central and peripheral corneal iron deposits after implantation of a small-aperture corneal inlay for correction of presbyopia". Journal of Refractive Surgery 27 (12): 856-857	n=32 emmetropic presbyopes	ACI7000 inlay 18 eyes developed corneal iron deposits. Median interval between implantation and diagnosis was 18±9 months. Report no noticeable influence on any visual acuity measure	3-year follow-up of same case series in table 2.
Dexl AK, Seyeddain O, Grabner G. Follow-up to "Central and peripheral corneal iron deposits after implantation of a small-aperture corneal inlay for correction of presbyopia". Journal of Refractive Surgery 2011: 27(12): 856-857	n=32 emmetropic presbyopes FU=18 months	Compares data from ACI7000 and ACI7000PDT trial. 1/24 of ACI7000PDT patients showed corneal iron deposit at 18 months. 10/32 of ACI7000 patients showed corneal iron deposit at 18 months.	Letter only. Related case series reported in table 2.

Dexl AK, Seyeddain O, Riha W et al. (2012) Reading Performance After Implantation of a Modified Corneal Inlay Design for the Surgical Correction of Presbyopia: 1-Year Follow-up. American Journal of Ophthalmology 153 (5): 994-1001	n=24 FU=12 months	ACI 7000PDT KAMRA corneal inlay. Reported changes in reading performance parameters in emmetropic presbyopic patients.	2-year follow-up of same case series in table 2.
Keates R, Martines E. Small diameter corneal inlay in presbyopic or pseudophakic patients. Journal of Cataract and Refractive Surgery 1995; 21(5): 519-21	n=5 FU=7 to 12 months	UNVA improved from J4 or worse to J2 or better in 4 out of 5. 2 patients had inlay explanted and exchanged for increased dioptric power. No corneal haze, inlay opacification or complications.	Small case series, unknown device used.
Seyeddain O, Riha W, Hohensinn M. Refractive surgical correction of presbyopia with the AcuFocus small aperture corneal inlay: two-year follow-up. Journal of Refractive Surgery 2010;26 (10): 707-715	n=32 emmetropic presbyopes FU=2 years	ACI7000 inlay. Improvement in mean binocular UNVA from J6 to J1. Mean binocular UDVA 20/16 at 24 months. No inlays explanted, 2 recentred.	3 year follow-up of same case series in table 2.
Tomita M, Kanamori T, Waring GO. Simultaneous corneal inlay implantation and laser in situ keratomileusis for presbyopia in patients with hyperopia, myopia, or emmetropia: six-month results. Journal of Cataract & Refractive Surgery 38 (3): 495-506	n=180 patients. FU=6 months	KAMRA Inlay Improvement in UNVA and UDVA. Decrease in dependence on reading glasses. Some occurrence of symptoms such as halo, glare, dry eye or night vision.	Bilateral LASIK with corneal inlay in non-dominant eye.
Yilmaz OF, Bayraktar S, Agca A. Intracorneal inlay for the surgical correction of presbyopia. Journal of Cataract & Refractive Surgery 2008; 34 (11): 1921-1927	n=39, at 1 year n=34 FU=1 year	ACI 7000 inlay. Mean UNVA improved from 20/50 to 20/16. Mean binocular UDVA 20/16 at 1 year. 3 inlays explanted	4 year follow-up of same case series in table 2.

Appendix B: Related NICE guidance for corneal inlay implantation for correction of presbyopia

Guidance	Recommendations
Interventional procedures	**Intraocular lens insertion for correction of refractive error, with preservation of the natural lens. NICE interventional procedure guidance 289 (2009)** 1.1 Current evidence on intraocular lens (IOL) insertion for correction of refractive error, with preservation of the natural lens is available for large numbers of patients. There is good evidence of short-term safety and efficacy. However, there is an increased risk of cataract, corneal damage or retinal detachment and there are no long-term data about this. Therefore, the procedure may be used with normal arrangements for clinical governance and audit, but with special arrangements for consent. 1.2 Clinicians wishing to undertake IOL insertion for correction of refractive error, with preservation of the natural lens should ensure that patients understand the risks of having an artificial lens implanted for visual impairment that might otherwise be corrected using spectacles or contact lenses. They should understand the possibility of cataract, corneal damage or retinal detachment, and the lack of evidence relating to long-term outcomes. Patients should be provided with clear information. In addition, the use of NICE's information for patients is recommended (available from www.nice.org.uk/IPG289publicinfo). 1.3 Both clinicians and manufacturers are encouraged to collect long-term data on people who undergo IOL insertion, and to publish their findings. NICE may review the procedure on publication of further evidence. **Corneal implants for the 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. **Photorefractive (laser) surgery for the correction of refractive error. NICE interventional procedure guidance 164 (2006)** 1.1 Current evidence suggests that photorefractive (laser)

	surgery for the correction of refractive errors is safe and efficacious for use in appropriately selected patients. 1.2 Clinicians undertaking photorefractive (laser) surgery for the correction of refractive errors should ensure that patients understand the benefits and potential risks of the procedure. Risks include failure to achieve the expected improvement in unaided vision, development of new visual disturbances, corneal infection and flap complications. These risks should be weighed against those of wearing spectacles or contact lenses. 1.3 Clinicians should audit and review clinical outcomes of all patients who have photorefractive (laser) surgery for the correction of refractive errors. Further research will be useful and clinicians are encouraged to collect longer-term follow-up data. 1.4 Clinicians should have adequate training before performing these procedures. The Royal College of Ophthalmologists has produced standards for laser refractive surgery (www.rcophth.ac.uk/docs/publications/RefractiveSurgeryStandardsDec2004.pdf). **Scleral expansion surgery for presbyopia. NICE interventional procedure guidance 70 (2004)** 1.1 Current evidence on the safety and efficacy of scleral expansion surgery for presbyopia is very limited. There is no evidence of efficacy in the majority of patients. There are also concerns about the potential risks of the procedure. 1.2 It is recommended that this procedure should not be used. The Institute's *Information for the public* complements this guidance in explaining the concerns about the procedure.

Appendix C: Literature search for corneal inlay implantation for correction of presbyopia

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	12/12/2012	Issue 11 of 12, November 2012	0
Database of Abstracts of Reviews of Effects – DARE (CRD website)	12/12/2012	Issue 4 of 4, October 2012	0
HTA database (CRD website)	12/12/2012	Issue 4 of 4, October 2012	0
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	12/12/2012	Issue 11 of 12, November 2012	27
MEDLINE (Ovid)	12/12/2012	1946 to November Week 3 2012	4
MEDLINE In-Process (Ovid)	12/12/2012	December 06, 2012	7
EMBASE (Ovid)	12/12/2012	1974 to 2012 Week 49	19
CINAHL (NLH Search 2.0 or EBSCOhost)	12/12/2012	1981 to present	34
JournalTOCS	12/12/2012	n/a	1

Trial sources searched on

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- Evidence Updates (NHS Evidence)
- 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	presbyop*.tw.
2	Presbyopia/

3	(((short adj1 arm) or "short arm" or shortarm) adj2 syndrom*).tw.
4	((old or age* or aging or deteriorat* or degenerat*) adj3 (eye* or lens)).tw.
5	(Emmetrop* or myopes or hyperopes).tw.
6	or/1-5
7	((intracorneal or corneal) adj3 (inlay* or implant* or flap* or tunnel* or pocket* or ring*)).tw.
8	(karma or flexivue or presbylens or acufocus or presbia or invue or incolens).tw.
9	ACI 7000.tw.
10	(intrastromal adj3 inlay*).tw.
11	pinhole.tw.
12	or/7-11
13	Corneal Stroma/ or cornea/
14	"Prostheses and Implants"/ or prosthesis implantation/
15	13 and 14
16	12 or 15
17	6 and 16
18	Animals/ not Humans/
19	17 not 18