SAFETY OF THE ARTISAN IRIS-FIXATED PHAKIC INTRAOCULAR LENS

Gwyneth van Rijn

Safety of the Artisan iris-fixated phakic intraocular lens
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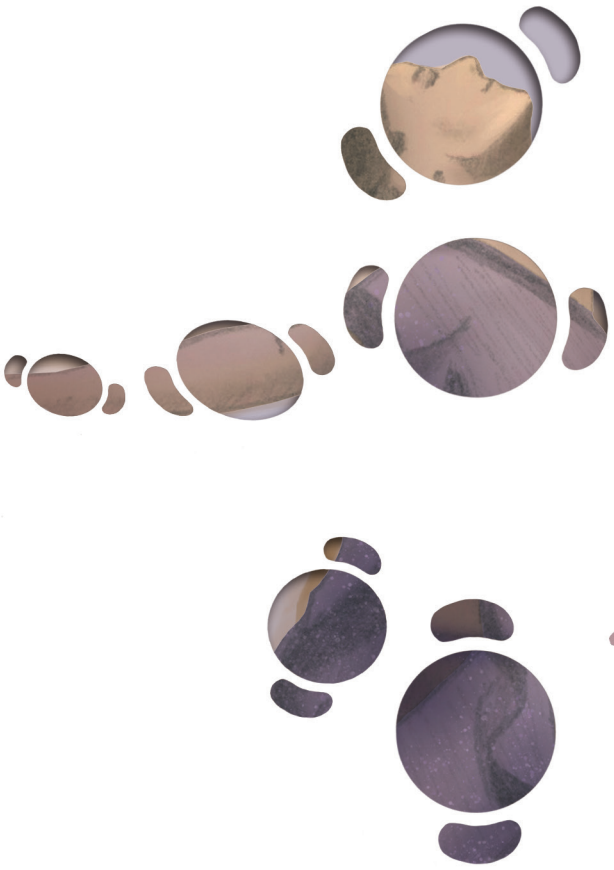
“Om innerlijke rust te vinden,
moet je afmaken waaraan je begonnen bent”

Boeddha

CONTENTS



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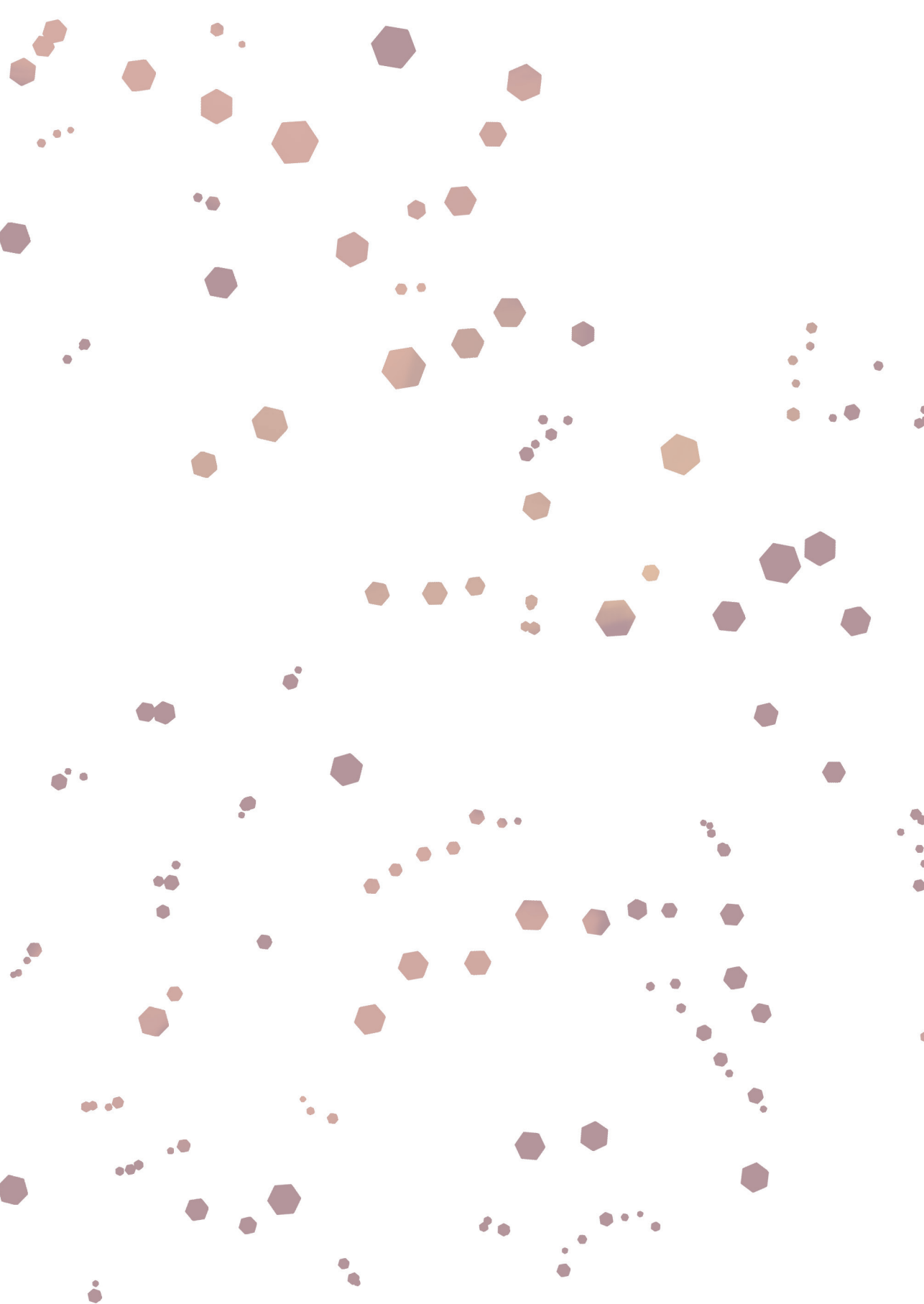

Chapter 1

General Introduction

1.1 REFRACTIVE ERROR

Refractive error is the leading cause of reversal visual loss, and its complications are considered to be one of the most significant causes of blindness and visual impairment in young and professionally active people, which points out the social and economic importance of this disease.[1-3]

Refraction is defined as the deflection of light rays (or energy waves) when passing from one medium to another medium with a different velocity or refractive index. The refractive power of the eye is measured in diopters (D). The refractive power of a lens is the reciprocal of its focal length in meters.

Light is refracted by the tear film, cornea, aqueous humor, crystalline lens and vitreous body and converges onto the retina where an image will be formed. The refractive system of the eye can essentially be divided into two groups: the corneal- and the lens system. The corneal system accounts for approximately 2/3 of the refractive power, and the lens system accounts for 1/3 of the refractive power, when the eye is in an un-accommodative state.

In emmetropia, the refractive power of the refractive system of the eye perfectly matches the axial length of the eye. Parallel light rays are focused precisely on the retina, and a clear and sharp image can be perceived. When incident light is not properly focused on the retina an unclear image is perceived, a condition referred to as ametropia. Ametropia, also known as refractive error, can be classified as myopia or nearsightedness, hyperopia or farsightedness, astigmatism or mixed. Myopia is defined as a state of refraction which results in parallel incident light rays being focused onto a theoretical point in front of the retina. This occurs when the length of the eye is too long in proportion to the power of its refractive system, or the refractive system is too strong for the axial length. Hyperopia is defined as a state of refraction in which incident light rays are focused onto a theoretical point behind the retina. This occurs when the eye is too short in relation to the power of its refractive system, or when the refractive system is not powerful enough for its axial length. Astigmatic refractive error arises when the refractive system of the eye has a different refractive power in various meridians, due to difference in curvature, resulting in a distorted or displaced image on the retina rather than one focal point. Myopia and hyperopia may occur together with astigmatism.

Refractive surgery is a subfield in ophthalmology that focusses on the surgical correction of ametropia. A multitude of refractive surgical methods are available to refractive surgeons. Corneal laser refractive surgery is the most frequently used method to correct

refractive errors. It has been shown to be a safe and effective method, especially with advancing techniques.[4] Intraocular refractive procedures to correct refractive errors are usually reserved for patients with contraindications to traditional corneal laser refractive surgery, or with refractive errors that are unsuitable for traditional laser refractive surgery, such as extremely high myopia or hyperopia. In general, there are two types of intraocular refractive procedures: refractive lens exchange (also known as clear lens extraction) and phakic intraocular lens implantation. Phakic intraocular lenses (pIOLs) are implanted into the human eye without taking out the natural crystalline ocular lens. PIOLs can be classified according to their site of implantation, which is either the anterior chamber or the posterior chamber. There are two types of anterior chamber pIOLs: the angle-supported and iris-supported pIOLs. Posterior pIOLs are implanted between the iris and the crystalline lens.

Individualized refractive correction, i.e. choosing the best available method for a particular patient, is one of the greatest challenges in refractive surgery. Choosing the appropriate treatment option should be based on the individual's risk-benefit profile. For this, it is necessary for refractive surgeons to know the short- and long-term results of all current refractive correction methods and to be aware of the pitfalls and drawbacks of the anterior segment imaging techniques used for patient selection and follow-up.

1.2 A BRIEF HISTORY

The first iris-fixated IOLs were aphakic pupillary fixated lenses following cataract surgery, such as the Medallion lens or platinum clip lens designed by J.G. Worst in the late 1970s. They were widely used by ophthalmic implant surgeons.[5,6] Dr. Worst serendipitously discovered the iris claw principle in 1978. He observed that, with the Medallion lens, part of the iris was sometimes caught in the slot of this lens, which subsequently led to the discovery of iris fixation as a new treatment option. He developed an anterior chamber lens with 2 claws that could be fixated on the iris without the use of sutures. This lens was referred to as the Iris Claw or Lobster Claw lens.

The first phakic IOLs were angle-fixated anterior chamber lenses. In 1953, Benedetto Strampelli implanted the first pIOL in the anterior chamber to correct myopia.[7,8] Unfortunately, the use of this lens was associated with severe complications, the volume and diameter of the lens were large, and the material was heavy with a poor finish of the IOL. In addition, surgical techniques were primitive, with surgery being performed without a microscope, and no precautions were taken to avoid trauma to the delicate structures of the eye, such as the endothelium and crystalline lens.

Subsequent attempts in the 1960s with pIOLs designed by Joaquin Barraquer[9] and Peter Choyce[10], with improved dimensions better suited for the anatomical dimensions of the anterior chamber of the eye, still led to severe complications requiring pIOL explantation. Hereafter, the idea of using a pIOL was largely abandoned.

In time, with technological development, pIOLs were redesigned and relaunched, and by the 1980s the negative perception of pIOLs started to disappear. Baikoff relaunched angle-supported pIOLs, Fyodorov introduced the concept of the posterior chamber IOL, and Fechner and Worst the iris-fixated pIOL (IF-pIOL).

On the second of November 1986, Dr. Fechner implanted the first-generation bi-concave iris-fixated pIOL to optically correct a myopic error of -20D. The published results were promising.[11] In 1986, the first Worst Iris Claw lenses were also implanted for the correction of hyperopia.[12] After the early studies on the original biconcave shaped Iris Claw pIOL [11,13-15], the design of the pIOL was changed in 1997 to a concave-convex shape to improve the safety profile of the IF-pIOL. The name of the IF-pIOL was changed from Worst Iris Claw or Lobster Claw Lens to Artisan to recognize the special skills of the ophthalmic surgeon Jan Worst and to honor one of the world's first ophthalmological Artisans. This new version of the Artisan pIOL was made to create greater distance to

the iris and corneal endothelium and to allow aqueous humor to circulate freely. Since then, several reports have been published on the results following implantation of the Artisan IF-pIOL for the correction of ametropia.[16-22]

In 2001, a toric version of the Artisan IF-pIOL became available to correct astigmatism in combination with myopia or hyperopia. In 2004, the American Food and Drug Administration approved the identical Verisyse (Abbott Medical Optics, Abbott Park, IL).[23-25]

In 2003, a foldable alternative, called the Artiflex (Ophtec BV Groningen, the Netherlands) and identical Veriflex (Abbott Medical Optics, Abbott Park, IL), was marketed to facilitate the need for smaller incision upon implantation.

An opaque polycarbonate IF-(p)IOL now exists for the correction of intractable diplopia in the case of pupil occlusion. It can be implanted in phakic and aphakic eyes.[26]

A bifocal IF-pIOL was developed in 2019 and is still under clinical investigation.

1.3 THE NON-FOLDABLE IRIS-FIXATED PHAKIC INTRAOCULAR LENS

1.3.1 Lens Design

The IF-pIOL is a concave-convex shaped pIOL and is designed to be supported by the mid-iris tissue by attaching this tissue to the claws of the lens, a procedure called enclavation. The rigid, non-foldable form of the IF-pIOL (Artisan and Verisyse) is manufactured from a single piece of Perspex CQ-UV in combination with poly(methyl-methacrylate). The foldable version (Artiflex and Veriflex) is made of hydrophobic polysiloxane with rigid haptics of Perspex CQ UV poly(methyl methacrylate). It has a 5 mm or 6 mm diameter optic, it has a total length of 8.5 mm and an absolute height of 0.76 to 1.43 mm (depending on the type of pIOL and dioptric power), with an available diopter range of +12.0 to -23.5 to correct a wide spectrum of ametropia. Toric versions are available as well. The designs of IF-pIOLs are shown in Figure 1.

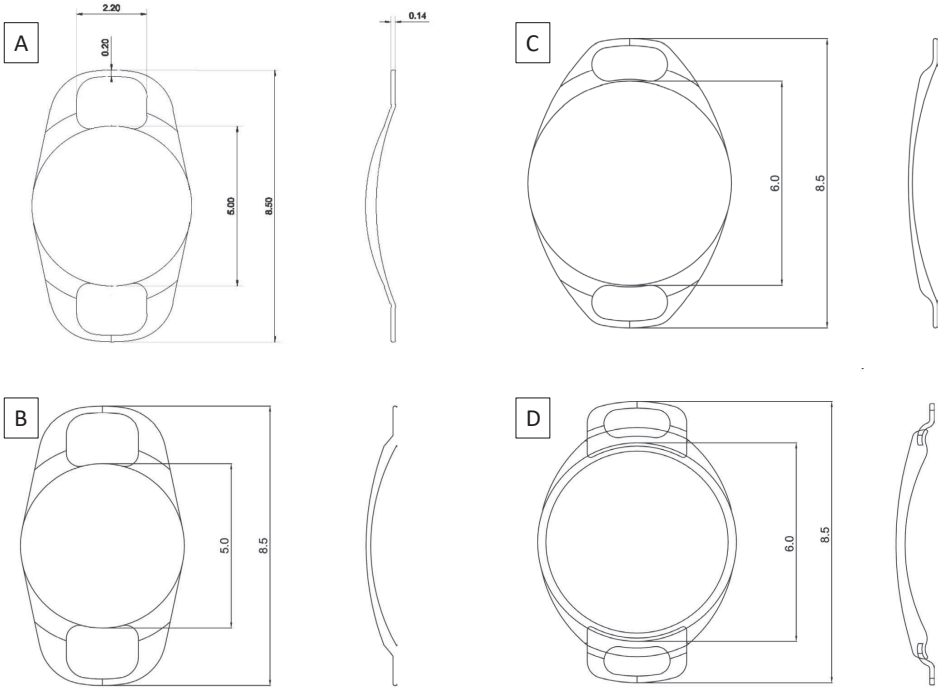

Figure 1. Details of the iris-fixated phakic intraocular lens. A; Artisan hyperopia ref. 203. B; Artisan myopia ref 206. C; Artisan myopia ref 204. D; Artiflex myopia ref 401.

(Courtesy of Ophtec BV)

1.3.2 Lens Power Calculation

IF-pIOL power calculations are performed using the Van der Heijde formula (Equation 1).[27] This formula takes into account the (cycloplegic) spectacle refraction, corneal power and anterior chamber depth (ACD).

$$IOLpower = \frac{n}{\frac{n}{\frac{K1 + K2}{2} + \frac{SE}{1 - (t^{*}\, SE)}} - d} - \frac{n}{\frac{n}{\frac{K1 + K2}{2} + \frac{DPR}{1 - (t^{*}\, DRP)}} - d}$$

Equation 1. The Van der Heijde formula is used for IF-pIOL power calculations

n= refractive index of aqueous (1.336)
*K*1 + *K*2 = corneal power
SE = spherical equivalent of the preoperative refraction (Sphere + (0.5*Cylinder)
t: effective lens position (anterior chamber depth -0.6)
DRP: desired postoperative refraction
d: spectacle vertex (normally 12 mm)

1.3.3 The Implantation Technique of the Non-Foldable Iris-Fixated PIOL

Implantation of an IF-pIOL can be performed under local or general anesthesia, as is preferred by the surgeon and patient.

Pharmacological installation of a miotic solution is necessary to avoid contact with the crystalline lens and to facilitate proper centration of the pIOL. Three incisions are made, preferably at the superior location: A main incision is made at 12 o'clock and 2 side incisions are made at 10 and 2 o'clock. These incisions should extend toward the enclavation zones. At this location, the IF-pIOL can easily be symmetrically positioned over the pupil and enclavated. The eyelid will cover any used sutures. The width of the main incision depends on the type and diameter of the implanted IF-pIOL. For the IF-pIOL with an optic of 5.0 mm, an incision of 5.5 mm is required. The IF-pIOL with a 6.0 mm optic requires an incision of 6.5 mm. One should keep in mind that a high-powered myopic IF-pIOL is slightly thicker, and one might therefore require a slightly larger incision. The type of incision depends on the surgeon: a clear corneal incision at the limbus, a sclerocorneal incision or the creation of a scleral tunnel, with each type of incision having its own advantages and disadvantages. This thesis describes surgeries carried out with a sclerocorneal incision. The main incision may be made in a two-step process, completing the full incision after injecting a viscoelastic substance into the anterior chamber. The viscoelastic substance is injected to create a bed between the

pIOL, the iris and the anterior pole of the crystalline lens, as well as a barrier between the pIOL and the corneal endothelium. It is recommendable to cover the posterior area close to the incision with a viscoelastic substance to ensure easy introduction of the IF-pIOL in the anterior chamber and to avoid contact between the IF-pIOL and the conjunctival flora. The pIOL is introduced in the anterior chamber in a vertical position, using implantation forceps. Additional viscoelastic substance is added, making sure not to overfill the anterior chamber but making just enough space to facilitate intraocular maneuvers in order to correctly position the IF-pIOL and to stabilize the pIOL while enclavating the haptics to the iris. The pIOL may be rotated to the desired position and placed over the center of the pupil by using a lens manipulator. Enclavation of the iris tissue between the haptics is performed by holding the center of the pIOL optic with the forceps, since this is the furthest point from the anterior capsule of the crystalline lens and allows the surgeon to achieve the greatest stability and stillness of the IF-pIOL. The iris tissue can be enclavated with the use of enclavation needles, forceps or a vacuum-based enclavation system. To prevent pupil block, an iridectomy should be performed at the end of the implantation procedure or an iridotomy should be performed prior to operation with a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser. The main incision is closed with sutures, preferably 10-0 nylon, taking care not to introduce high astigmatism. Finally, all of the intraocular viscoelastic substance is removed and intracameral antibiotics are injected. A topical regimen of slowly tapered steroidal drops should be administered postoperatively, optionally in combination with non-steroidal topical therapy.

1.4 PATIENT SELECTION

Fundamental characteristics of the patient's eye, a detailed patient and family history, the history of the refraction and optical methods of correction, and the reason for seeking help from a refractive ophthalmic surgeon should be carefully assessed. Patients who wish to be completely free of spectacles and contact lenses may not be fully satisfied following refractive surgery if some residual refraction persists. Clarification of the methods, risks and expected results of each available method should be explained by the refractive surgeon. An adequate informed consent form must be given to the patient for signing.

Choosing the appropriate refractive correction option should be based on the individual's risk-benefit profile, the patient's age and expectations. In general, pIOLs may be the best choice for severe ametropic eyes in patients who still have accommodative abilities but cannot or do not want to use spectacles or contact lenses. When considering an IF-pIOL, minimum safety requirements have been proposed with the essential conditions as recommended nowadays by the IF-pIOL manufacturer listed in Table 1. It is recommended to solely implant (IF-)pIOLs in adult eyes with no other abnormalities other than refractive error, although studies are ongoing in eyes with comorbidity, such as keratoconus, and in younger patients.

Table 1. Minimum safety criteria for implantation of an IF-pIOL*

Minimum preoperative anterior chamber depth	3.0 mm from corneal endothelium (critical distance of >1.0 mm)	
Minimum preoperative endothelial cell count	<25 years of age	2800 cells/mm^2
	26-30 years of age	2650 cells/mm^2
	31-35 years of age	2400 cells/mm^2
	36-41 years of age	2200 cells/mm^2
	>45 years of age	2000 cells/mm^2
Pupil size in scotopic conditions	≤ body size of pIOL +1.00 mm	
Iris configuration	Not convex	

* As recommended by Ophtec BV (manufacturer of the IF-pIOL). IF-pIOL= iris-fixated phakic intraocular lens; mm=millimeters

1.5 AIMS AND OUTLINE OF THIS THESIS

This thesis will focus on the safety of ametropic eyes optically corrected with the non-foldable iris-fixated pIOL.

The first part of this thesis covers clinical results after implantation of the non-foldable iris-fixated phakic intraocular lens (IF-pIOL). Chapter 2 gives a pooled analysis and review of medium- and long-term data on modern IF-pIOLs from peer-reviewed papers. Chapters 3 and 4 discuss the results of a cohort of hyperopic and a cohort of myopic eyes after refractive correction with the Artisan IF-pIOL with a follow-up of up to 16 and 22 years. Chapter 5 describes a case series on patients with oculocutaneous albinism with successful implantation of an Artisan IF-pIOL and a follow-up of 8 to 14 years.

The second part of this thesis covers some aspects of safety considerations with respect to patient selection criteria and follow-up. The safety and compatibility of the historical platinum clip lens (which in rare cases may still be in situ in a living patient's eye), the modern rigid and foldable iris-fixated (p)IOLs, the occludable iris-fixated IOL, as well as other IOLs were tested using very high field magnetic resonance imaging (MRI). The results of these tests are presented in chapter 6.

Since endothelial cell (EC) loss is a major safety concern in any type of intraocular surgery, but especially in anterior segment surgery combined with an implant in the anterior chamber, quantitative EC analysis is a key safety feature in patient selection and follow-up. During long follow-up, instruments used inevitably wear out necessitating repair, update and replacement. Chapter 7 describes a method to enhance the reliability of endothelial cell counts by improving interchangeability when different corneal specular microscopes are used.

In chapter 8, two widely used anterior segment imaging modalities, the Pentacam and anterior segment optical coherence tomography (AS-OCT), are compared with respect to safety parameters when considering an IF-pIOL and follow-up of patients with an IF-pIOL. The difference in outcomes of these 2 anterior segment imaging modalities has to be considered in patient selection and follow-up.

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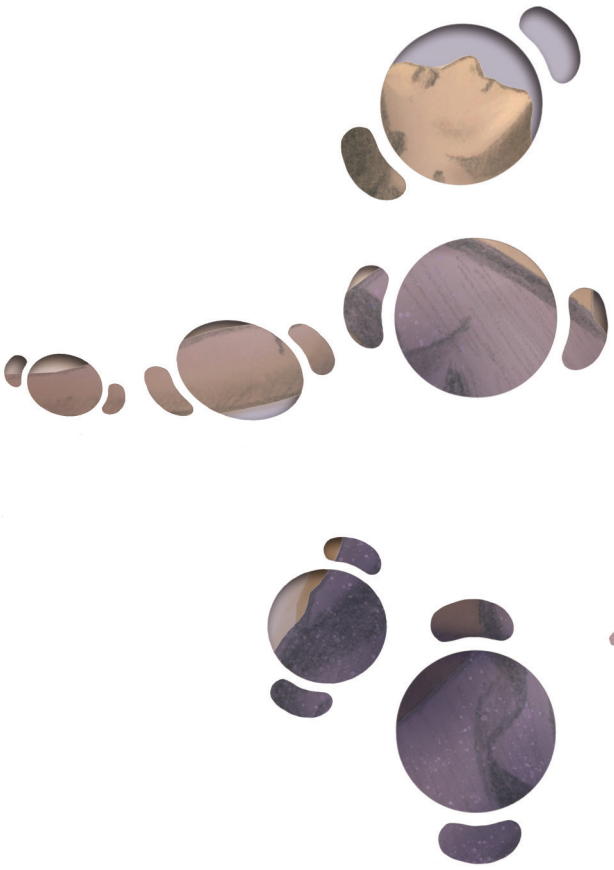

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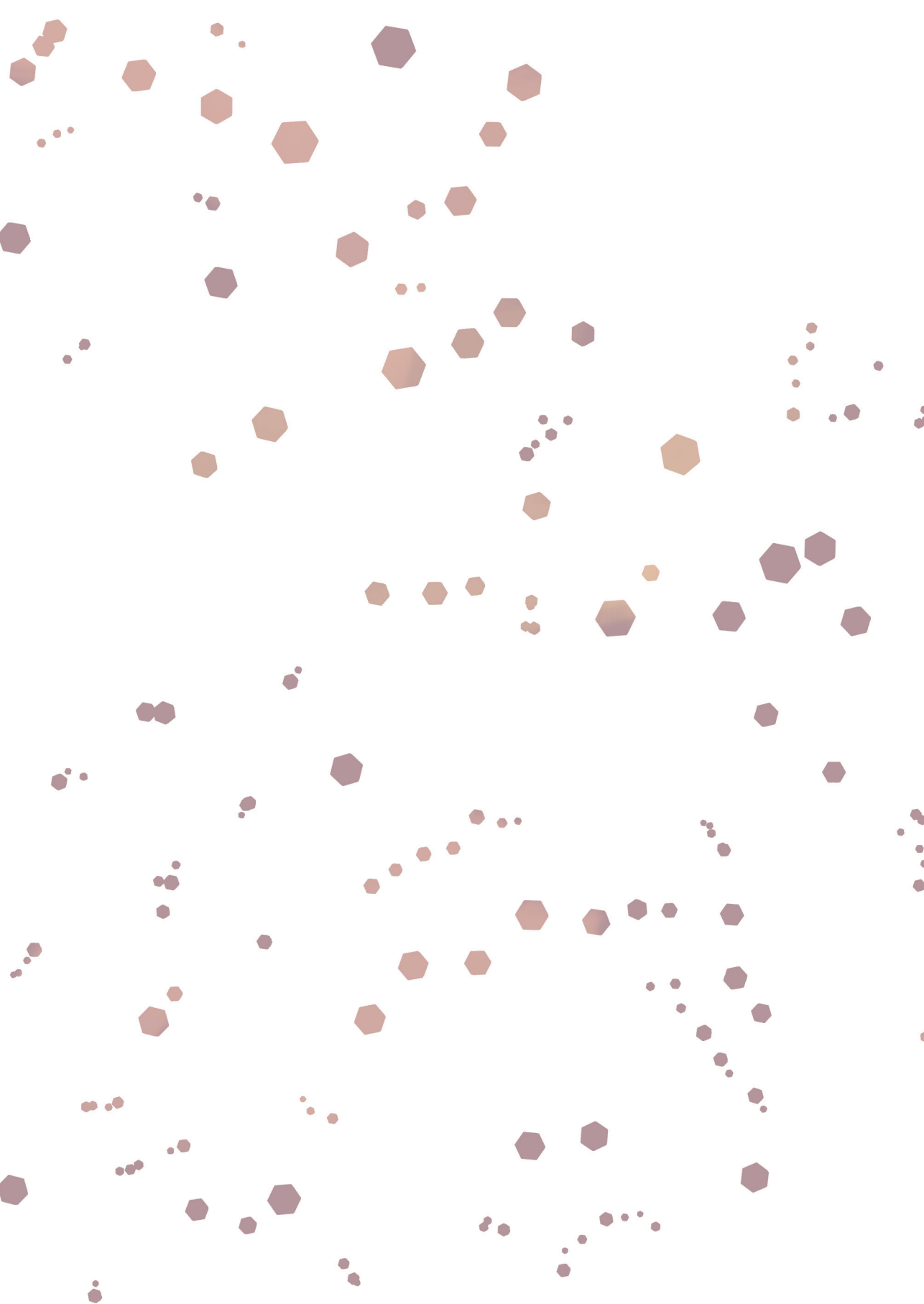

Chapter 2

Middle- and Long-Term Results after Iris-Fixated Phakic Intraocular Lens Implantation in Myopic and Hyperopic Patients: a Meta-Analysis

Gwyneth A. van Rijn, Zoraida S. Gaurisankar, Antonio P. Ilgenfritz, José Eduardo E. Lima, Geert W. Haasnoot, Jan-Willem M. Beenakker, Yanny Y. Y. Cheng, Gregorius P. M. Luyten

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ABSTRACT

The iris-fixated phakic intraocular lens (pIOL) has been available for over 25 years. To provide a clear picture of outcomes and risks, for this systematic review and meta-analysis, the literature was searched for reports on middle- and long-term effects of iris-fixated pIOLs on myopic and hyperopic eyes with a follow-up of at least 2 to 4 years.

Visual and refractive results after implantation for correction of myopia are positive and the complication rate is low. Endothelial cell loss appears to be at an acceptable rate, although the range of endothelial cell change is too wide to draw firm conclusions. Care should be taken when considering an iris-fixated pIOL for hyperopic eyes because complication rates, particularly pigment dispersion, might be higher than those in myopic eyes. More well-designed, long-term studies are needed, especially in hyperopic eyes. The authors advocate for standardized reporting of refractive surgery data. Initiatives proposed by journal authors and editors to achieve uniformity should be supported.

INTRODUCTION

When it comes to the correction of high myopia and hyperopia, the advent of phakic intraocular lens (pIOL) implantation and its improvements in methods and materials were a breakthrough. Inspired by Harold Ridley, Kees Binkhorst, Svyatoslav Fyodorov, and Klaas Otter, among other pioneers in the field of IOLs, Jan Worst introduced an IOL that attached to the iris. In 1978, he implanted the first iris-claw lens for aphakia after cataract surgery. In 1984, an opaque iris-claw lens was implanted in a phakic eye for pupil occlusion to relieve complaints of intractable diplopia. During an ophthalmology meeting in 1986, Worst developed the idea of a "contact lens in the eye." [A] On November 2, 1986, Worst and Fechner implanted the first-generation biconcave iris-fixated pIOL (ref. 209) in a myopic eye of -20 diopter (D).[A] The name of the iris-fixated pIOL was changed from Worst iris-claw or lobster-claw lens to Artisan lens. This name was chosen to honor the special skills of Dr. Worst.[1] Despite the positive visual and refractive results, unacceptable complications occurred and the biconcave Artisan was discontinued.[1,2] In 1991, a convex-concave-shaped design (ref. 206) to create more distance from the edge of the iris-fixated pIOL to the corneal endothelium was introduced and has been implanted successfully since. The first iris-fixated pIOL for the correction of hyperopia (ref. 203) was released in 1993 and first implanted by Krumeich in April 1993, and Worst in early 1994. In 1997, an iris-fixated pIOL for myopia was developed, with a larger optic diameter (ref. 204) to reduce optic phenomena such as glare and halos.

The modified convex-concave-shaped Artisan iris-fixated pIOL (Ophtec) has been in use since 1998. In 2004, the U.S. Food and Drug Administration approved the use of the Artisan and the identical Verisyse (Abbott Medical Optics, Inc.), and the Artisan/Verisyse iris-fixated IOL has found global acceptance. The iris-fixated pIOL is available in refractive powers ranging from -3.0 to -23.5 D in 1.0 D increments before 1997, and after 1997 in 0.5 D increments. The Artisan Small (ref. 202), which was made available in the year 2000 for eyes with proportionally reduced dimensions of the anterior chamber, is no longer available.

Since the iris-fixated pIOL has been marketed for more than 25 years, an assessment of the long-term effects after implantation of this pIOL for refractive errors seems called for. In this systematic review and meta-analysis, we searched the literature for articles on the middle- and long-term effects (from 2 to 10 years) of the iris-fixated pIOL, to provide a clear picture of the results and risks of implantation.

METHODS

We applied the tenets of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. The databases PubMed, EMBASE, Web of Science, and Cochrane Library were searched; no time limit was used for the search. Figure 1 shows the eligibility and exclusion criteria. The 4 databases were last searched on the following dates:

1. PubMed on August 3, 2018, yielding 539 references;
2. Web of Science (Thomson Reuters) on August 28, 2018, yielding 476 references;
3. EMBASE on August 28, 2018, yielding 586 references;
4. Cochrane Library on August 28, 2018, yielding 42 references.

Although foldable iris-fixated pIOLs (i.e., Artiflex/Veriflex) were an exclusion criterion, the terms "Artiflex" and "Veriflex" were included in the search to avoid missing any relevant articles. Search strings can be found in Appendix 1. The search strategy was developed by an information specialist in consultation with the researchers. No restrictions were placed on the levels of evidence required for inclusion in the search because it was expected that most studies would be of observational nature.

All 1643 references were then uploaded in a citation manager (EndNote X7) for organization purposes. After checking for and removing duplicates, a total of 750 unique references remained. The title and abstract of every unique publication were analyzed. Two researchers (G.R., A.I.) independently screened and selected the articles retrieved by the search, the results were compared, and disagreements were resolved by discussion; if necessary, a third party was invited to the discussion. References that met any of the established exclusion criteria were excluded. The assessment of the full texts and bibliographies of 137 articles resulted in 32 studies being included in this review and meta-analysis.[3–35] Relevant articles in which complications were reported as case series but no incidence could be calculated are not listed in the Results section but are still included in the Discussion section.[35–37]

The bibliography of each eligible reference was searched manually for additional articles that may not have been identified previously by our systematic search. No further articles were found at this stage. However, 1 additional reference that was not included in the databases was found through a simple web search.[30] See Figure 2 for the selection process. All relevant information was extracted from each reference and recorded in the spreadsheet software (Microsoft Excel 2010; Microsoft Corp.). Statistics for pooled estimates were performed in IBM SPSS Statistics for Windows software

(version 23, IBM Corp.). Studies in which eyes underwent additional corneal refractive surgery were reviewed but were excluded from the meta-analysis for refractive and visual acuity outcome measures. Data on visual acuity were converted to logarithmic of the minimum angle of resolution for calculation purposes. Charts and figures were assembled using either SPSS or Excel.

Eligibility criteria

- Implantation of an Artisan/Verisyse IF-pIOL
- Human adults with myopic or hyperopic eyes with no ocular abnormalities other than refractive error
- Reported follow-up of at least 2 years
- Presents at least one of the following categories of outcome: spherical equivalent, endothelial cell change, corrected and uncorrected distance visual acuity, safety index, efficacy index, complications

Exclusion criteria

- Study type (letters, comments, animal trials, in vitro studies, editorial, reviews, and case series and case reports were excluded)
- Studies solely about foldable or toric IF-pIOLs
- Patients operated for problems other than myopia or hyperopia
- Studies in children (< 18 years)
- Follow-up of less than 2 years
- Article not in English
- Publication date before 2000

Figure 1. Eligibility and exclusion criteria (IF-pIOL= iris-fixated intraocular lens)

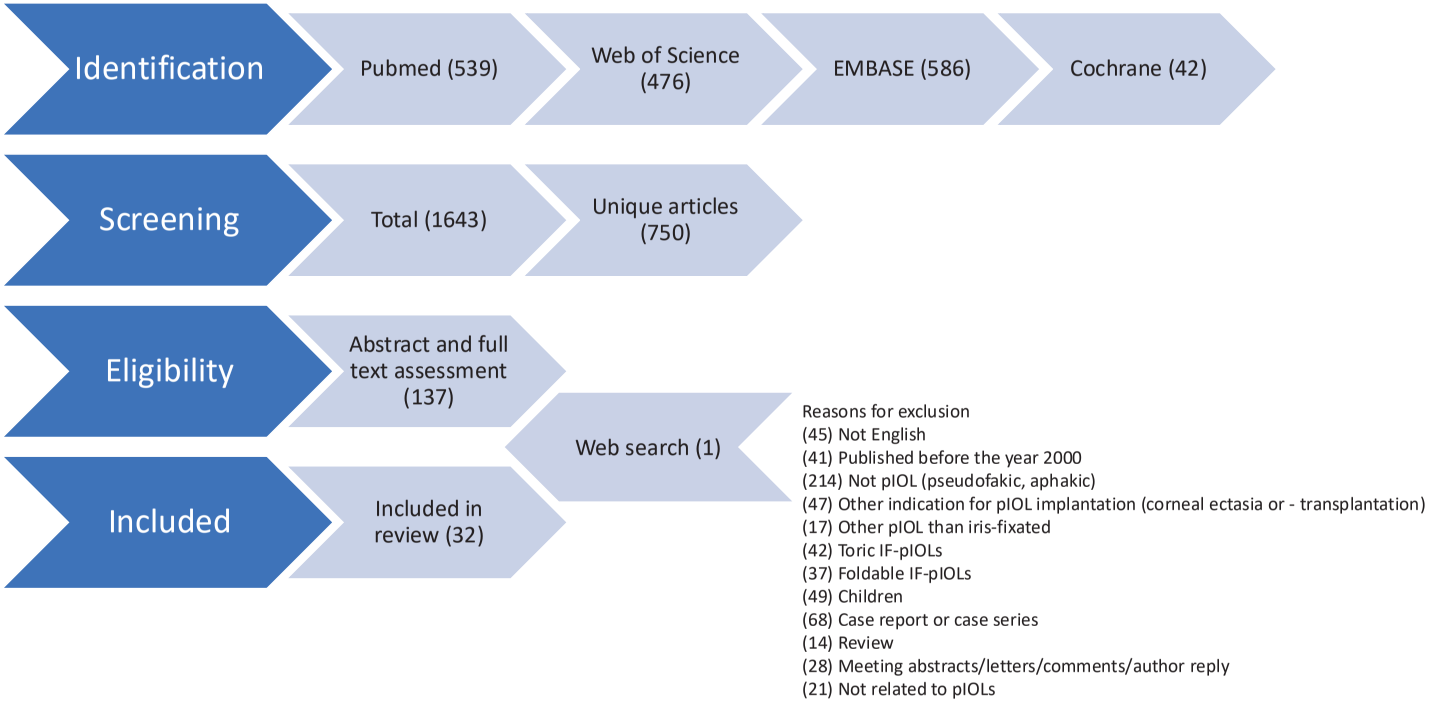

Figure 2. Selection process (IF-pIOL= iris-fixated intraocular lens)

RESULTS

The selected studies comprised 5523 myopic eyes and 217 hyperopic eyes. The sample sizes in the articles range from 26 to 1140 myopic eyes and from 14 to 136 hyperopic eyes. Twenty-nine articles describe the results after iris-fixated pIOL implantation in myopic eyes.[3–18,20–32] Four articles describe the results after iris-fixated pIOL implantation in hyperopic eyes.[19,20,32,33]

In most of the studies, not all participating patients reached the last follow-up visit, and the number of examined patients varies from one follow-up period to another. The mean age at the time of iris-fixated pIOL implantation ranges from 22 to 51 years in the myopic study groups and from 32 to 44 years in the hyperopic study groups.

All 32 studies were reviewed and are summarized in the Appendices 2 to 5. In two studies, a significant percentage of eyes had additional corneal refractive surgery[32,33] and were excluded from the pooled estimate calculations for refractive outcome and visual acuity.

Type of Iris-Fixated pIOL

Of all studies selected, 1 study included only the Artisan 6/8.5,[30] and 2 studies included only the Artisan 5/8.5.[3,23] Four studies report on results after the implantation of the Artisan Hyperopia,[19,20,32,33] and 1 study included the Artisan Myopia Small 5/7.5.[14]

Refractive Outcome

Refractive outcome may be presented as changes in the manifest refractive spherical equivalent (MRSE) and deviation in the MRSE from the targeted refraction.

Changes in the MRSE

Fifteen studies with a total of 1400 eyes report on changes in the MRSE in myopic eyes. Two studies do not specify the follow-up period of the reported MRSE data. The preoperative pooled MRSE ranges from -18.9 to -10.4 D (median -13.3 D), and the postoperative pooled median MRSE ranges from -0.8 to -0.4 D at various follow-up times (see Table 1). The MRSE per study is summarized in Appendix 2.

Two studies report on changes in the MRSE in hyperopic eyes. In the study by Guell et al.,[32] 41.4% of the eyes were treated with a combined pIOL implantation and additional corneal refractive surgery. In the study by Saxena et al.,[19] the preoperative MRSE was 6.80 D, and the postoperative MRSE was 0.10 D at 3-year follow-up (see Table 2).

Changes in the MRSE during follow-up periods are described as being not significant. However, only a limited number of studies have statistically proven this.[4,12,13,15–17,23,28,31] Changes in the MRSE per study are graphically plotted against time in Figure 3.

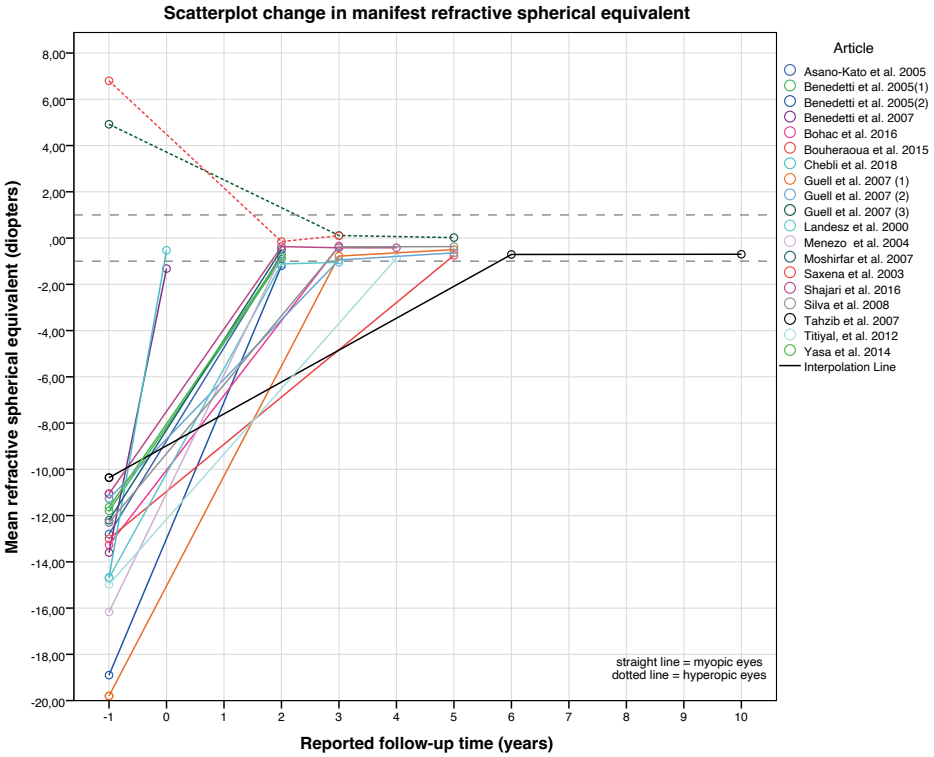

Figure 3. Scatterplot of published data on change in the manifest refractive spherical equivalent

Deviation in the MRSE from Target Refraction

Fourteen studies with a total of 1602 eyes report on the percentage of myopic eyes within 1.0 D of the targeted refraction. Ten studies report on the deviation in the postoperative MRSE from emmetropia; 4 studies report on the deviation from the intended (calculated) correction.

The percentage of eyes within 1.0 D of emmetropia ranges from 55% to 98%. The overall pooled median of eyes within 1.0 D of emmetropia is 94% (all follow-up periods). A slightly smaller range of 65% to 93% of eyes is within 1.0 D of the intended correction. The overall pooled median of eyes within 1.0 D of the intended correction is 78.8% (all follow-up periods). See Tables 3 and 4 and Appendix 2.

Two studies report on hyperopic eyes combined with additional corneal refractive surgery.[32,33] Details are given in Appendix 2.

Table 1. Pooled estimates of changes in MRSE pre- versus post-implantation of an iris-fixated phakic IOL in myopic eyes

Follow-up time	2 years	3 years
Number of eyes	534	589
Mean SE pre-op (D) (range) (SD)	-13.6 (-18.9;-11.6) (2.3)	-13.7 (-19.8;-11.06) (2.9)
Median SE pre-op (D) (range) (SD)	-12.2 (-18.9;-11.6) (2.3)	-13.3 (-19.8;-11.06) (2.9)
Mean SE post-op (D) (range) (SD)	-0.8 (-1.2;-0.4) (0.25)	-0.7 (-1.1;-0.3) (0.29)
Median SE post-op (D) (range) (SD)	-0.8 (-1.2;-0.4) (0.25)	-0.8 (-1.1;-0.3) (0.29)
Number of studies	7	5

D=diopters; MRSE=manifest refractive spherical equivalent; SE=spherical equivalent; pre-op=preoperative; post-op=postoperative; IOL=intraocular lens; SD=standard deviation

Table 2. Changes in MRSE in hyperopic eyes pre- versus post-implantation of an iris-fixated phakic IOL in hyperopic eyes

Study	Publication	Eyes (count)
Guell et al.[δ]	2008	34
		28
Saxena et al.	2003	15
		10

D=diopters; pre-op=preoperative; post-op=postoperative; MRSE=manifest refractive spherical equivalent; FU time=follow-up time; δ41.4% additional corneal refractive surgery; IOL=intraocular lens

4 years	5 years	6 years	10 years
146	341	89	89
-12.4 (-15.0;-11.1) (1.9)	-13.9 (-19.8;-11.3) (3.6)	-10.4 (-10.4) (0)	-10.4 (-10.4) (0)
-11.1 (-15.0;-11.1) (1.9)	-12.3 (-19.8;-11.3) (3.6)	-10.4 (-10.4) (0)	-10.4 (-10.4) (0)
-0.6 (-0.9;-0.4) (0.2)	-0.6 (-0.8;-0.4) (0.1)	-0.7 (-0.7) (0)	-0.7 (-0.7) (0)
-0.4 (-0.9;-0.4) (0.2)	-0.6 (-0.8;-0.4) (0.1)	-0.7 (-0.7) (0)	-0.7 (-0.7) (0)
2	3	1	1

Mean pre-op SE (D)	Mean post-op SE (D)	Reported FU time (Year)
4.92±1.7	-0.11±0.74$^{\delta}$	3
4.92±1.7	0.02±0.51$^{\delta}$	5
6.80±1.97	-0.15±0.89	2
6.80±1.97	+0.10±0.85	3

Table 3. Pooled estimates of MRSE within the range of emmetropia in myopic eyes (%)

Follow-up	**2 years**		**3 years**	
Deviation from emmetropia	**within0.5D**	**within1.0D**	**within0.5D**	**within1.0D**
Number of eyes	172	172	505	505
Median	55.0	84.0	85.4	97.7
Mean	53.3	82.1	79.5	94.9
Minimum	33.3	55.0	31.4	74.5
Maximum	68.0	90.0	85.4	97.7
Standard deviation	14.1	10.7	16.3	7.3
Number of studies	5	5	4	4

D=diopters; MRSE=manifest spherical equivalent; % = percentage of eyes

Table 4. Pooled estimates of MRSE within the range of intended correction in myopic eyes (%)

Follow-up	**3 years**		**5 years**	
Deviation intended	**within0.5D**	**within1.0D**	**within0.5D**	**within1.0D**
Number of eyes	317	317	68	68
Median	57.1	78.8	36.8	70.5
Mean	53.0	76.7	36.8	70.5
Minimum	38.2	69.1	36.8	70.5
Maximum	57.1	78.8	36.8	70.5
Standard deviation	7.8	4.0	0	0
Number of studies	2	2	1	1

D=diopters; MRSE=manifest refractive spherical equivalent; %=percentage of eyes

4 years		5 years		Overall	
within0.5D	within1.0D	within0.5D	within1.0D	within0.5D	within1.0D
146	146	19	19	909	909
72.0	94.0	73.7	94.7	73.7	94.0
59.2	86.5	73.7	94.7	68.8	89.1
35.3	72.5	73.7	94.7	31.4	55.0
72.0	94.0	73.7	94.7	85.4	97.7
17.6	10.3	0	0	19.6	10.1
3	3	2	2	10	10

6 years		10 years		Overall	
within0.5D	within1.0D	within0.5D	within1.0D	within0.5D	within1.0D
89	89	89	89	563	647
50.5	65.1	43.8	68.8	50.5	78.8
50.5	65.1	43.8	68.8	49.2	75.5
50.5	65.1	43.8	68.8	36.8	65.1
50.5	65.1	43.8	68.8	57.1	93.2
0	0	0	0	8.1	5.5
1	1	1	1	4	4

Table 5. Pooled estimates of UDVA in myopic eyes

Follow-up time	2 years	3 years
Number of eyes	560	733
Mean % UDVA ≥ 20/40 (range)	85 (67;87)	81 (67;100)
Median % UDVA ≥ 20/40 (range)	87 (67;87)	79 (67;100)
Standard deviation	5.2	8.3
Number of studies	4	7
Number of eyes	475	733
Mean % UDVA ≥ 20/20 (range)	32 (16;35)	32 (4;60)
Median % UDVA ≥ 20/20 (range)	35 (16;35)	31 (4;60)
Standard deviation	5.9	14.7
Number of studies	3	7

UDVA=uncorrected distance visual acuity; % = percentage of eyes

Table 6. Pooled data on efficacy and safety indices in myopic eyes

Follow-up time	2 years	3 years
Number of eyes	153	88
Median efficacy index (range)	0.90 (0.83;0.93)	0.98 (0.43;0.98)
Mean efficacy index (range)	0.89 (0.83;0.93)	0.86 (0.43;0.98)
Standard deviation	0.04	0.23
Number of studies	2	2
Number of eyes	153	68
Median safety index (range)	1.19 (1.12;1.39)	1.02 (1.02)
Mean safety index (range)	1.19 (1.12;1.39)	1.02 (1.02)
Standard deviation	0.09	0
Number of studies	2	1

EI=efficacy index; SI=safety index

4 years	5 years	6 years
162	210	89
81 (57;92)	86 (45;100)	79 (79)
92 (57;92)	82 (45;100)	79 (79)
13.3	15.5	0
3	5	1
162	210	-
36 (7;53)	28 (6;74)	-
53 (7;53)	21 (6;74)	-
20.3	20.6	
3	5	-

4 years	5 years	6 years	10 years
51	87	89	89
0.96 (0.96)	1.02 (0.63;1.02)	0.83(0.83)	0.8 (0.8)
0.96 (0.96)	0.93 (0.63;1.02)	0.83 (0.83)	0.8 (0.8)
0	0.16	0	0
1	2	1	1
51	68	89	89
1.46 (1.46)	1.10 (1.10)	1.10 (1.10)	1.10 (1.10)
1.46 (1.46)	1.10 (1.10)	1.10 (1.10)	1.10 (1.10)
0	0	0	0
1	1	1	1

Table 7. Safety: change in lines of CDVA in myopic eyes

Study	Publication	Eyes	FU time	≥Lines (%)	≤ 2 Lines (%)
Asano-Kato et al.	2005	44	2	95.5	4.5
Bohac et al.	2017	166	3	99.5	0.5
Bouheraoua et al.	2015	68	5	98.5	0
Budo et al.	2000	249	3	95.8	1.2
Landesz et al.	2000	67	3	92.5	3
Landesz et al.	2001	78	2	91	2.6
Qasem et al.	2010	151	5	100	0
Shajari et al.	2016	95	4	93	0
Silva et al.	2008	26	5	-	0
Stulting et al.	2008	355	2	96	0.3
		228	3	92,5	0.9
Tahzib et al.	2007	89	10	-	3.6
Titiyal, et al.	2012	51	4	96.1	1.9
Yasa et al.	2016	62	2	100	0
Yuan et al.	2012	84	5	100	0

≤ = loss of 2 or more lines of CDVA; ≥ = stable or gain in lines of CDVA; - = no data available; FU-time = follow-up time; %=percentage of eyes

Table 8. Pooled estimates of CDVA in myopic eyes

Follow-up time	2 years
Number of eyes	333
Mean CDVA pre-op in logM (range) (SD)	0.17 (0.17) (0)
Median CDVA pre-op in logM (range) (SD)	0.17 (0.17) (0)
Mean CDVA post-op in logM (range) (SD)	0.05 (0.02;0.06) (0.02)
Median CDVA post-op in logM (range) (SD)	0.05 (0.02;0.06) (0.02)
Number of studies	2

logM=logarithmic angle of minimum resolution; pre-op=preoperative; post-op=postoperative; CDVA=corrected distance visual acuity; SD=standard deviation

	Notes
	2 eyes; age-related cataract
	1 eye; choroidal neovascularization at 18-month follow-up
	3 eyes; 1 eye nuclear cataract, 2 eyes macular myopic degeneration
	2 eyes cataract, 1 eye unclear reason
	2 eyes nuclear cataract
	1 eye; progressive cataract at 3–year follow-up
	2 eyes; 1 eye retinal detachment & macular hole, 1 eye posterior capsular opacification
	3 eyes; 1 eye myopic maculopathy, 1 eye guttate dystrophy, 1 eye cataract
	1 eye, reason not specified

3 years	4 years	5 years	10 years
499	84	84	89
0.17 (0.17) (0)	0.17 (0.17)	0.17 (0.17) (0)	0.16 (0.16) (0)
0.17 (0.17) (0)	0.17 (0.17)	0.17 (0.17) (0)	0.16 (0.16) (0)
0.07 (0.02; 0.11) (0.03)	0.02 (0.02)	0.02 (0.02) (0)	0.12 (0.16) (0)
0.06 (0.02; 0.11) (0.03)	0.02 (0.02)	0.02 (0.02) (0)	0.12 (0.16) (0)
3	1	1	1

Visual Acuity

Uncorrected (UDVA) and corrected (CDVA) distance visual acuity, safety index (SI), and efficacy index (EI) are common parameters to assess the effect of the iris-fixated pIOL on visual acuity; details are in Appendix 3.

UDVA and Efficacy

Data on UDVA are commonly reported as the cumulative percentage of eyes within a visual acuity range. Efficacy can be described as the percentage of eyes achieving a postoperative UDVA of 20/40 and 20/20 or better. The pooled median of the percentage of myopic eyes with a UDVA of 20/40 or better is 87% and 82% at 2- and 5-year follow-up, respectively. The pooled median of the percentage of myopic eyes with a UDVA of 20/20 or better was 35% and 21% at 2- and 5-year follow-up, respectively (see Table 5).

The EI reflects the ratio between the preoperative CDVA and postoperative UDVA: (mean postoperative UDVA)/ (mean preoperative CDVA). The pooled median EI at 2, 5, and 10 years is 0.90, 1.02, and 0.80, respectively (Table 6). Efficacy indices have a wide range from 0.43 to 1.03; only Silva et al.[17] describe an EI of below 0.8. They note a slight undercorrection immediately postoperatively but give no explanation.

Only Qasem et al.[33] report on a small number of hyperopic eyes, with 100% having a UDVA of 20/30 or better at 2- and 3-year follow-up and 28.6% of eyes having additional corneal refractive surgery after iris-fixated pIOL implantation. Efficacy indices are 0.81 and 0.9 at 2 and 5 years, respectively, as reported by Guell et al.,[32] with 41.4% of eyes having additional corneal refractive surgery after implantation.

CDVA and Safety

Data on CDVA are often reported as the change in visual acuity preimplantation vs post-implantation; 14 studies report on changes in CDVA in myopic eyes (Table 7). All studies report that more than 91% of myopic eyes have a stable or a gain in CDVA. The pooled median postoperative CDVA increased compared with the preoperative CDVA to 0.05, 0.02, and 0.12 logarithmic angle of minimum resolution units at 2, 5, and 10 years of follow-up, respectively, which equals 0.89, 0.96, and 0.76 Snellen (Table 8). Nine studies report on a loss of 2 or more lines of CDVA in up to 4.5% of the eyes.[4,5,7,12,13,15,27,28,33] The primary reason for a loss of 2 or more CDVA lines is cataract (9 eyes) (Table 7).

The SI is defined as the ratio of (mean postoperative CDVA)/(mean preoperative CDVA). All reported safety indices for myopic eyes are above 1.0. The pooled median SI at 2, 5, and 10 years of follow-up is 1.19, 1.10, and 1.10, respectively (see Table 6).

Although no specific number is given by Qasem et al.,[33] no hyperopic eye lost a line of CDVA. Saxena et al.[19] describe a CDVA of 0.75 at 3-year follow-up, with 50% of hyperopic eyes having a stable or a gain in CDVA. A SI of 0.95 and 1.25 is reported by Guell et al.[32] at 2- and 5-year follow-up, respectively.

EC Loss

Most studies report on EC change from baseline. Other articles report on EC change from 6 months to 1 year after implantation, attempting to describe chronic EC change by excluding the acute EC loss induced by surgery. Some articles only report the yearly percentage of EC loss, some only on absolute EC counts, and others on both. Details per study are in Appendix 4.

Various conclusions on EC change are drawn by the different authors, ranging from a gain in EC[10,23,31] to no significant EC change or a significant EC loss over the follow-up period. For the pooled estimates of absolute EC change given in this article, a linear decrease in EC over time is assumed, as in the reviewed articles. Saxena et al.[21] and Qasem et al.[33] (2- and 3-year follow-up) are excluded from the pooled estimates because the reported EC change in these studies included different types of iris-fixated pIOLs.

Twenty-three articles on myopic eyes report on EC change in the period of 2 to 4 years after implantation, ranging from a small gain of 0.26% to a loss of 14.58%.[3–7,9–13,15–18,21,22,24,27–30,32] Twelve articles on myopic eyes report on EC change in the period of 5 to 7 years after implantation, with a range of 0% to 15.6% EC loss.[6,7,12,16–18,21,23,26,29,30,33] Four studies report on a follow-up period of longer than 7 years, with EC loss ranging from 4.9% to 22.5%.[6,23,26,30] The number of eyes examined at given follow-up periods per study ranges from 6 to 293. Pooled estimates for the percentage of the annual EC change per follow-up period are presented in Table 9. The overall median annual EC loss is 60 cells/mm^2 (ranging from -96 to 144 cells/mm^2). Figure 4 shows a stem-and-leaf plot of the overall annual EC loss and median annual EC change per study.

Two studies on hyperopic eyes report on EC change in the period of 2 to 4 years, ranging from 5.4% to 11.7%.[19,32] The number of examined eyes ranges from 10 to 35. Pooled estimates for the percentage of the annual EC change per follow-up period are presented in Table 10. In Figure 5, absolute EC counts are plotted against time for both groups. The overall median annual EC loss is 65.5 cells/mm^2 (ranging from 44 to 93 cells/mm^2; see also Figure 4).

A variable minimum anterior chamber depth (ACD) was used as a selection criterion, ranging from 2.6 to 3.2 mm across the various studies. There seems to be no difference in EC loss between the studies that adopted a minimum ACD of 3.0 mm or smaller compared with studies adopting a minimum ACD of greater than 3.0 mm (Figure 4). This may be explained by the fact that the mean ACD is above 3.11 mm in all studies (ranging from 3.11 to 3.87 mm).

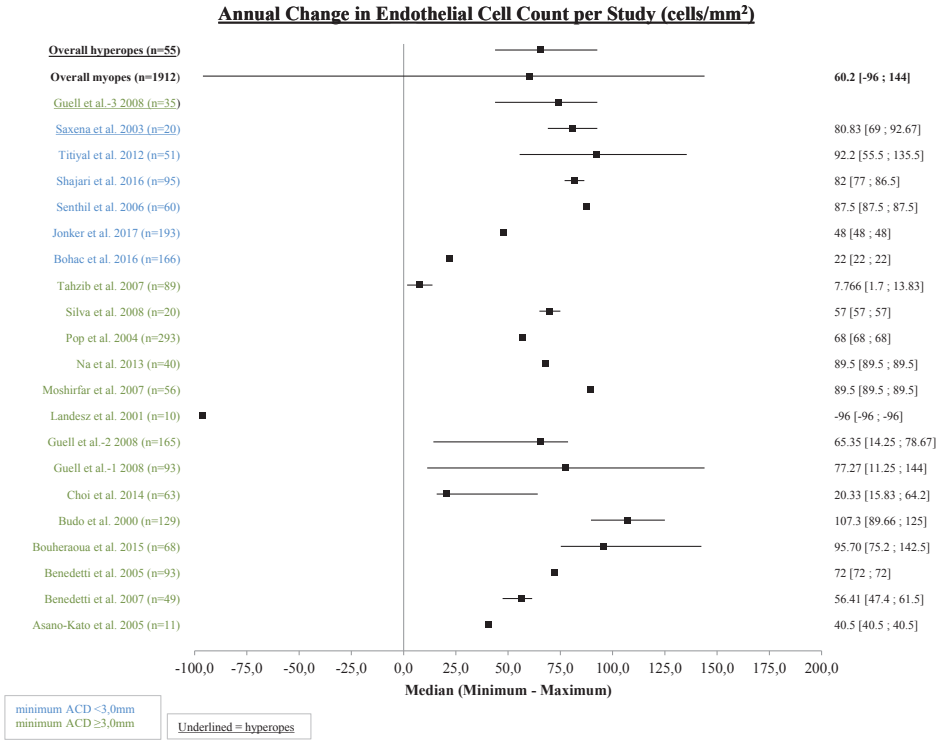

Figure 4. Stem-and-leaf plot annual endothelial cell count change (ACD=anterior chamber depth)

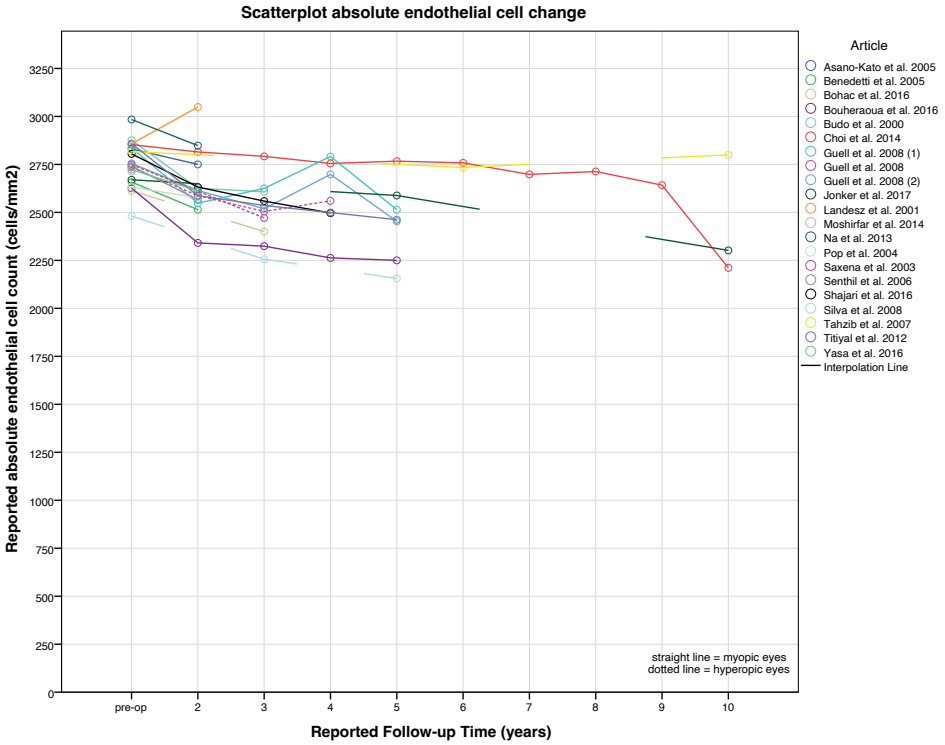

Figure 5. Scatterplot of reported absolute endothelial cell changes

Table 9. Pooled estimates of annual absolute EC change in myopic eyes

Follow-up time	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Number of eyes	1174	772	610	610	131	45	43	20	222
Median (cells/mm^2)	70.5	78.7	77.0	60.2	13.8	22.1	17.5	23.4	36.8
Mean (cells/mm^2)	81.8	67.6	49.1	46.5	14.5	22.1	17.5	23.4	23.5
Standard deviation	39.1	30.5	34.0	25.6	0.9	0.0	0.0	0.0	18.4
Minimum (cells/mm^2)	-96.0	20.3	11.3	16.4	13.8	22.1	17.5	23.4	1.7
Maximum (cells/mm^2)	144.0	107.3	90.8	92.2	15.8	22.1	17.5	23.4	64.2
Number of studies	14	9	6	7	2	1	1	1	3

EC=endothelial cell

Table 10. Pooled estimates of annual absolute EC change in hyperopic eyes

Follow-up time	2 years	3 years	4 years
Number of eyes	49	44	28
Median (cells/mm^2)	74.0	76.7	43.8
Mean (cells/mm^2)	72.5	80.3	43.8
Standard deviation	2.3	6.8	0
Minimum (cells/mm^2)	69.0	76.7	43.8
Maximum (cells/mm^2)	74.0	92.7	43.8
Number of studies	2	2	1

EC=endothelial cell

Secondary Surgical Intervention

The need for secondary surgical intervention after the iris-fixated pIOL implantation is summarized in Tables 11 and 12 as well as in Figure 6 and specified in more detail in Appendix 5.

A total of 23 studies report on secondary surgical intervention in myopic eyes, with a total of 3636 myopic eyes. Secondary surgical intervention was needed in 0% to 27.1% of the myopic eyes. Four studies report on secondary surgical intervention in hyperopic eyes, with a total of 217 eyes. Secondary surgical intervention was needed in 2.2% to 46% of the hyperopic eyes.

Repositioning

Repositioning of the iris-fixated pIOL may be necessary due to inadequate surgical fixation or due to inadequate fixation after trauma. Overall, pIOL repositioning or re-enclavation was reported in a total of 59 myopic eyes, of which 23 were due to posttraumatic causes.[3,5,12,13,15,16,22,27,31,32]

IOL Exchange

Iris-fixated pIOL exchange was performed in a total of 20 myopic eyes and in 2 hyperopic eyes reported in 6 studies due to refractive undercorrection or overcorrection.[3,12,22,27,30,31] In 4 eyes, the pIOL was exchanged because of a pupil diameter exceeding the optic diameter/glare or halo complaints.[27,31]

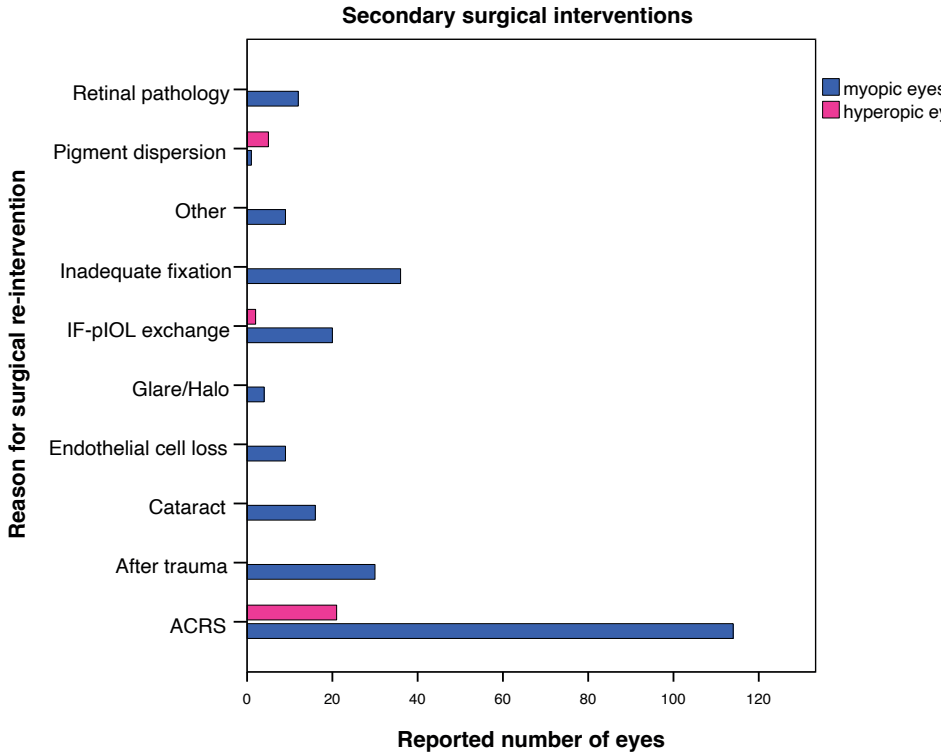

Figure 6. Reasons for secondary surgical intervention (ACRS = additional corneal refractive surgery; IF-pIOL = iris-fixated phakic intraocular lens)

Correction of Residual Refractive Error

An undesirable amount of residual refractive error can be corrected by exchanging the iris-fixated pIOL either for an iris-fixated pIOL of different dioptric power or for a different iris-fixated pIOL model. Another way of correcting residual refractive error is to combine the iris-fixated pIOL implantation with additional corneal refractive surgery, which was performed in 114 myopic eyes and 21 hyperopic eyes.[3,23,31,32]

IOL Explantation

The main reason for explantation of the iris-fixated pIOL in the myopic eye study was due to the formation of significant visual cataract.[3,8,17,18,23,27,30,31] Patients were between 46 and 62 years at the time of cataract extraction with iris-fixated pIOL removal. Almost all cataracts described were of the nuclear sclerotic type.[11,17,18,27,32] Cataract formation is overall described as having no direct causative relationship with the iris-fixated pIOL implantation. Only 1 study describes a case that can be attributed to the surgical procedure, acute glaucoma followed by crystalline lens opacification.[22]

Table 11. Reasons for surgical re-intervention in myopic eyes

Secondary surgical intervention	Reason	Eyes (count)	Studies (count)
IF-pIOL explantation (Total = 41)	Cataract	16	9
	After trauma	7	3
	Endothelial cell loss	9	5
	Other	9	4
IF-pIOL repositioning / re-enclavation (Total = 59)	Inadequate fixation	36	10
	After trauma	23	7
Correction of residual refractive error (Total = 134)	IF-pIOL exchange	20	5
	ACRS	114	4
Other (Total = 17)	Retinal pathology	12	4
	Glare/Halo	4	2
	Pigment dispersion	1	1

IF-pIOL= iris fixated phakic intraocular lens; ACRS=additional corneal refractive surgery

Table 12. Reasons for surgical re-intervention in hyperopic eyes

Secondary surgical intervention	Reason	Eyes (count)	Studies (count)
IF-pIOL explantation (Total = 5)	Pigment dispersion	5	2
Correction of residual refractive error (Total = 23)	ACRS	21	2
	IF-pIOL exchange	2	1

IF-pIOL= iris fixated phakic intraocular lens; ACRS=additional corneal refractive surgery

Iris-fixated pIOL explantation due to excessive EC loss ranged from 0% to 0.9%.[3,6,8,16,31] Explantation after traumatic causes was reported in 7 eyes.[3,15,27] In 3 myopic eyes, the pIOL was explanted because of an inflammatory response.[27]

Iris-fixated pIOL explantation due to glare/halo complaints or a pupil diameter exceeding the optic diameter was described in 4 eyes.[3,17,27] The need for retinal repair is reported to be in the range of 0% to 2.4%.[15,16,27,32,33] The main reason for explantation in hyperopic eyes is the formation of posterior synechiae and pigment cell deposits.[19,20]

Other Complications

A concern with AC pIOLs is the development of secondary glaucoma due to pigment dispersion, pupillary block, or an uncontrollable inflammatory response. Pigment dispersion is likely to be caused by abnormal pressure on the iris.[20,38] Baïkoff et al.[20] describe that of a total of 273 implanted iris-fixated pIOLs (137 myopic and 136 hyperopic eyes), 9 eyes developed pigment dispersion, 8 (5.9%) of which were in hyperopic patients. Although ACs in all eyes were deep enough and irides that were considered too convex were excluded, they found a significant difference in crystalline lens anatomy between the hyperopic and myopic eyes. Saxena et al.[19] report a percentage as high as 15% with pigment dispersion in hyperopic eyes.

To prevent pupillary block, an iridotomy or iridectomy is placed in eyes with iris-fixated pIOLs. There were cases of pupillary block reported in which no iridotomy or iridectomy was placed or the original iridotomy was closed.[27] There was also 1 case of malignant glaucoma for which filtration surgery was needed.[15] However, overall, increased intraocular pressure is uncommon in the long term. Transient intraocular pressure elevation is mostly described as an early phenomenon arising from corticosteroid use in the early postoperative period.

Optic phenomena such as glare and halo complaints can be related to surgical factors of poor centration or cases in which the pupil diameter exceeded the optic.[3] Glare/halos were reported to be within a range of 0% to 22.2%. Of the highest percentage reported by Landesz et al.,[11] only 2 of 8 patients were disturbed enough by the halos at night that they sometimes used pilocarpine. Moshirfar et al.[22] and Titiyal et al.[16] report 2.7% and 3.9% of glare/halo complaints at 2- and 4-year follow-up, respectively. Tahzib et al.[23] scored optic phenomena with a valued questionnaire at 10-year follow-up and reported low scores. Optic phenomena seem to decrease over time and rarely require further action.[5,7,16]

DISCUSSION

The aim of this systematic review and meta-analysis was to gather all relevant data from the literature on the middle- and long-term effects after implantation of the convex-concave-shaped rigid iris-fixated pIOL (Artisan/Verisyse) for the correction of myopia and hyperopia. After a systematic search, 32 articles were selected and data were collected, reviewed, and summarized in pooled estimates.

Visual Outcome

Overall visual outcomes of the iris-fixated pIOL are encouraging, with stable safety indices of above 1.0 in myopic eyes up to 5 years after implantation. Thus, most eyes have a stable or a gain in CDVA. This outcome can be explained by the image magnification effect on the retina with a pIOL in place compared to refractive correction with spectacles, being partly due to the high optical and surface quality of the pIOL.[39,40] Safety indices in hyperopic eyes are reported to be lower than those in myopic eyes. This can be explained by the retinal minification effect after pIOL implantation compared with spectacles. Most studies report less than 1% of the eyes losing 2 or more lines of CDVA. In eyes with a loss of 2 or more Snellen lines of CDVA, the authors claim that the main reasons are age-related cataract formation or the nature of myopic eye disease and not directly related to the implantation of the iris-fixated pIOL. In terms of efficacy, a significant gain in UDVA pre-implantation vs post-implantation is reported by all authors, with all pooled estimates of the EI being above 0.8.

Refractive Results

A fair to excellent refractive outcome and high stability of the SE over time has been demonstrated by the articles included in this review. Although a wide range of 55% to 98% of eyes is reported to have a deviation within 1.0 D from the targeted refraction, a clear majority of the studies report a mean MRSE within 1.0 D of emmetropia at the last follow-up, without any significant change in the SE over time. When interpreting the results on the deviation of the postoperative SE of targeted refraction, it is important to consider that pure predictability reflects the accuracy of the Van der Heijde formula combined with the surgically induced changes in refraction and is best determined in the period of 3 to 6 months after implantation.[24] When describing long-term data on the SE within a certain range, we can only speak of refractive stability because refractive changes due to other reasons might have occurred over time (e.g., cataract, progressive elongation of the axial length, and corneal changes).

Corneal Endothelium

Accelerated EC loss has been, and still is, a great concern after any type of intraocular surgery, especially with the implantation of any type of AC IOL. Multiple pIOLs have been withdrawn from the market because of an unacceptable EC loss. The extent of EC change varies widely among the different studies involving the iris-fixated pIOL, ranging from a loss to a gain in ECs. The general trend, demonstrates a decrease in the EC density over time, with a comparable result between the myopic and hyperopic eyes. Pooled estimates reveal an annual decrease of 60 cells/mm^2 in myopic eyes and 65.5 cells/mm^2 in hyperopic eyes.

In clinical trials, corneal specular microscopy (CSM) is used to noninvasively study the EC layer of the cornea. The evaluation of the corneal ECs with CSM is susceptible to various errors. Internal CSM errors may arise from different sources, such as the accuracy of operator-software interaction, software imprecision, specular reflection limitations generating low-quality images, versatility for acquiring endothelial images, and sampling processes.[41] It has also been shown that different brands of CSM cannot be interchanged reliably.[42–44] Protocols to evaluate the corneal endothelium are not consistent among the studies included in this review and are mostly not described in detail. The long follow-up time generates additional errors in which changes, updates, or repairs of CSMs may have taken place, and new insights into how to perform and evaluate the corneal endothelium might lead to updates and adjustments in evaluation methods. Other reasons for a wide range of EC change may be due to surgical experience, patient selection criteria, characteristics of the patient population (e.g., race and distribution of age in cohorts), the method of calculating and reporting EC change, a selection bias, the multicenter nature of the study, or reasons still unknown. There is no definite explanation for the wide range reported by the various authors. It may be multifactorial, and in this case, the extent to which each factor may contribute to the wide range in EC change also remains unknown. This fact emphasizes the need for regular follow-up visits and well-controlled prospective and comparative studies and studies with a long follow-up period. Guidelines on how to perform accurate analysis of the corneal endothelium and how to minimize the variability of CSM measurements should be encouraged.[41,45]

Cataract Formation

Most cataracts reported after iris-fixated pIOL implantation in myopic eyes were of the nuclear type and were the main reason for iris-fixated pIOL explantation. In hyperopic eyes implanted with iris-fixated pIOLs, cataract formation has not been described, but the study population is far smaller and the follow-up time far shorter compared with studies concerning myopic eyes. In their meta-analysis, Chen et al. report an incidence

of cataract formation after Artisan/ Verisyse pIOL implantation of 1.11% and 0.32% in myopic and hyperopic eyes, respectively, with half of the new onset of cataracts being of the nuclear sclerotic type.[34] The mean time to cataract development was 37.65 months. Alio et al.[35] describe the reasons for the explantation of various types of pIOLs in one of the largest consecutive case series. They report that almost half of the cases of iris-fixated pIOL explantation were due to nuclear cataract formation. The mean time between iris-fixated pIOL implantation and cataract development was 9.19 years, and the time between iris-fixated pIOL implantation and explantation was 9.55 years. Menezo et al.[37] also report a case series of 7 out of 231 eyes (3%) that developed nuclear cataract after the implantation of an iris-fixated pIOL after a mean period of 4.7 years and, in which cataract extraction was performed, after a mean period of 11.4 years. Although 20% of the eyes were reported as being implanted with the older type of the biconcave Worst–Fechner iris-fixated pIOL, the type of cataract formation and time to cataract extraction is comparable to Alio et al. and the articles analyzed in this review.

Cataract formation is a potential complication of any surgical intraocular procedure, although a direct relationship between cataract formation and the iris-fixated pIOL has not been clearly shown. In cases in which iris-fixated pIOLs are implanted in highly myopic eyes, it is unclear whether cataract formation is due to the implantation procedure (complexity of the procedure and surgical experience) or related to the pIOL itself (material, metabolic effects, and intermittent touch), patient risk factors (trauma, medications, other diseases, and genetic predisposition), or high myopia. Data reported in long-term follow-up studies appear to support author claims that cataract development does not appear to be directly related to iris-fixated pIOL implantation. Evidence in long-term, population-based follow-up studies has been provided to support the hypothesis that myopia and hyperopia itself may increase the risk of cataract development, especially of the nuclear type, compared with emmetropic eyes.[46,47] However, more in-depth studies are needed to prove such statements and to clarify what factors contribute, and to what extent, to possibly earlier cataract development after pIOL implantation.

Glare/Halo

Optical phenomena, such as glare and halo may be caused by various factors such as a scotopic pupil size that exceeds the size of the lens optic, false light through a too large or not adequately located peripheral iridectomy or iridotomy, or a lens that is not stable and/or not adequately centered over the pupil entrance. The surgical procedure of enclavating an iris-fixated pIOL requires skill and practice and has a steep learning curve. A certain amount of enclavated iris tissue is required to ensure proper, stable, and well-centered enclavation. Greater surgical experience increases the ability to

accurately enclavate the proper amount of the iris and center the iris-fixated pIOL over the pupil, which will lower the rate of re-enclavations.[3,48] Although no standardized method is used to evaluate these subjective visual complaints in the various studies, optic phenomena seem to decrease over time and rarely require secondary surgical intervention.[5,7,16]

Other Complications

The factors mentioned as contributing to an increased risk of spontaneous subluxation include the quality and quantity of enclavated iris tissue at the initial implantation, the amount of iris manipulation during surgery, iris color, anatomy and architecture, and the amount of atrophy and depigmentation at the enclavation site.[16,36,48] In addition to the articles studied in this review, Moran et al.[36] have published a retrospective case series in which 2% of 609 eyes required re-enclavation with a follow-up of 11 years after Artisan or Artiflex implantation, which globally seems in line with the articles included in this review.

Reported rates of the need for retinal repair are low, ranging between 0% and 1.3%. However, there is no consistent protocol among the studies reviewed concerning prophylactic treatment of the retina; in one study, prophylactic panretinal laser photocoagulation was performed in all treated eyes.[15] A higher risk for retinal detachment after pIOL implantation has been associated with an axial length of greater than 30 mm.[35,49] In comparison with refractive clear lens exchange (RCLE), an alternative option to correct high refractive errors, Nanavaty and Daya[50] state that pIOL implantation for the correction of myopic refractive errors may be a safer option than RCLE because retinal detachment in myopic eyes is a concern after RCLE, with incidences reported up to 8%.

Other complications, such as secondary glaucoma or other retinal problems, are rarely reported in myopic eyes. In hyperopic eyes though, severe pigment dispersion seems to present a problem, with an incidence rate of up to 15%.[19] Moreover, the main reason for iris-fixated pIOL explantation in hyperopic eyes is the formation of pigment deposits and posterior synechiae formation. In a short-term study on iris-fixated pIOL implantation in primary and secondary hyperopia, Alio et al.[38] also reported that 5% of eyes developed posterior synechiae. It is believed that a convex-shaped iris increases the incidence of pigment dispersion.[20,38] To decrease the risk Baïkoff et al.[20] suggested adding the objective measurement of a crystalline lens rise to the safety criteria, instead of using the subjective observation of a convex iris configuration. Prospective or comparative studies to verify a reduction in the incidence of severe pigment dispersion in hyperopic eyes when considering the crystalline lens rise are unfortunately not available.

In conclusion, most articles in the literature present the results on myopic eyes with a medium-term follow-up of 2 to 4 years. Only a few studies present the results from a follow-up of 7 years or longer.

Main findings of our meta-analysis are:

1. Visual and refractive results after the implantation of an iris-fixated pIOL for the correction of myopia are positive.
2. The complication rate is low. Age-related cataract is the main reason for iris-fixated pIOL explantation. Endothelial cell loss seems acceptable, or perhaps better said incalculable, although the range of EC change is too wide to draw firm conclusions.
3. Great care should be taken when considering implanting an iris-fixated pIOL in hyperopic eyes because complication rates, particularly pigment dispersion, might be higher than those in myopic eyes.
4. More well-designed long-term studies are needed, especially in hyperopic eyes.

To provide more evidence for the long-term safety of the iris-fixated pIOL and other IOLs, and to enable proper comparison of different pIOLs and other methods to correct refractive errors, we advocate for standardized reporting methods for refractive surgery data. Initiatives proposed by journal authors and editors to achieve uniformity should be supported.[26,51,52]

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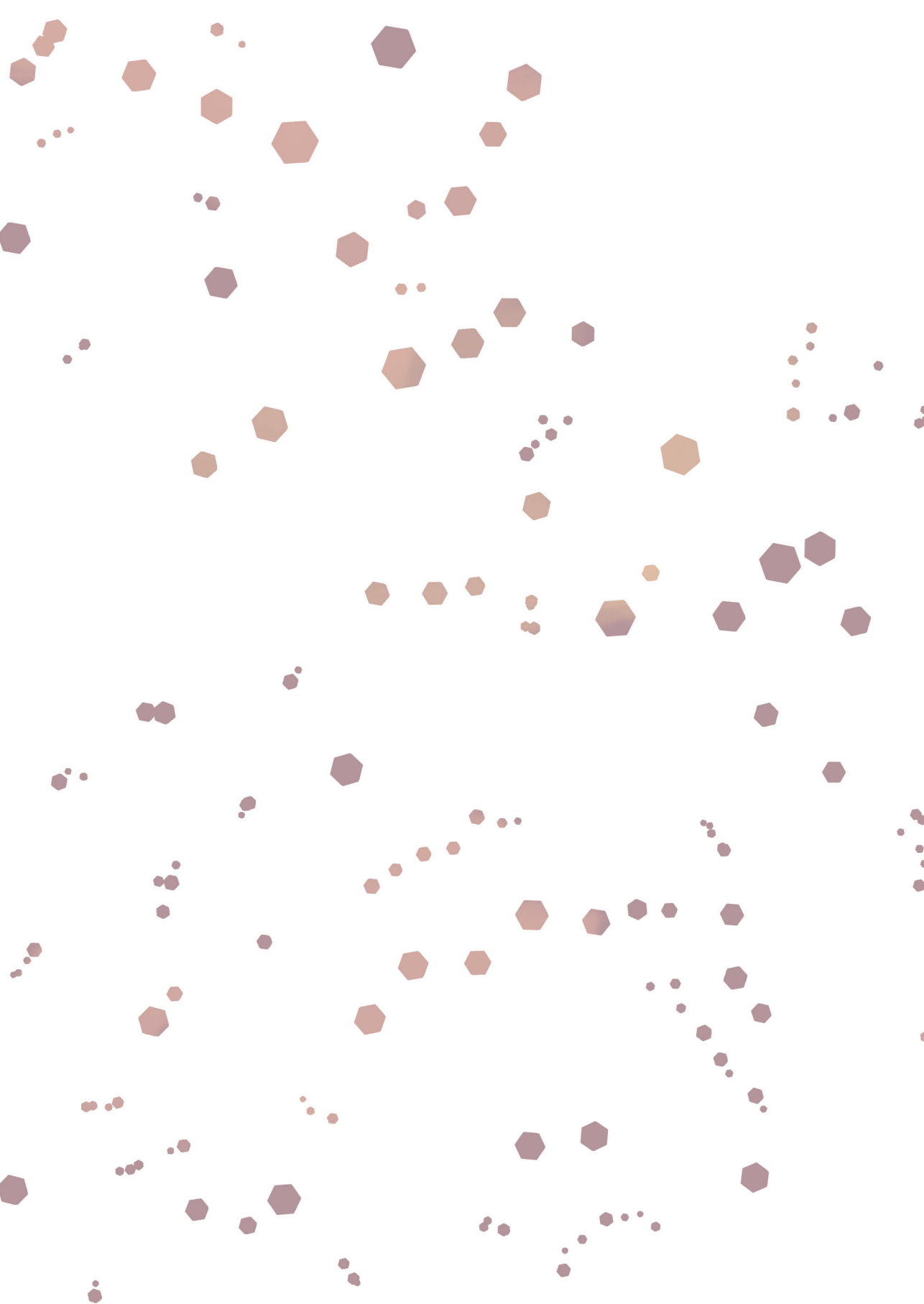

Chapter 3

Implantation of an Iris-Fixated Phakic Intraocular Lens for the Correction of Hyperopia: a 15-Year Follow-Up

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ABSTRACT

Purpose

To assess the predictability, efficacy, stability, and safety of implantation of an Artisan iris-fixated phakic intraocular lens (IF-pIOL) for the correction of hyperopia with a follow-up of up to 15 years.

Setting

Leiden University Medical Center, the Netherlands.

Methods

Patients operated by a single surgeon up to 2007 were identified, and data on refraction, corrected distance visual acuity (CDVA), uncorrected distance visual acuity, endothelial cell (EC) density, and complications were collected.

Results

A total of 61 eyes (32 patients) were analysed. The mean spherical equivalent decreased from +6.43 ± 1.78 diopters (D) preimplantation to -0.22 ± 0.57 D at 1 year post-implantation and remained stable throughout follow-up. A stable CDVA with safety indices ranging from 0.91 to 1.10 and efficacy indices between 0.43 and 0.86 were observed. Follow-up time had a significant effect on EC density with an estimated annual decline of 58 cells/mm^2 after IF-pIOL implantation. IF-pIOL explantation was performed in 10 eyes (16.4%) after 8.13 ± 5.11 years. The main reason for IF-pIOL explantation was EC loss (4 eyes [6.6%]). Pigment dispersion was the most encountered complication, observed in 9 eyes (14.8%).

Conclusions

Visual and refractive results after implantation of an IF-pIOL to correct hyperopia show favorable and stable results with long-term follow-up. Lifelong monitoring of EC counts is mandatory. Pigment dispersion might be a problem in hyperopic eyes implanted with an IF-pIOL; a shallower anterior chamber depth and a convex iris configuration might be predisposing factors.

INTRODUCTION

Phakic intraocular lens (pIOL) implantation offers some well-defined advantages over the more popular corneal refractive surgery, such as its reversibility and its broader treatment range. The pIOLs can be classified according to their site of implantation, in the anterior or in the posterior chamber of the eye. A further categorization of anterior chamber pIOLs can be made based on the fixation method: iris-fixated or angle-supported pIOLs. Of these IOLs, only the Artisan (Ophtec BV) iris-fixated pIOL (IF-pIOL) and the Visian ICL (STAAR Surgical Company) posterior chamber pIOL are currently available for the correction of hyperopia. Alshamrani and Alharbi recently reviewed literature on hyperopic refractive errors corrected with a pIOL. They found only a limited number of studies on IF-pIOLs.[1–10] Although the first IF-pIOL for the correction of hyperopia was implanted in 1986, studies with a follow-up of more than 5 years after implantation of an IF-pIOL are either lacking or outdated; only 1 preliminary study of the first-generation IF-pIOLs with a follow-up up to 120 months has been published in 1998, and surgical techniques, IOL design, and safety considerations have advanced greatly since.[10] We describe the results of a cohort of 61 hyperopic eyes in 32 patients implanted with an Artisan IF-pIOL with a 15-year follow-up.

METHODS

Study Population

This is a retrospective observational cohort study where charts were searched to identify patients who had undergone Artisan IF- pIOL implantations (model 203) and 32 patients were identified who had been treated by 1 surgeon (G.P.M.L.) with an IF-pIOL for the correction of hyperopic refractive error from 1997 to 2007. The study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all participating patients. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center. Follow-up visits took place 1 month, 3 months, and 6 months postoperatively and yearly thereafter. To assess predictability, efficacy, safety, stability, and complication rate, data on corrected distance visual acuity (CDVA) and uncorrected distance visual acuity (UDVA), refraction, endothelial cell (EC) count, complications, and secondary surgical interventions were collected. EC measurements were acquired with 3 models of the Topcon SP-series corneal specular microscope (CSM; Topcon Medical Systems, Inc.): SP1000, SP2000P, and SP3000P, because of changes in equipment throughout the years. To increase reliability of the EC counts, converting factors were calculated to improve the interchangeability of EC counts. Details are described elsewhere.[11] Central corneal thickness (CCT) measurements were preoperatively acquired with the Topcon SP-series corneal specular microscope. Postoperative CCT measurements were acquired with Pentacam (OCULUS Optikgeräte GmbH).

As per safety guidelines of the manufacturer, at the time of implantation, all patients had (1) to be of general good health, (2) a minimum of 18 years of age, (3) to have had a stable hyperopic refraction for at least 1 year, (4) a central EC density (ECD) of more than 2000 cells/mm^2, and (5) an anterior chamber depth (ACD) of at least 2.6 mm (first 8 patients). After 1998, eligibility criteria were adjusted to a minimum ACD of 3.0 mm (measured from the corneal epithelium), and a convex iris configuration was considered an exclusion criterion. Other exclusion criteria for IF-pIOL implantation were a mesopic pupil size of 5.0 mm or greater and an intraocular pressure more than 21 mmHg and/or glaucoma.

The pIOL power calculations were performed by Ophtec BV with the Van der Heijde formula.[12] This formula uses the mean corneal curvature (mean keratometry (Km)), the adjusted ACD, and the manifest refraction spherical equivalent (MRSE) at a vertex distance of 12.0 mm. A factor of 0.6 for the effective lens position was applied. The surgical procedure as described by Saxena et al. was used for all eyes.[8]

Statistical Analysis

Outcome variables were tested for normality with the Shapiro Wilks test. A paired *t*-test was used to compare preoperative to postoperative data. One-way analysis of variance with post-hoc Tukey honestly significance difference was applied to compare the differences between follow-up periods. When the distribution of data was nonparametric or the number of eyes was less than 10, a Wilcoxon signed-rank test was used to compare preoperative and postoperative data, and a Kruskal-Wallis test with post-hoc Mann-Whitney U test was applied to compare the differences between follow-up periods. In addition, a linear mixed model was applied to examine the development over time of our main parameters of interest: CDVA, UDVA, MRSE, and EC counts. As fixed effect in the model, follow-up time was measured in years. As random effects, "patient" and "eye within patient" were entered to estimate an intercept of each eye within each patient. A p-value less than 0.05 was considered statistically significant. When using multiple comparisons, a Bonferroni adjustment was applied. Statistics were performed using IBM SPSS Statistics for Windows software (version 23, IBM Corp.).

The MRSE was calculated by using the subjective refraction according to the formula: MRSE in diopters (D) = Sphere + (0.5 × Cylinder). Data on visual acuity was converted to logarithmic angle of minimum resolution units for calculation purposes. The efficacy index is the ratio of mean postoperative UDVA (decimal) to mean preoperative CDVA (decimal). The safety index is the ratio of mean postoperative CDVA (decimal) to mean preoperative CDVA (decimal). To allow for comparisons with previously published literature, EC change was defined as the paired difference between the preoperative and postoperative examination and expressed as an annual change in percentage from the preoperative cell density. Amblyopic eyes, defined as a preoperative CDVA of less than 0.40 Snellen or a difference of more than 2 Snellen lines in CDVA compared with the fellow eye with a recorded history of strabismus, in an ametropic but otherwise normal eye, were excluded from analysis for visual and refractive outcomes but were included in the analysis for EC change and complication rates.

RESULTS

Study Population

Thirty-two patients were included in this study of which 17 were men (32 eyes, 52.5%) and 15 were woman (29 eyes, 47.5%). A total of 61 eyes were implanted with an IF-pIOL, of which 30 were right eyes and 31 left eyes. In 3 patients, only 1 eye was included for analysis because the fellow eye was implanted with a toric IF-pIOL (2 eyes), and 1 patient had undergone unilateral IF-pIOL implantation. The baseline characteristics are listed in Table 1. Three patients (9.4%) were lost to follow-up, and 2 patients (6.3%) died during the study. Thirteen eyes (21.3%) met the criteria for amblyopia. These 13 eyes were excluded for analysis for visual and refractive outcomes but were included in the analysis for EC change and complication rates.

Table 1. Baseline characteristics

Preoperative demographics	N	Mean	SD	Range [min ; max]	Percentiles		
					25	50	75
Age at implantation (years)	61	41.60	8.71	[25.34 ; 59.54]	35.07	41.89	47.12
MRSE (D)	61	6.64	1.85	[1.88 ; 10.50]	5.38	6.88	7.88
Implanted IF-pIOL power (D)	61	8.47	2.45	[2.50 ; 12.00]	6.50	9.00	10.25
Axial length (mm)	61	21.25	0.76	[19.47 ; 22.96]	20.87	21.23	21.59
ACD (mm)	61	3.30	0.28	[2.70 ; 3.91]	3.08	3.30	3.48
IOP (mmHg)	61	14.97	3.08	[7.00 ; 20.00]	12.00	15.00	18.00
CDVA (LogMAR)	61	0.09	0.21	[-0.18 ; 1.00]	0.00	0.00	0.10
Follow-up time (years)	61	10.55	3.92	[0.00 ; 15.09]	9.13	10.93	13.96
Endothelial cell density (cells/mm^2)	50	2818	410	[2009 ; 3721]	2500	2821	3188

MRSE=manifest refraction spherical equivalent; IF-pIOL=iris-fixated phakic intraocular lens; ACD=anterior chamber depth including corneal pachymetry; IOP=intraocular pressure; CDVA=corrected distance visual acuity; SD=standard deviation; min=minimum; max=maximum; D=diopters; mm=millimeters; N=number of eyes; mmHg= millimeters of mercury; logMAR= logarithmic angle of minimum resolution

Refractive Results

A total of 83% of eyes were within ±1.00 D from intended correction at 1 year follow-up. All eyes outside of this range were overcorrected (average overcorrection 0.40 ± 0.56 D); 90% of eyes were within ±1.00 D from emmetropia at 1 year follow-up (Figures 1 and 2).

The MRSE decreased significantly after implantation of the IF-pIOL from +6.43 ± 1.87 D preoperative to -0.22 ± 0.57 D at 1 year post-implantation (P < .001). The postoperative MRSE remained stable, with no statistically significant change throughout the follow-up period (Tables 2 and 3 and Figure 3).

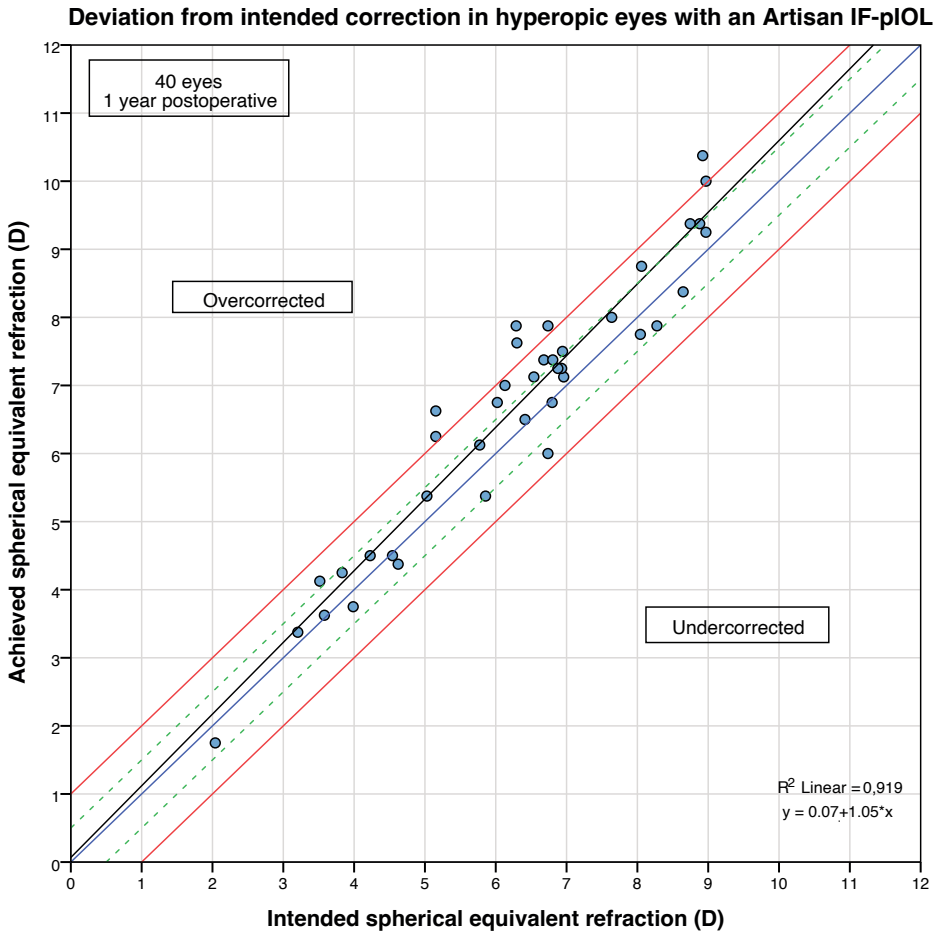

Figure 1. Predictability, deviation from intended correction 1 year after implantation of an Artisan iris-fixated phakic intraocular lens in hyperopic eyes in diopters. The red line represents 1.00 D deviation from intended correction, the green line represents 0.50 D deviation from intended correction, the blue line shows that $x = y$, and the black line is the interpolation line.

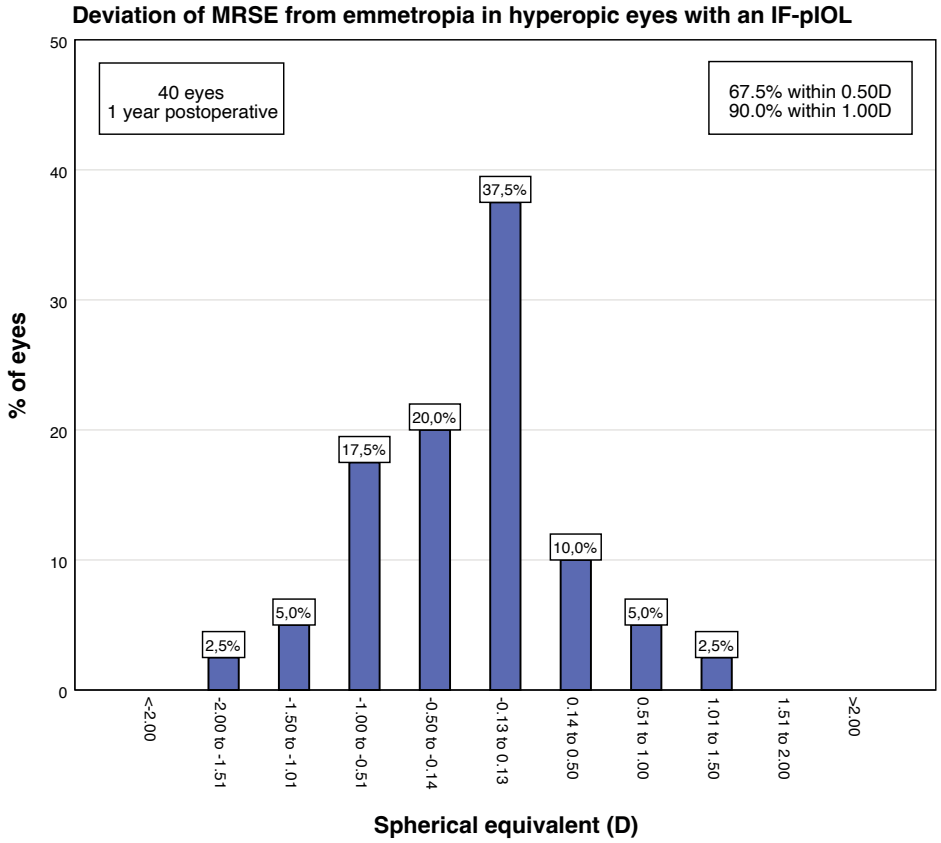

Figure 2. Deviation from emmetropia 1 year after implantation in hyperopic eyes implanted with an Artisan iris-fixated phakic intraocular lens

Visual Acuity

At 1 year, 5 years, 10 years, and 15 years after implantation the efficacy indexes were 0.73, 0.69, 0.66, and 0.72, respectively (Table 4 and Figure 4). The UDVA is plotted against time in Figure 5, A. Post-hoc testing with Bonferroni adjustment from 5 years postoperatively showed no statistically significant difference in UDVA at the different follow-up periods compared with that of the 1- year follow-up period. More details on UDVA can be found in Table 5. In addition, linear regression showed no statistically significant effect of time on UDVA (Table 3).

At 1 year, 5 years, 10 years, and 15 years after implantation the safety indexes were 0.98, 0.99, 1.10, and 1.02, respectively (Table 4). At 1 year postoperatively, the mean change of CDVA compared with preoperative was 0.01 ± 0.05 logarithmic angle of minimum resolution units, with 97.5% having no change in CDVA and no eye losing 2 or more lines in CDVA (Figure 6). At the final individual follow-up visit, 3 eyes (6.3%) had a decrease in CDVA of more than 2 Snellen lines, all due to cataract. The Kruskal-Wallis test revealed no statistically significant difference in CDVA between the different follow-up periods (p = .085). Similar to the UDVA, linear regression showed no statistically significant effect of time on CDVA. More details on CDVA can be found in Tables 3 and 6 and Figure 5, B.

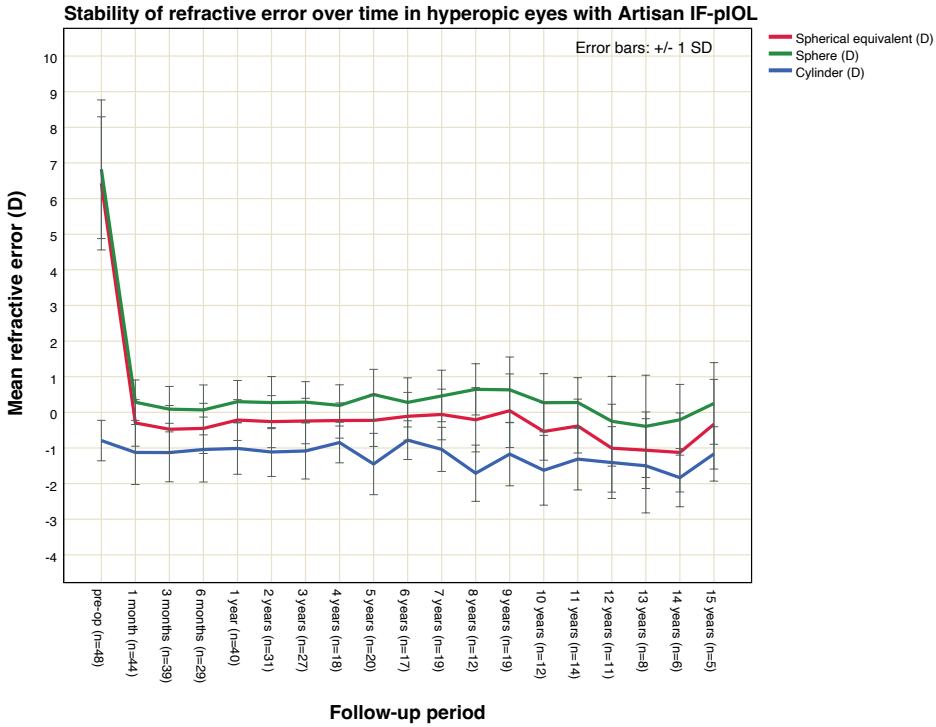

Figure 3. Stability of refractive error over time in hyperopic eyes with an Artisan iris-fixated intraocular lens.

Table 2. Manifest refraction spherical equivalent in hyperopic eyes implanted with an Artisan IF-pIOL

Follow-up period	N	Mean (D)	SD	Min ; Max	95% CI	p-value*
pre-op	48	6.43	1.87	1.88 ; 9.63	5.88 ; 6.97	<0.001
1 month	44	-0.30	0.65	-2.00 ; 1.63	-0.50 ; -0.10	1.000
3 months	39	-0.47	0.67	-2.00 ; 0.88	-0.69 ; -0.26	.999
6 months	29	-0.45	0.70	-1.75 ; 1.50	-0.72 ; -0.18	1.000
1 year	40	-0.22	0.57	-1.63 ; 1.13	-0.40 ; -0.03	-
2 years	31	-0.26	0.73	-1.75 ; 1.00	-0.53 ; 0.01	1.000
3 years	27	-0.24	0.64	-1.63 ; 0.88	-0.50 ; 0.01	1.000
4 years	18	-0.23	0.49	-1.50 ; 0.50	-0.48 ; 0.02	1.000
5 years	20	-0.23	0.73	-1.50 ; 1.38	-0.57 ; 0.12	1.000
6 years	17	-0.11	0.67	-1.88 ; 0.88	-0.45 ; 0.23	1.000∞
7 years	19	-0.06	0.71	-1.50 ; 1.00	-0.40 ; 0.28	1.000
8 years	12	-0.21	0.90	-1.88 ; 0.88	-0.78 ; 0.36	1.000
9 years	19	0.05	1.03	-2.00 ; 1.38	-0.45 ; 0.54	.999
10 years	12	-0.54	0.81	-2.00 ; 0.38	-1.05 ; -0.02	.999
11 years	14	-0.38	0.76	-2.00 ; 0.63	-0.82 ; 0.05	1.000
12 years	11	-1.01	1.23	-2.81 ; 1.00	-1.83 ; -0.18	.167
13 years	8	-0.87	1.14	-2.81 ; 0.63	-1.82 ; 0.08	1.000∞
14 years	6	-1.13	1.11	-2.63 ; 0.50	-2.29 ; 0.04	.306∞
15 years	5	-0.45	0.94	-1.50 ; 1.00	-1.62 ; 0.72	1.000∞

*Anova post-hoc Tukey HSD compared to 1 year postoperative. ∞ Mann-Whitney U compared to 1 year postoperative with Bonferroni correction; MRSE=manifest refraction spherical equivalent in diopters (D); SD=standard deviation; CI= confidence interval for mean; N=number of eyes; pre-op=preoperative; Min=minimum; Max=maximum; ; IF-pIOL=iris fixated phakic intraocular lens

Table 3. Estimated time slopes for main interest variables

Variable	β-time	95% CI	p-value*
MRSE post-implantation (D)	-0.005	[-0.018 ; 0.007]	0.391
CDVA (logMAR)	-0.001	[-0.002 ; 0.000]	0.068
UDVA (logMAR)	-0.003	[0.000 ; 0.005]	0.061
EC change (cells/mm^2)	-57.776	[-63.246 ; -52.305]	<0.001

*linear mixed model, a p-value of <0.05 is considered statistical significant. MRSE=manifest refraction spherical equivalent in diopters (D); CDVA=corrected distance visual acuity; UDVA=uncorrected distance visual acuity; EC=endothelial cell; CI=confidence interval; logMAR=logarithmic angle of minimum resolution; β-time= regression coefficient of follow-up time in years

Table 4. Safety and efficacy index per follow-up period

Period	N	Safety index [min ; max]	N	Efficacy index [min ; max]
1 month	43	0.94 [0.53 ; 1.20]	44	0.75 [0.33 ; 1.20]
3 months	39	0.93 [0.50 ; 1.20]	39	0.69 [0.36 ; 1.20]
6 months	29	0.94 [0.76 ; 1.20]	29	0.69 [0.38 ; 1.00]
1 year	40	0.98 [0.72 ; 1.20]	40	0.73 [0.42 ; 1.11]
2 years	31	0.96 [0.70 ; 1.20]	29	0.72 [0.30 ; 1.20]
3 years	27	1.00 [0.70 ; 1.20]	29	0.73 [0.40 ; 1.00]
4 years	18	0.98 [0.80 ; 1.26]	19	0.81 [0.42 ; 1.26]
5 years	20	0.99 [0.70 ; 1.20]	22	0.69 [0.30 ; 1.06]
6 years	18	1.02 [0.80 ; 1.33]	22	0.81 [0.50 ; 1.09]
7 years	19	1.00 [0.83 ; 1.27]	19	0.79 [0.50 ; 1.02]
8 years	14	1.05 [0.83 ; 1.27]	12	0.74 [0.42 ; 1.11]
9 years	19	1.04 [0.63 ; 1.33]	18	0.77 [0.38 ; 1.15]
10 years	12	1.10 [0.80 ; 1.64]	11	0.66 [0.41 ; 0.83]
11 years	14	1.06 [0.72 ; 1.45]	11	0.86 [0.41 ; 1.22]
12 years	11	0.94 [0.63 ; 1.15]	8	0.54 [0.22 ; 0.91]
13 years	8	0.91 [0.63 ; 1.15]	6	0.65 [0.34 ; 1.00]
14 years	6	0.99 [0.91 ; 1.05]	4	0.43 [0.37 ; 0.48]
15 years	5	1.02 [0.80 ; 1.45]	5	0.72 [0.32 ; 1.15]

N=number of eyes; min=minimum; max=maximum

Table 5. Details on uncorrected distance visual acuity in hyperopic eyes implanted with an Artisan IF-pIOL

Follow-up period	N	Median UDVA logMAR (dec)	Percentile 25	Percentile 75	Min ; Max	p-value*
pre-op	48	-	-	-	-	-
1 month	44	0.15 (0.71)	0.03	0.23	0.50 ; -0.08	-
3 months	39	0.16 (0.70)	0.10	0.30	0.52 ; -0.09	-
6 months	29	0.16 (0.70)	0.05	0.30	0.50 ; -0.08	-
1 year	40	0.16 (0.70)	0.04	0.22	0.42 ; -0.08	-
2 years	29	0.16 (0.70)	0.05	0.22	0.52 ; -0.08	-
3 years	29	0.12 (0.76)	0.05	0.28	0.42 ; -0.08	-
4 years	19	0.10 (0.80)	0.02	0.18	0.38 ; -0.10	-
5 years	22	0.19 (0.65)	0.06	0.30	0.52 ; -0.02	1.000
6 years	22	0.07 (0.86)	0.00	0.10	0.30 ; -0.08	0.200
7 years	19	0.09 (0.82)	0.05	0.12	0.32 ; 0.00	1.000
8 years	12	0.15 (0.72)	0.07	0.23	0.34 ; 0.00	1.000
9 years	18	0.07 (0.85)	0.04	0.20	0.52 ; 0.00	1.000
10 years	11	0.12 (0.76)	0.09	0.40	0.48 ; 0.02	1.000
11 years	11	0.04 (0.91)	0.00	0.24	0.48 ; -0.06	1.000
12 years	8	0.31 (0.49)	0.06	0.51	0.66 ; -0.04	1.000
13 years	6	0.23 (0.58)	0.06	0.41	0.42 ; 0.00	1.000
14 years	4	0.38 (0.42)	0.29	0.46	0.48 ; 0.26	0.051
15 years	5	0.06 (0.87)	0.04	0.20	0.50 ; -0.06	1.000

*Mann-Whitney U test compared to 1 year postoperative with Bonferroni correction. UDVA= uncorrected distance visual acuity in logMAR (Snellen equivalent); N=number of eyes; pre-op=preoperative; Min=minimum; Max=maximum; LogMAR= logarithmic angle of minimum resolution; IF-pIOL=iris-fixated phakic intraocular lens

Table 6. Details on corrected distance visual acuity in hyperopic eyes implanted with an Artisan IF-pIOL

Follow-up period	N	Median CDVA logMAR (dec)	Percentile 25	Percentile 75	Min ; Max	p-value*
pre-op	48	0.00 (1.00)	-0.03	0.04	0.12 ; -0.18	-
1 month	43	0.00 (1.00)	0.00	0.09	0.22 ; -0.08	-
3 months	39	0.00 (1.00)	0.00	0.07	0.30 ; -0.09	-
6 months	29	0.00 (1.00)	0.00	0.08	0.22 ; -0.08	-
1 year	40	0.00 (1.00)	-0.01	0.05	0.10 ; -0.10	-
2 years	31	0.00 (1.00)	-0.02	0.05	0.16 ; -0.08	-
3 years	27	0.00 (1.00)	-0.04	0.02	0.16 ; -0.08	-
4 years	18	0.00 (1.00)	-0.02	0.02	0.12 ; -0.14	-
5 years	20	0.00 (1.00)	0.00	0.06	0.16 ; -0.08	-
6 years	18	-0.03 (1.07)	-0.06	0.00	0.10 ; -0.20	1.000
7 years	19	0.00 (1.00)	-0.02	0.02	0.08 ; -0.08	1.000
8 years	14	0.00 (1.00)	-0.04	0.02	0.05 ; -0.16	1.000
9 years	19	-0.06 (1.15)	-0.08	0.07	0.20 ; -0.10	1.000
10 years	12	-0.03 (1.07)	-0.06	0.02	0.10 ; -0.22	1.000
11 years	14	0.00 (1.00)	-0.04	0.02	0.14 ; -0.16	1.000
12 years	11	0.04 (0.91)	-0.06	0.07	0.20 ; -0.14	1.000
13 years	8	0.03 (0.93)	-0.06	0.10	0.20 ; -0.06	1.000
14 years	6	0.01 (0.98)	-0.04	0.02	0.04 ; -0.10	1.000
15 years	5	0.00 (1.00)	-0.06	0.02	0.04 ; -0.16	1.000

*Mann-Whitney U test compared to 1 year postoperative with Bonferroni correction. CDVA=corrected distance visual acuity in logMAR (Snellen equivalent); N=number of eyes; pre-op=preoperative; Min=minimum; Max=maximum; LogMAR= logarithmic angle of minimum resolution; IF-pIOL=iris fixated phakic intraocular lens

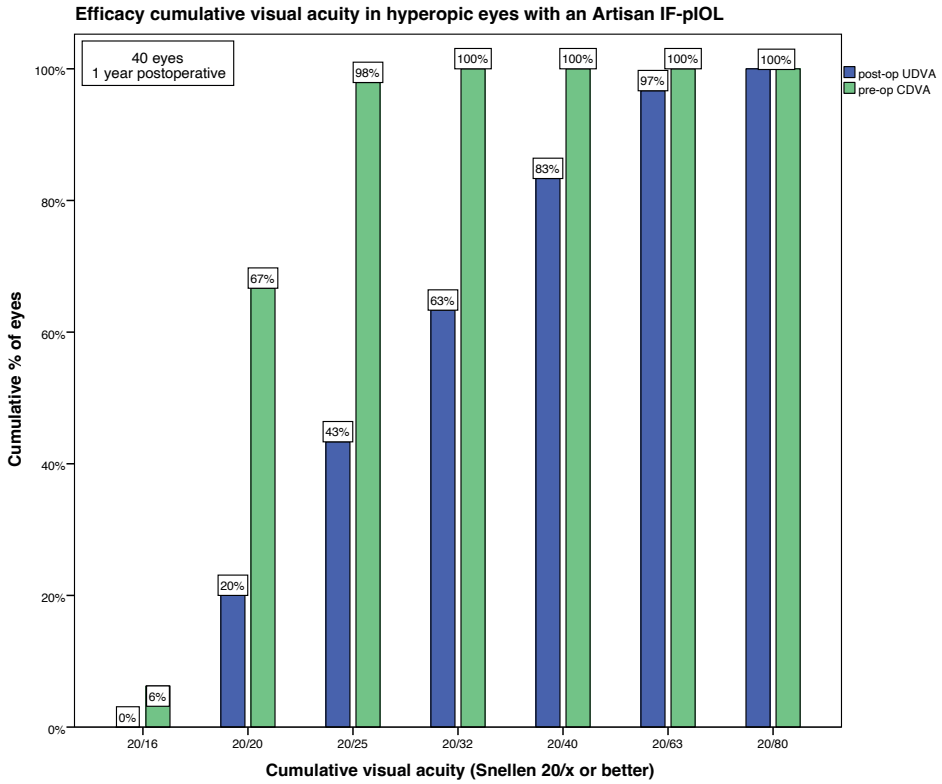

Figure 4. Efficacy at 1 year post-implantation of an Artisan iris-fixated intraocular lens in hyperopic eyes. The cumulative percentage of eyes with a preoperative CDVA (green bars) and postoperative UDVA (blue bars) is shown

Complications

Cataract

In 15 eyes (24.6%), a degree of cataract formation was noted, of which 73% was classified as nuclear. The mean time to cataract formation was 11.10 years (SD 2.17 years; range 8.44 to 14.55 years). The mean age at cataract formation was 55.70 years (SD 7.17; range 43.77 to 67.43 years). The cataract was clinically significant enough in 3 eyes (2 nuclear and 1 cortical combined with posterior capsule cataract) that phacoemulsification with concomitant IF-pIOL explantation and pseudophakic IOL implantation was performed, after 9.2 years, 13.1 years, and 12.6 years, respectively. The age of the patients at the time of explantation was 44.3, 61.5 years, and 62.2 years.

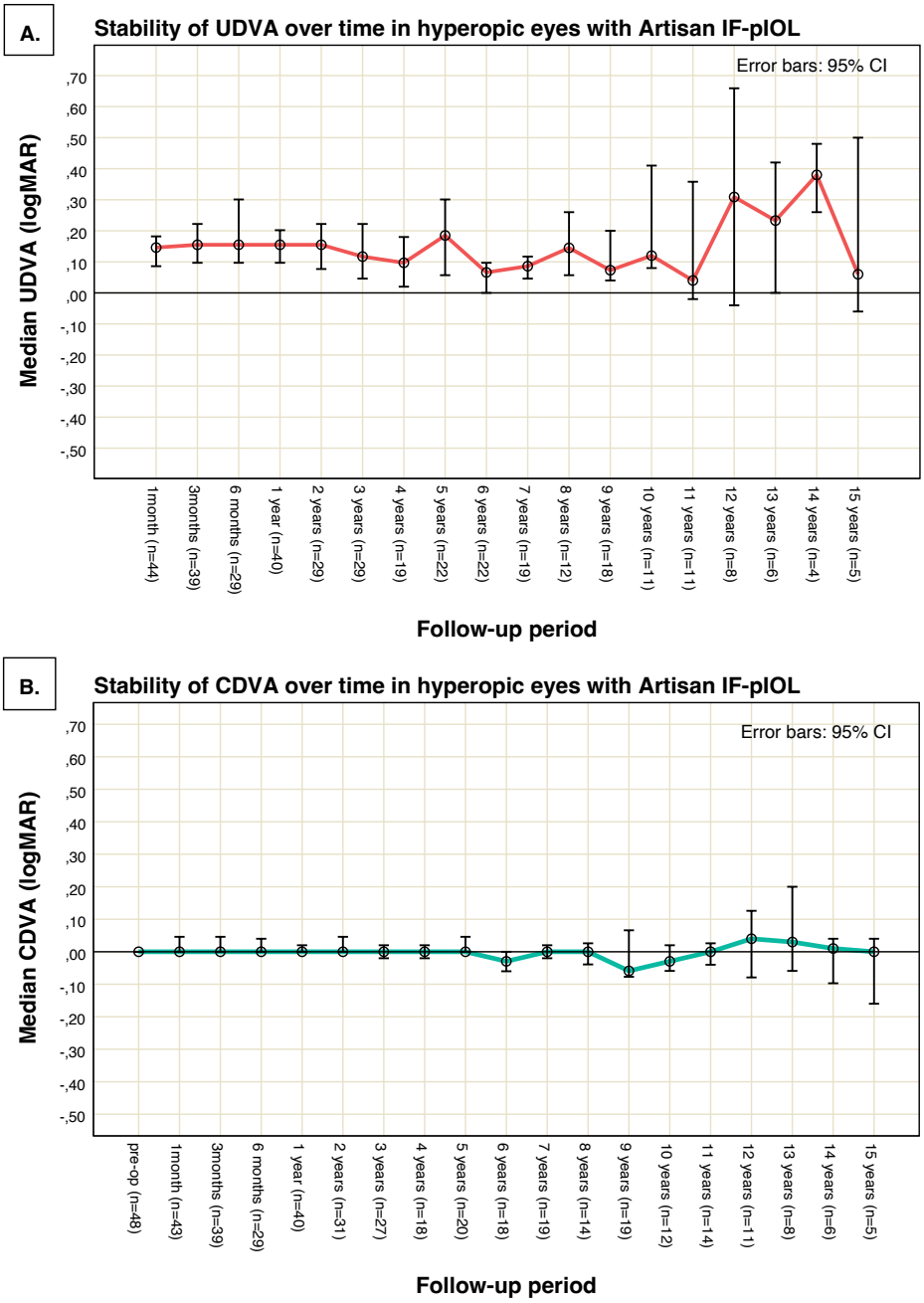

Figure 5. Stability over time of the (A) UDVA and (B) CDVA in hyperopic eyes implanted with an Artisan iris-fixated intraocular lens

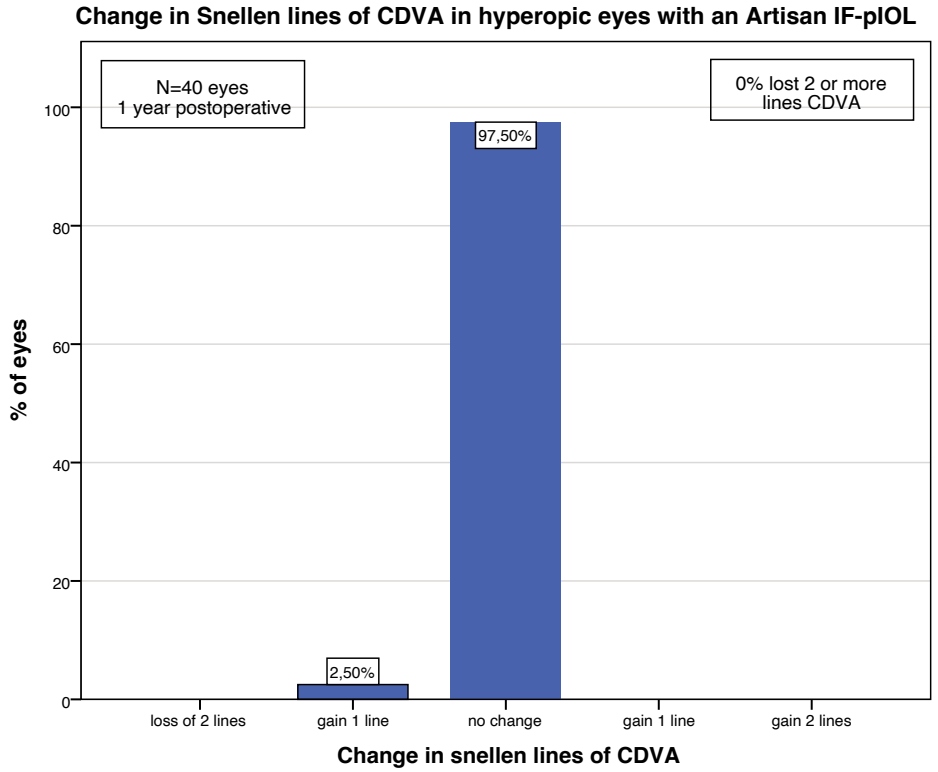

Figure 6. Bar graph demonstrating the change in Snellen lines of CDVA 1 year post-implantation compared with preoperative in hyperopic eyes with an iris-fixated phakic intraocular lens. One Snellen line change in CDVA equals 0.10 logMAR

Pigment Dispersion and Inflammation

Several degrees of inflammation and pigment dispersion with concomitant posterior synechiae formation were observed. Formation of posterior synechiae was noted in 11 eyes (18%) of 8 patients. Two eyes had an early uncontrollable inflammatory reaction that was unresponsive to medical therapy, which led to IF-pIOL explantation. In the other 9 eyes (14.8%), posterior synechiae formation occurred quietly, without active signs of inflammation, which led to explantation in 1 eye (Figure 7, A); none of the other 8 eyes experienced secondary elevation of intraocular pressure or loss of CDVA, and they are monitored strictly. The mean time to synechiae formation was 88.66 ± 65.77 months (range 0.62 to 161.05 months). The group with synechiae formation had a significantly shallower preoperative ACD compared with that of the group without synechiae formation: 3.09 ± 0.19 mm compared with 3.34 ± 0.28 mm (p = .006, *t*-test).

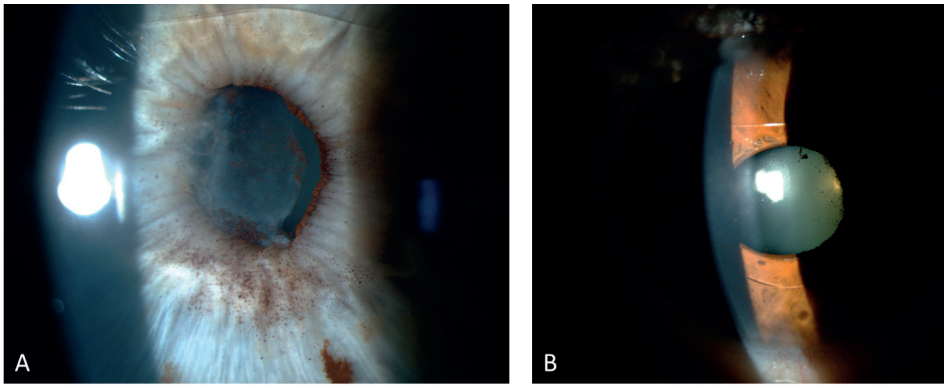

Figure 7. Photograph of a hyperopic eye with an Artisan iris-fixated phakic intraocular lens in situ and pigment dispersion. A: Severe pigment dispersion; note the pigment deposits, posterior synechiae, and the formation of a fibrin membrane over the iris and crystalline lens. B: Mild pigment dispersion; note the mild posterior synechiae and mild pigment deposits

EC Change

Figure 8 displays the EC change for all eyes during the different follow-up periods. A trend toward EC loss might be noticed from the box plot although the range per period is wide. Paired comparison (paired *t*-test) between preoperative and postoperative EC values are listed in Table 7. There is a statistically significant difference between preoperative ECD and 6 years, 7 years, 9 years, and 11 years postoperatively. Linear regression analysis showed a statistically significant effect of follow-up time on EC loss, indicating a decline in ECD of 58 cells/mm^2 per year (Table 3). Six eyes (9.8%) had an ECD of below 1500 cells/mm^2 at final individual visit after a mean of 10.63 ± 3.15 years. There was no statistically significant difference in preoperative ECD (P = .327), but the median preoperative and postoperative ACD in the group with less than 1500 cells/mm^2 was statistically significantly shallower compared with the eyes with an ECD of more than 1500 cells/mm^2 (P = .044 and P = .016, respectively) (Table 8). Four eyes have undergone IF-pIOL explantation due to EC loss, and 2 eyes are closely monitored with additional follow-up visits every 4 to 6 months. Overall, there was a mean increase of 38.81 ± 13.07 µm (range 17.00 to 73.00 µm) in CCT from 10 years postoperatively compared with preoperative values (P < .001, paired *t*-test). The reason for this increase is believed to be a measurement inconsistency caused by difference in measurement devices used for preoperative measurements and postoperative measurement of CCT (corneal specular microscope vs Pentacam). There was no statistically significant difference in CCT between the group with an ECD less than 1500 cells/mm^2 and the group with an ECD more than 1500 cells/mm^2 at the last postoperative visit (P = .139) (Table 8).

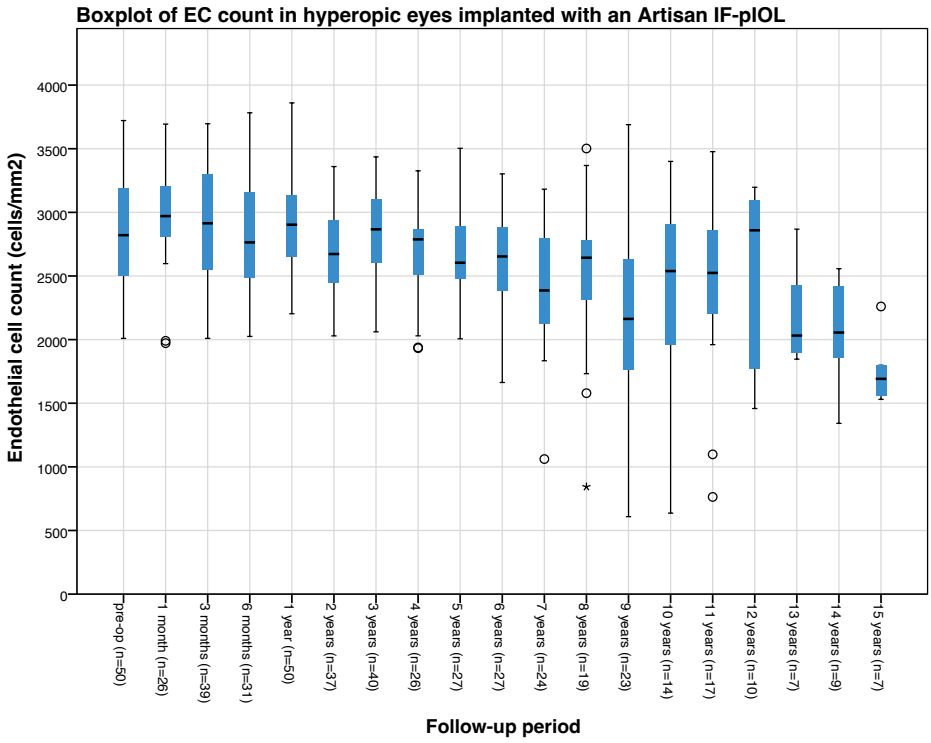

Figure 8. Box plots of all available endothelial cell count data over time in the study cohort of 61 hyperopic eyes with an Artisan iris-fixated phakic intraocular lens

Table 7. Paired endothelial cell counts before and after Artisan IF-pIOL implantation in hyperopic eyes

Period	N	Mean pre-op ECD ± SD	Mean post-op ECD ± SD	p-value	Yearly rate of loss (%)
pre-op	50	2818 ± 410	-	-	
1 month	22	2983 ± 397	2996 ± 442	1.000*	
3 months	33	2823 ± 429	2873 ± 485	1.000*	
6 months	27	2776 ± 407	2761 ± 467	1.000*	
1 year	40	2850 ± 392	2934 ± 412	0.744*	-3.98
2 years	29	2798 ± 346	2646 ± 383	0.114*	2.73
3 years	32	2953 ± 341	2843 ± 373	0.482*	1.24
4 years	19	2772 ± 407	2595 ± 397	0.214*	1.59
5 years	22	2917 ± 404	2692 ± 368	0.172*	1.54
6 years	20	2817 ± 334	2583 ± 416	0.014*	1.39
7 years	18	2823 ± 323	2397 ± 512	0.005*	2.16
8 years	13	2873 ± 470	2405 ± 742	0.130*	2.04
9 years	19	2863 ± 439	2108 ± 763	0.000*	2.93
10 years	13	2824 ± 467	2329 ± 768	0.108*	1.75
11 years	15	2976 ± 466	2441 ± 730	0.004*	1.63
12 years	9	2940 ± 487	2471 ± 742	1.000∞	1.33
13 years	7	2858 ± 221	2199 ± 393	0.420∞	1.77
14 years	8	2900 ± 393	2090 ± 438	0.176∞	2.00
15 years	6	2904 ± 158	1752 ± 267	0.416∞	2.64

*Paired *t*-test with Bonferroni correction; ∞Wilcoxon signed-rank test with Bonferroni correction. ECD=endothelial cell density in cells/mm^2; SD=standard deviation; N=number of available eyes; pre-op=preoperative; post-op =postoperative; CI 95= 95% confidence interval of the mean difference of preoperative ECC to mean postoperative ECC; %=annual percentage loss from preoperative (a positive number indicates a decline).

Table 8. Difference in anterior chamber depth , endothelial cell density and central corneal thickness in hyperopic eyes implanted with an iris-fixated phakic intraocular lens with endothelial cell densities below and above 1500 cells/mm² at last individual follow-up

Data	Eyes with ECD <1500 cells/mm²	Eyes with ECD >1500 cells/mm²	p-value*
N	5	45	0.327
Median pre-op ECD [range] (cells/mm²)	2606 [2226 ; 3188]	2826 [2009 ; 3121]	
25th percentile ; 75th percentile	2318 ; 2875	2505 ; 3191	
N	6	55	0.044
Median pre-op ACD [range] (mm)	3.09 [2.97 ; 3.21]	3.33 [2.70 ; 3.91]	
25th percentile ; 75th percentile	3.05 ; 3.20	3.10 ; 3.49	
N	5	38	0.016
Median post-op ACD [range] (mm)	2.78 [2.66 ; 2.90]	3.10 [2.57 ; 3.56]	
25th percentile ; 75th percentile	2.69 ; 2.80	2.89 ; 3.36	
N	5	36	0.139
Median post-op CCT [range] (µm)	535 [527 ; 572]	569 [459 ; 644]	
25th percentile ; 75th percentile	529 ; 562	544 ; 590	

*Mann-Whitney U test a value of <0.05 is considered statistically significant. ACD=anterior chamber depth from epithelium; ECD=endothelial cell density; CCT= central corneal thickness; pre-op=preoperative; post-op=postoperative; N=number of available eyes; mm=millimeters; µm=micrometers

Other Complications

At the last follow-up visit, no eye had developed glaucoma or ocular hypertension. No retinal complications developed.

Secondary Surgical Interventions

Repositioning

One IF-pIOL (1.6%) was repositioned 6 years after implantation to enlarge the iris enclavation site to prevent lens dislocation.

Explantation

IF-pIOL explantation with concomitant phacoemulsification and posterior chamber IOL implantation was performed after a mean of 8.13 ± 5.11 years (range 0.14 to 13.14 years) in 10 eyes of 7 patients (16.4%). A total of 4 IF-pIOLs (6.6%) were explanted due to EC loss after a mean of 10.77 ± 1.52 years, 3 (4.9%) due to early postoperative uncontrollable inflammatory reactions or pigment dispersion after a mean of 1.06 ±

1.29 years, and another 3 (4.9%) due to clinically significant cataract after a mean of 11.67 ± 2.14 years. Of the 4 eyes requiring explanation due to EC loss, all eyes had a post-explantation CDVA of 1.00 or better, no lines CDVA were lost compared with pre-IF-pIOL implantation, and corneal clarity is maintained. Of the 3 eyes explanted due to early uncontrollable inflammation or pigment dispersion, 1 eye lost 1 line of CDVA, and the other 2 eyes returned to baseline CDVA. The CDVA of all 3 eyes explanted due to cataract returned to baseline. At 10 years, 85% of the IF-pIOLs was still in situ, and after 15 years, 72% of the IF-pIOLs was still in situ. Figure 9 shows the survival curve of the Artisan hyperopic IF-pIOL of the study cohort.

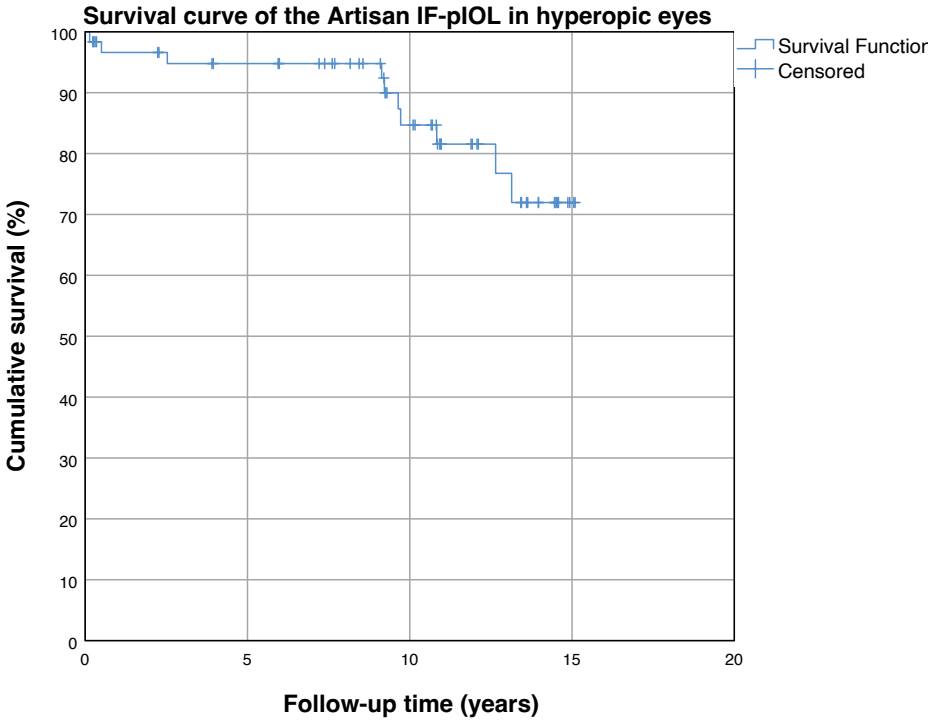

Figure 9. Kaplan-Meier curve showing the explantation/survival curve of the Artisan IF-pIOL in a cohort of 61 hyperopic eyes. Within the first 5 years, 3 IF-pIOLs were explanted due to inflammatory reactions or pigment dispersion. In the 5 years thereafter, 1 IF-pIOL was explanted due to cataract formation, and 2 due to excessive EC loss. After 10 years, 2 IF-pIOLs were explanted due to excessive EC loss and 2 IF-pIOLs due to cataract. IF-pIOL = iris-fixated phakic intraocular lens

DISCUSSION

The past 2 decades have shown that refractive errors can be successfully corrected with implantation of IFpIOLs.[3,9,13–16] Most of the findings, however, concern myopic correction. To date, there is a paucity of studies reporting long-term outcomes in hyperopic patients. In this study, we report the results of a cohort of 61 hyperopic eyes implanted with an Artisan IF-pIOL with a follow-up of up to 15 years. This is the first study, to our knowledge, to report such long-term results for the correction of hyperopic refractive error with an Artisan IF-pIOL.

The refractive predictability was good, with 90% of eyes having a post-implantation MRSE within ±1.00 D from emmetropia at the 1-year follow-up, without statistically significant changes during the follow-up period. Our results are comparable with previously published papers in predictability where rates between 64% and 97% have been reported to be within ±1.00 D of attempted correction.[2,3,5,9]

Visual results were favorable. We found a stable CDVA throughout the follow-up of up to 15 years, with concomitant good safety indices between 0.91 and 1.10. These high safety indices indicate that the expected minification effect of the retinal image after hyperopic correction did not significantly influence the CDVA, comparable with findings of the study by Alio et al.[2] Regarding efficacy, we found a wide range of UDVA from 0.42 to 0.91 Snellen. There was no statistically significant change in UDVA during follow-up. Although there is no statistically significant change in MRSE, there is a slight trend toward myopisation of the MRSE from 10 years onward (Figure 3). Age-related crystalline lens changes might lead to a change in MRSE, although it should be considered that this tendency toward myopisation might have been caused by a patient selection effect.

Clinically significant cataract formation occurred in 4.9% of eyes, which is in line with previously published articles.[17] Anterior capsular cataract could be a result of surgical trauma during enclavation or intermittent touch with the pIOL and crystalline lens; none of the eyes in this study developed anterior capsular cataract. This is in contrast with studies regarding the posterior chamber phakic implantable collamer lens (ICL) where anterior subcapsular cataract was described more often.[18,19] Similar to previously published literature on the IF-pIOL, the cataract in the patient population of this study was mainly of the nuclear sclerotic type.[20] Long-term population-based follow-up studies have provided evidence to support that hyperopia might increase the risk for nuclear cataract development compared with emmetropic eyes.[21] Earlier cataract formation in IF-pIOL-implanted hyperopic

eyes vs un-operated hyperopic eyes might be related to various factors such as the material of the IF-pIOL itself, metabolic effects, intermittent touch, or sterile intraocular (subclinical) inflammation processes.

This study showed a decrease of EC density over time and a wide range of data and an increasingly smaller sample size in later follow-up periods. Caution should be exercised in interpreting results because statistical tests might have limited power. In an earlier review and meta-analysis by us in hyperopic eyes, we found estimated annual loss of 65.5 cells/mm^2. Jonker et al. reported an annual decline of 48 cells/mm^2 and 61 cells/mm^2 in a myopic and toric IF-pIOL groups, respectively.[22,23] We found a comparable estimated overall decline of 58 cells/mm^2 per follow-up year after implantation of an IF-pIOL. The studies by Saxena et al. and Güell et al. reported on EC changes from 5.4% to 11.7% in the period of 2 to 4 years after IF-pIOL implantation in hyperopic eyes.[3,8] Literature on myopic eyes implanted with an IF-pIOL, with a follow-up of more than 7 years, reported an EC loss from 4.9% to 22.5%.[13,23–25] The result of this study, with a cumulative EC loss at 10 years of 17.5%, is comparable with these previously published articles.

EC loss seems a bigger concern with anterior chamber pIOLs compared with posterior chamber pIOLs because of the location of the pIOL and the proximity to the endothelium. It seems that, with ICL implantation EC loss occurs mainly during the first postoperative period and stabilizes thereafter.[18,26] With the IF-pIOL, EC loss might accelerate during long follow-up because the ACD might become shallower with increasing age. In this study, the annual percentage of EC loss remained within a stable range with a mean annual rate of 1.6% decline in ECD, which is comparable with the annual EC loss of 1.8% with the ICL reported by Packer.[27] To be able to compare the magnitude of EC loss, a detailed meta-analysis or comparison study between anterior and posterior chamber pIOLs with long-term follow-up would be of great value for the future. An ECD of below 1500 cells/mm^2 is considered an explantation criterion by the AFSSAPS (French Health Products and Safety Agency) and American Academy of Ophthalmology task force for recommendations on specular microscopy for pIOLs.[28,29] It is believed that this is a safe ECD to perform cataract surgery without compromising corneal clarity. In this study population, 6 eyes (9.8%) had an ECD of below 1500 cells/mm^2 after a mean of 10.63 years. In 2 of these 6 eyes, explantation was postponed after careful consideration of physician and patient. Corneal clarity is maintained in all 6 eyes with excellent CDVAs, although 3 eyes with EC densities between 500 and 800 cells/mm^2 are prone to corneal decompensation in the near future. Close monitoring of the corneal clarity and ECD is performed with an interval of 4 to 6 months and patients are explicitly

reminded not to rub their eyes. A shallower preoperative ACD was found in these eyes compared with the group with EC densities above 1500 cells/mm^2. Moreover, evidence has been provided by previous articles that a shallow and crowded ACD is related to higher rates of EC loss.[17,23,30–32]

Reliability of the evaluation of the corneal endothelium is a recurrent topic for discussion. Accurate and reliable EC analysis is not easy to perform. Reasons for imprecise EC measurements are known to be (1) the accuracy of operator–software interaction, (2) software precision, (3) specular reflection limitations leading to the generation of a low-quality image, (4) versatility for acquiring endothelial mosaic images, and (5) sampling processes.[33] Moreover, with long follow-up, change in equipment and analyzing technicians is inevitable. This poses a threat and weakness for long-term (retrospective) studies. Measurements acquired with different CSMs are prone to interchangeability problems. We discovered an interchangeability problem with the CSMs, the Topcon SP-2000P and SP-3000P, manufactured by the same company (Topcon Medical Systems). The interchangeability concern in this case was caused by software imprecision and erroneous calibration and led to a difference in ECD of up to 500 cells/mm^2. To increase the reliability of the EC measurements, we have incorporated a method we have described in detail elsewhere.[11] Using this method, we were able to (retrospectively) calculate a correction factor for ECD measurements performed by different specular microscopes, improving the reliability of the ECD measures for the purpose of longitudinal comparison. In future prospective trials, great attention should be given on evaluation of the corneal endothelium. EC mapping would ideally be integrated in the study protocol, enabling evaluation of EC loss in relation to the proximity of the pIOL to the corneal endothelium.

In this study population, 16.4% of the IF-pIOLs were explanted after a mean of 8.13 ± 5.11 years. With a predicted 72% of pIOLs still in situ after 15 years, we report a slightly better survival of the IF-pIOL than that reported in the study by Jonker et al.[17] EC loss was the main reason for IF-pIOL explantation (6.6%) and was comparable with the incidence reported by Jonker et al., who also reported EC loss to be the main reason for explantation of IF-pIOLs in hyperopic eyes.[17] Posterior synechiae formation with or without active signs of inflammation, however, was the most encountered complication. We observed posterior synechiae formation in 18% of the eyes. Previous articles reported from 6% up to 15% pigment dispersion and synechiae formation.[8,34] Noteworthy is that the study by Saxena et al. (15%) partly consists of the same eyes reported in this article. A high rate of pigment dispersion in 15 (68.2%) of 22 hyperopic eyes was described in a long-term ICL study by Kocova et al.[19] Although a selection bias might be present in their study, the incidence of pigment dispersion in hyperopic eyes

was significantly higher than that in myopic eyes, and they concluded that hyperopic eyes seem to be more prone to pigment dispersion because of their crowded anatomical ratios. A distinction should be made between immediate postoperative uveitis-like inflammatory reactions responsible for posterior synechiae formation and pigment deposits.[34] The immediate postoperative inflammatory uveitis-like reaction can usually be treated topically with steroids and mydriasis.[35] In cases of pigment dispersion after IF-pIOL implantation without active inflammatory signs, the only medical solution is to explant the IF-pIOL in seriously affected cases. In 2 eyes, an early postoperative active inflammatory reaction preceded and accompanied posterior synechiae formation. In the 9 other eyes (14.8%), synechiae formation developed in a quiet eye with no other signs of active inflammation. We found a mean time to synechiae formation of 7.38 ± 5.48 years after implantation. This silent formation of posterior synechiae is probably caused by abnormal pressure on the iris through being sandwiched between the crystalline lens and the IF-pIOL. Slowly progressive pigment dispersion might be due to progressive shallowing of the ACD because of age-related crystalline lens thickening, which in turn might be accompanied by a slow but progressive convex bowing of the iris, leading to abnormal iris compression between the posterior pIOL and anterior pole of the crystalline lens and a concomitant increase in stress on the enclavation sites. Messina et al. additionally hypothesized that enclavating the full thickness of the iris, including the iris pigment epithelium, might predispose eyes to pigment dispersion.[36] The slightly less concave shape of the hyperopic IF-pIOL might also play a role. We believe that the high incidence of pigment dispersion in the hyperopic IF-pIOL population is multifactorial. First, we found evidence that the preoperative ACD in eyes that developed synechiae was significantly shallower than eyes that did not develop synechiae. Additional statistical analysis revealed that 12.2% of the eyes with an ACD more than 3.0 mm measured from the epithelium developed synechiae, in contrast to 0% in eyes with an ACD of more than 3.0 mm measured from the endothelium (Appendices 6 and 7). We, therefore, recommend a slight adjustment in eligibility criteria where the minimum ACD should be measured from the corneal endothelium instead of the currently proposed safety guidelines in which the ACD is measured from the corneal epithelium. Second, iris configuration and/or a high crystalline lens rise might have contributed to the incidence of synechiae formation in this study because 4 eyes were recorded to have a subjective convex iris configuration, and in 5 of 11 eyes with posterior synechiae formation, the IF-pIOL was implanted before 1998, before iris configuration became a safety criterion.[34] Unfortunately, we were not able to retrospectively determine the crystalline lens rise in this study population because preoperative measurements of ACD were mostly performed with A-scan biometry. Further studies are needed to evaluate to what extend each of these previous and possible other, still unknown, factors contribute to pigment dispersion.

It should be considered that selection bias and variations in examination protocols, material, and technicians because of a long follow-up period might have influenced the results of the outcome variables. Patients who forget regular follow-up visits might have fewer complaints, resulting in overestimating complication rates in this study. Still, in the preoperative informed consent of eligible patients, the risk for pigment dispersion, EC loss, and cataract formation should be included. Because lifelong yearly follow-up visits are a mandatory safety requirement, patients and physicians should make an agreement on how to meet this obligation.

In conclusion, the visual and refractive results after IF-pIOL implantation to correct hyperopia were good and stable for 15 years. EC loss was the main reason for IF-pIOL explantation, which underlines the need for mandatory lifelong monitoring of EC counts. An estimated annual EC loss of 58 cells/mm^2 was found in this study, indicating a careful assessment of the minimum required age-dependent ECD preimplantation. Care should be taken when considering implanting and monitoring an IF-pIOL in a hyperopic eye because pigment dispersion might present an additional problem in hyperopic eyes seldom seen in myopic eyes. The mechanism behind this remains unclear. Until we have a better understanding of the mechanism behind the development of pigment dispersion with an IF-pIOL in place, we recommend an ACD more than 3.0 mm measured from the corneal endothelium and to closely evaluate and monitor the anterior chamber dimensions with modern anterior chamber imaging techniques, in addition to a proper and careful enclavation technique.

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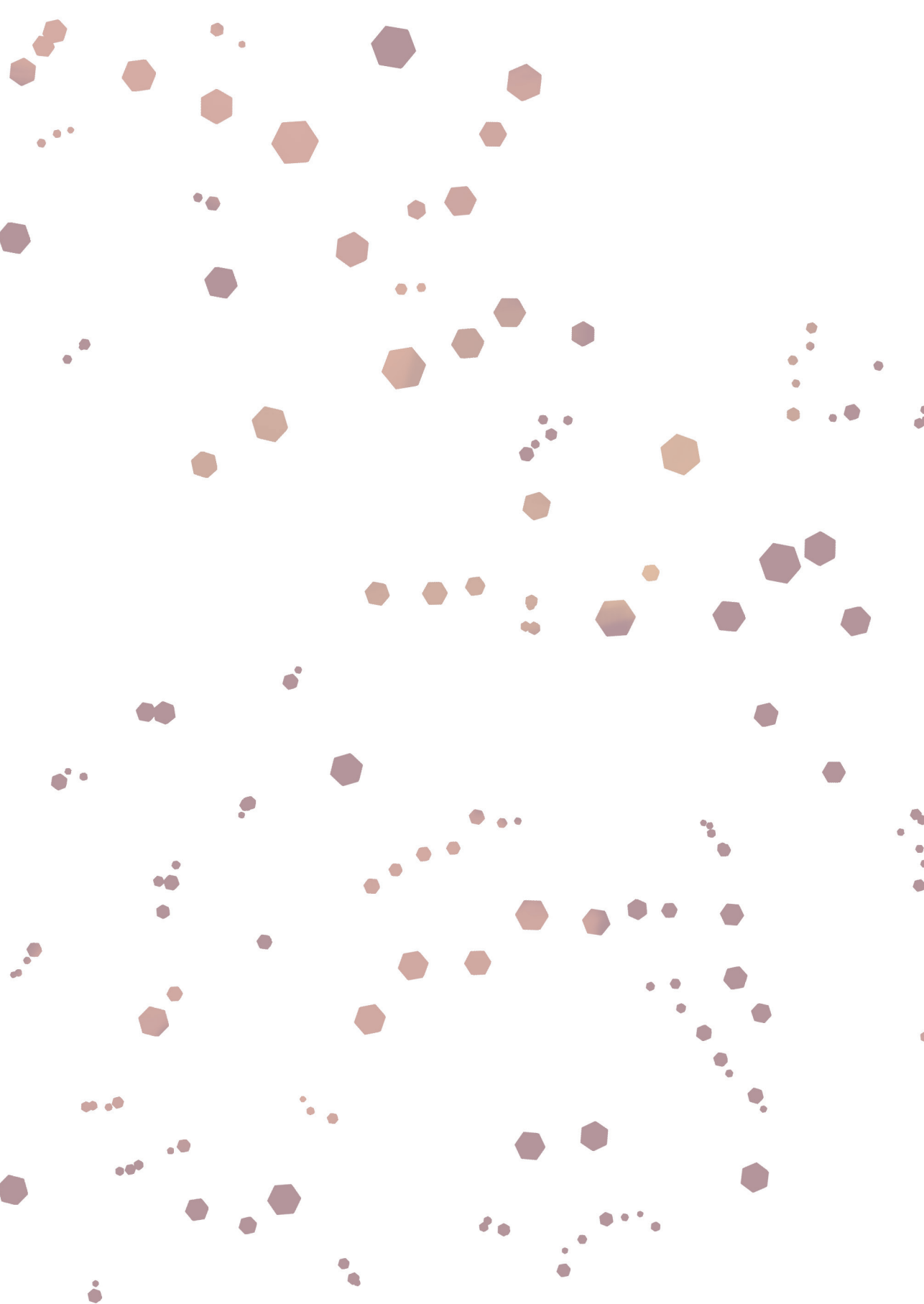

Chapter 4

Implantation of an Iris-Fixated Phakic Intraocular Lens for the Correction of Myopia: a Follow-Up Study of up to 22 Years

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Submitted

ABSTRACT

Purpose

To assess the predictability, efficacy, stability and safety of implanting an Artisan (Ophtec BV, the Netherlands) iris-fixated phakic intraocular lens (IF-pIOL) for the correction of myopia with a follow-up of up to 22 years.

Design

Retrospective observational study

Methods

Patients operated by a single surgeon between 1997 and 2007 were identified. Data was collected on refraction, visual acuity, endothelial cell (EC) density and complications.

Results

A total of 273 eyes (149 patients) were analyzed with a mean follow-up of 12.21 ± 4.33 years. The median refractive error decreased from -11.00 D [95CI -22.38 ; -6.50] pre-implantation to -0.25 D [95CI -1.63 ; 0.00] 6 months post-implantation. During the follow-up, we found a slight, but statistically significant, myopisation of 0.03 D per year. There was a significant gain ($p<0.001$) in corrected distance visual acuity (CDVA) of 0.07 ± 0.08 logMAR within the first 2 years of follow-up compared to preoperative CDVA. Thereafter, the CDVA remained stable. All mean safety indices were above 1.10 up to 22 years of follow-up. A yearly EC loss of 56.2 cells/mm^2 was found ($p<0.001$). In 69 eyes (25.0%), IF-pIOL explantation was performed after a mean time of 11.94 ± 5.50 years. The main reason for IF-pIOL explantation was cataract.

Conclusion

Visual and refractive results after IF-pIOL implantation to correct myopic refractive error are positive with high safety indices up to 22 years of follow-up. Lifelong monitoring of the corneal endothelium is mandatory with an IF-pIOL in place.

INTRODUCTION

Phakic intraocular lens (pIOL) implantation is a surgical method to correct highly myopic eyes of patients who are contact lens intolerant and dissatisfied with the quality of their vision with spectacles. PIOL implantation involves placing an intraocular lens either in the anterior or posterior chamber of the eye, without manipulating the crystalline lens and thereby preserving the eye's accommodative function. Three pIOLs are currently approved for correction of high myopia: the posterior chamber Implantable Collamer Lens (STAAR Surgical, USA), the Implantable Phakic Contact Lens (Caregroup Sight Solutions, India) and the anterior chamber iris-fixated pIOL (IF-pIOL) Artisan (Ophtec BV, the Netherlands) or the identical Verisyse (AMO, USA). The IF-pIOL has been implanted for the correction of refractive errors since the 1990s.[18,28] Short-, middle- and long-term studies of up to 10 years after IF-pIOL implantation in myopic eyes have been published.[17,29-36] The aim of this study is to report our findings on the correction of myopic refractive error with an Artisan IF-pIOL with a follow-up period of up to 22 years.

METHODS

Study Population

This is a retrospective observational cohort study where medical charts were reviewed to identify patients who had undergone an Artisan IF-pIOL implantation by a single surgeon (GL) between 1997 and 2007 in either the Leiden or the Erasmus University Medical Center the Netherlands for the correction of myopic refractive error.

The study was approved by the Medical Ethical Committee of the Leiden University Medical Center and was conducted in accordance with the Declaration of Helsinki. Eligible patients signed an informed consent form.

To assess predictability, efficacy, safety, stability and complication rate, data was collected on corrected distance visual acuity (CDVA) and uncorrected distance visual acuity (UDVA), refraction, endothelial cell (EC) density, complications and secondary surgical interventions.

Patient selection

As per safety guidelines of the manufacturer, at the time of implantation all patients had to 1) have a good general health status, 2) be at least 18 years of age, 3) have had a stable myopic refraction for at least 1 year, 4) have a central EC density of > 2000 cells/mm^2, and 5) have an anterior chamber depth (ACD) of at least 2.6 mm. Following a revision of the safety criteria, a minimum ACD of 3.0 mm (measured from the corneal epithelium) was applied, and a convex iris configuration was considered an exclusion criterion from 1998 onwards. Other exclusion criteria for IF-pIOL implantation were an intraocular pressure (IOP) >23mmHg and/or glaucoma. Data from regular follow-up visits was collected at 1, 3 and 6 months post-operation, and yearly thereafter.

PIOL power calculations were performed with the Van der Heijde formula.[27] This formula uses the mean corneal curvature (Kmean), the adjusted ACD, and the patient's manifest refraction spherical equivalent (MRSE) at a vertex distance of 12.0 mm. A factor of 0.6 for the effective lens position was applied.

Due to changes in equipment throughout the years, EC measurements were performed with 3 different versions of the Topcon SP series of the corneal specular microscope (Topcon Medical Systems, Tokyo, Japan) (CSM): SP1000, SP2000P, and SP3000P. To increase the reliability of the EC counts that were originally acquired and analyzed with different corneal specular microscopes, converting factors were calculated and applied. Details are described elsewhere.[37]

The surgical procedure as described by Saxena et al. was used for all patients included in this study.[22]

Statistical Analysis

Outcome variables were tested for normality with the Shapiro-Wilk test. The paired *t*-test and the chi-square test for independence were used to compare preoperative to postoperative data and to compare the difference between the two groups. One-way analysis of variance (ANOVA) with post-hoc Tukey HSD was applied to compare the differences between the follow-up periods. When data was not normally distributed or the number of eyes was smaller than 10, a Wilcoxon signed-rank test was used to compare pre- and postoperative data, and a Kruskal-Wallis Test with post-hoc Mann-Whitney U was used to compare the differences between the follow-up periods. When multiple comparisons were carried out, a Bonferroni correction was applied. Additionally, a linear mixed model was used to examine the development over time of our main parameters of interest: CDVA, UDVA, MRSE and EC counts. As a fixed effect in our model, follow-up time was measured in years. As random effects, we entered 'patient' and 'eye within patient' to estimate an intercept of each eye within each patient (i.e. individual slopes). This technique enabled us to make full use of all data gathered. A p-value of <0.05 was considered statistically significant. Statistics were performed in SPSS (IBM SPSS version 23 for Windows). In the predictability graph, the coefficient of determination (R^2) is given as a summary statistic to quantify the goodness-of-fit of the regression line.

Data on VA was converted to logarithm of the minimum angle of resolution (logMAR) units for calculation purposes. The MRSE was calculated by using the subjective refraction based on the formula: MRSE in diopters (D) = Sphere (S) + (0.5 x (Cylinder(C)). The efficacy index (EI) is the ratio of mean postoperative UDVA (decimal) to mean preoperative CDVA (decimal). The safety index (SI) is the ratio of mean postoperative CDVA (decimal) to mean preoperative CDVA (decimal). To allow for comparisons with previously published literature, EC density change was defined as the paired difference between the preoperative and postoperative examination and is expressed as an annual change in percentage from the preoperative cell density.

Amblyopic eyes, defined as a preoperative CDVA of <0.40 Snellen or a difference of >2 Snellen lines in CDVA compared to the fellow eye, in an ametropic but otherwise normal eye, were excluded from the analysis of visual and refractive outcomes but were included in the analysis of EC change and complication rates.

Results are given in two-year intervals. The early postoperative follow-up period (up to 6 months) is shown in order to be able to detect surgically induced changes in refraction and EC count: time point (T) 0=preoperative, T1=1 month, T2=3 months T3=6 months, T4=1-2 years (0.50 to 2.49), T5=3-4 years (2.50 to 4.49), T6=5-6 years (4.50 to 6.49), T7=7-8 years (6.50 to 8.49), T8=9-10 years (8.50 to 10.49), T9=11-12 years (10.50 to 12.49), T10=13-14 years (12.50 to 14.49), T11=15-16 years (14.50 to 16.49), T12=17-18 years (16.50 to 18.49), T13=19-20 years (18.50 to 20.49), T14=21-22 years (20.50 to 22.49).

RESULTS

Study Population

Two hundred and four patients (374 eyes) underwent IF-pIOL implantation between 1997 and 2007. Fifty-four patients (25.9%) (97 eyes) were lost to follow-up, of which 1 patient died. Two patients (1%) (4 eyes) refused to participate. A total of 149 patients (73.0%) (273 eyes) were analyzed. There was no significant difference between the baseline parameters of the group that was lost to follow-up and the group that is reported (Table 1).

Of the 149 patients, 32.9% (49 patients, 91 eyes) were male and 67.1% (100 patients, 182 eyes) were female. There were 135 right eyes (49.5%) and 138 left eyes (50.5%). In 25 patients, only 1 eye was included for analysis as the fellow eye was implanted with either a toric (10 eyes) or flexible IF-pIOL (6 eyes), or only 1 eye was implanted with an IF-pIOL for the correction of anisometropia (8 eyes), and 1 patient declined surgery for the second eye. The mean follow-up time was 12.21 ± 4.33 years (range 0.06-21.55 years). Nineteen eyes (6.9%) met our criteria for amblyopia. These 19 eyes were excluded from analysis of visual and refractive outcomes but were included in the analysis of EC change and complication rates. Thus, 254 eyes were analyzed for refractive and visual results, and 273 eyes for EC change and complication rates.

Refractive Results

Predictability

Seventy-seven percent of the eyes were within 1.00 D of the intended correction at T4. Eighty-six percent of the eyes had a postoperative MRSE within 1.00 D of emmetropia at T4. See Figures 1 and 2. There was a mean under-correction of -0.50 ± 0.73 D. Of the 7 eyes (3.0%) having a postoperative MRSE <-2.00 D, 1 eye (0.4%) could not be fully corrected with the available IF-pIOL powers due to a high preoperative refractive error of -31.00 D, and in 1 eye (0.4%) the pIOL was exchanged for a toric IF-pIOL after which the postoperative MRSE was within 0.5D of emmetropia. Of the other 5 eyes (2.1%) with a postoperative MRSE <-2.00 D of emmetropia, 3 eyes (1.3%) deviated more than 2.00 D from the intended correction; no satisfactory explanation for this deviation could be found.

Table 1. Preoperative demographics of the analyzed and non-analyzed sample

	Preoperative demographics of analyzed sample				
	N	**Median**	**Range [min ; max]**	**Percentiles**	
				25	**75**
Age at implantation (years)	273	38.83	[17.97 ; 61.18]	31.50	45.82
MRSE (D)	273	-11.25	[-32.50 ; -4.88]	-14.50	-9.13
Implanted IF-pIOL power (D)	273	-12.00	[-23.50 ; -5.50]	-15.00	-10.00
Axial length (mm)	273	27.68	[23.69 ; 37.27]	26.50	29.06
ACD (mm)	273	3.72	[2.86 ; 4.70]	3.47	3.91
CDVA (LogMAR)	273	0.05	[-0.18 ; 1.70]	0.00	0.18
Endothelial cell density (cells/mm$^{2)}$[§]	243	2821	[1824 ; 3754]	2609	3087
Keratometry (D)	273	43.81	[39.94 ; 49.19]	42.75	44.81
Intraocular pressure (mmHg)	271	15.00	[8.00 ; 23.00]	14.00	17.00
Gender (%) (male : female)	273	-	[33.33 ; 66.67]	-	-

*Mann-Whitney U test; [∞]Continuity Correction; a p-value of <0.05 is considered statistically significant. MRSE=manifest refraction spherical equivalent; IF-pIOL=iris-fixated phakic intraocular lens; ACD=anterior chamber depth including corneal pachymetry;

Change in manifest refraction spherical equivalent

The MRSE decreased significantly after implantation of the IF-pIOL from preoperative -11.00 D [95CI -22.38 ; -6.63] to -0.31 D [95CI -1.63 ; 0.13] at T4 (p<0.001). There was a slight but statistically significant change in postoperative MRSE with a mean decrease of -0.029 D per follow-up year (p<0.001) (Figure 3, and Tables 2 and 3). There was a small but statistically significant increase in axial length of 0.030 mm per year (p<0.001) (Table 3).

Visual Acuity

Uncorrected distance visual acuity and efficacy

At T4, T8 and T13, the EIs were 0.96, 0.85 and 1.02 respectively (see also Table 4 and Figure 4). At T4, T6, T8 and T11, the median UDVA was 0.07 (0.85), 0.15 (0.71), 0.13 (0.74) and 0.05 (0.89) logMAR (Snellen), respectively (Table 5). The UDVA is plotted against time in Figure 5A. Although linear regression showed a statistically significant effect of time on UDVA (p<0.001), the magnitude of 0.005 logMAR change in UDVA is clinically insignificant (see Table 3).

Preoperative demographics of non-analyzed sample					Difference
N	Median	Range [min ; max]	Percentiles		p-value*
			25	75	
97	40.00	[17.91 ; 60.82]	28.18	47.53	0.950
97	-10.75	[-33.00 ; -4.13]	-13.38	-8.50	0.246
97	-12.00	[-23.00 ; -4.50]	-14.00	-9.50	0.359
97	27.56	[24.50 ; 34.60]	26.25	29.27	0.551
97	3.68	[3.09 ; 4.43]	3.50	3.85	0.188
97	0.05	[-0.10 ; 1.30]	0.00	0.20	0.855
83	2908	[1753 ; 3755]	2612	3136	0.504
97	43.63	[39.50 ; 46.94]	42.81	44.88	0.800
96	16.00	[9.00 ; 17.00]	13.50	17.00	0.255
97	-	[34.0 ; 66.0]	-	-	0.694[∞]

CDVA=corrected distance visual acuity; SD=standard deviation; min=minimum; max=maximum; D=diopters; mm=millimeters; N=number of eyes; mmHg=millimeters of mercury; logMAR= logarithm of the minimum angle of resolution. [§]Uncorrected endothelial cell density

Corrected distance visual acuity and safety

At T4, T8 and T13 post-implantation, the SIs were 1.19, 1.21 and 1.20, respectively (Table 4). The Kruskal Wallis Test revealed a statistically significant difference in CDVA between follow-up periods ($p<0.001$). There was a significant gain in CDVA at T4 of 0.07 ± 0.08 logMAR compared to preoperation ($p<0.001$). The CDVA remained stable hereafter. Additional linear regression showed no statistically significant effect of time on postoperative CDVA ($p=0.634$). More details on CDVA can be found in Figure 5B and Tables 3 and 6. At T4, 73.6% of eyes had no change in CDVA and 24.7% gained 1 or more Snellen lines of CDVA (Figure 6). By this time, 1 eye (0.4%) had lost 2 lines of CDVA due to nuclear cataract development. Phacoemulsification with IOL implantation was performed and a gain in CDVA of 2 lines compared to pre-IF-pIOL implantation was achieved. At the final follow-up visit, 9 eyes (3.5%) showed a decrease in CDVA of more than 2 Snellen lines; in 6 eyes (2.4%), the reason was cataract, in 2 eyes (0.8%) this was due to macular neovascularization, and in 1 eye (0.4%) this was due to a retinal detachment with macular hole.

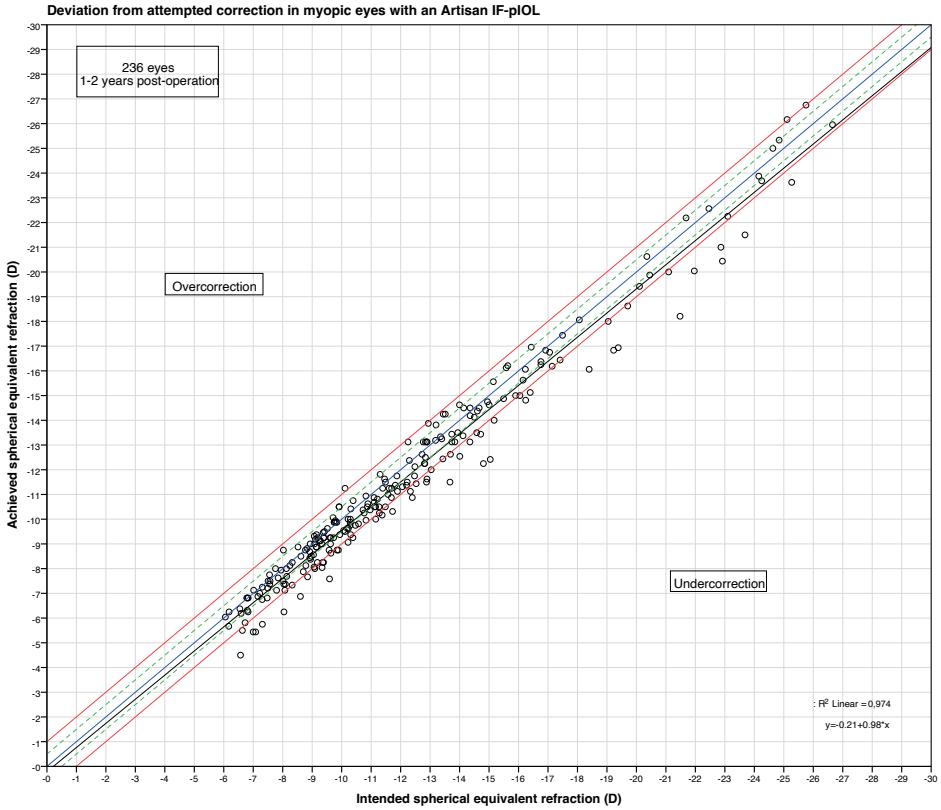

Figure 1. Predictability, deviation from intended correction after implantation of an iris fixated phakic intraocular lens (IF-pIOL) in myopic eyes. The red line represents 1.00 D deviation form intended correction, the green dotted line 0.50 D deviation from intended correction. D=diopters

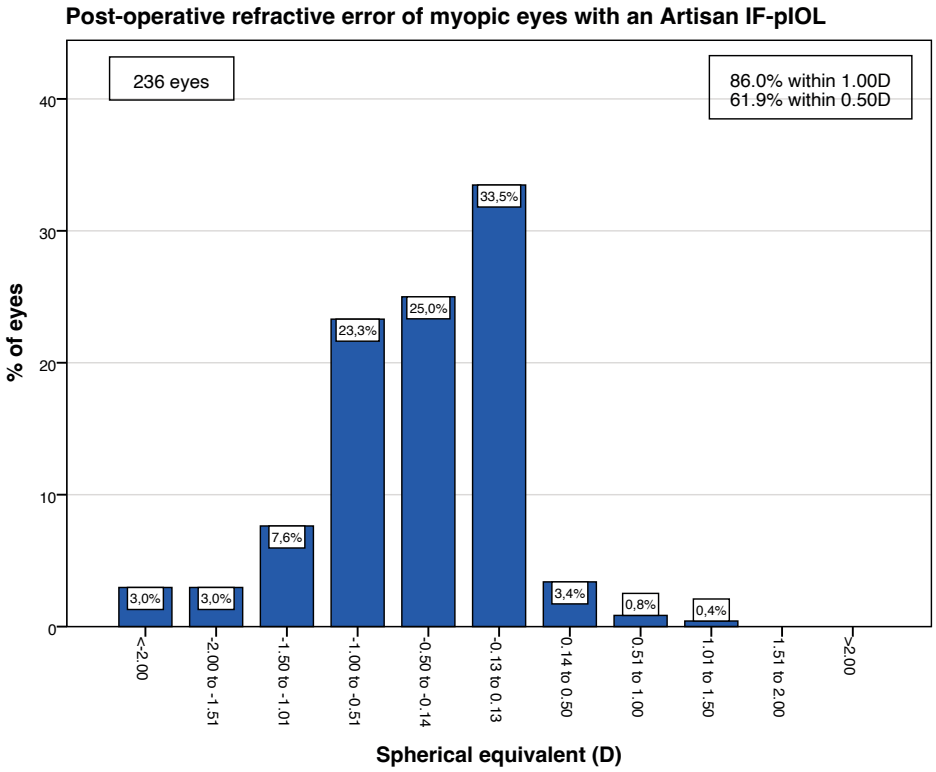

Figure 2. Deviation from emmetropia at T4 (1-2 years postoperative) in myopic eyes implanted with an iris fixated phakic intraocular lens (IF-pIOL). D=diopters; %=percentage of eyes

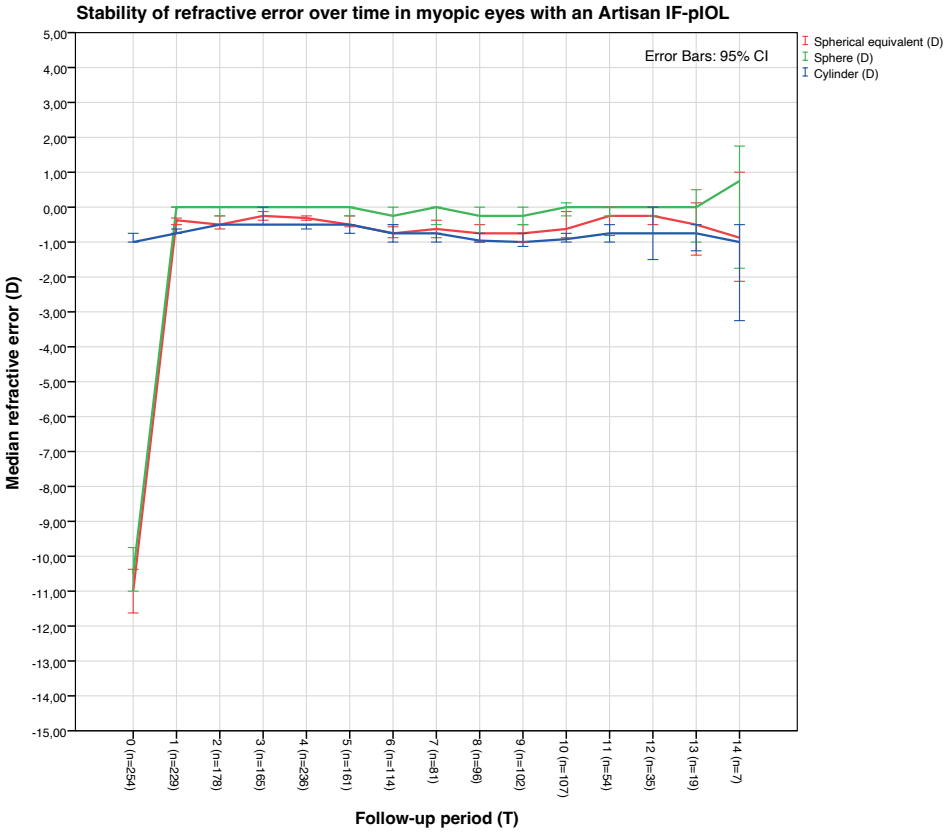

Figure 3. Stability of refractive error over time in myopic eyes with an Artisan IF-pIOL. D=diopters; pre-op=preoperative; n=number of eyes; T=time-point; T0= preoperative; T1= 1 month, T2= 3 months T3=6 months, T4= 1-2 years, T5= 3-4 years, T6= 5-6 years, T7= 7-8 years, T8= 9-10 years, T9= 11-12 years, T10= 13-14 years, T11= 15-16 years, T12= 17-18 years, T13= 19-20 years, T14= 21-22 years

Table 2. Manifest refraction spherical equivalent in myopic eyes implanted with an IF-pIOL

Follow-up period	N	MRSE (D) Median	Percentile 25	Percentile 75	Range [min ; max]	p-value*
pre-op (T0)	254	-11.00	-14.00	-9.13	[-31.00 ; -4.88]	<0.001
1 month (T1)	229	-0.38	-0.75	0.00	[-5.38 ; 0.75]	-
3 months (T2)	178	-0.50	-1.00	0.00	[-5.00 ; 0.88]	-
6 months (T3)	165	-0.25	-0.75	0.00	[-5.38 ; 0.50]	-
1-2 years (T4)	236	-0.31	-0.75	0.00	[-5.04 ; 1.06]	-
3-4 years (T5)	161	-0.50	-1.00	0.00	[-4.63 ; 1.13]	1.000
5-6 years (T6)	114	-0.75	-1.25	-0.25	[-4.00 ; 0.81]	<0.001
7-8 years (T7)	81	-0.63	-1.25	0.00	[-6.75 ; 1.50]	0.184
9-10 years (T8)	96	-0.75	-1.69	-0.13	[-4.13 ; 1.08]	0.001
11-12 years (T9)	102	-0.75	-1.50	0.00	[-6.00 ; 1.38]	0.004
13-14 years (T10)	107	-0.63	-1.63	0.00	[-7.38 ; 2.00]	1.000
15-16 years (T11)	54	-0.25	-1.25	0.06	[-4.25 ; 1.63]	1.000
17-18 years (T12)	35	-0.25	-1.00	0.00	[-5.19 ; 1.75]	1.000
19-20 years (T13)	19	-0.50	-1.38	0.13	[-2.13 ; 2.00]	1.000
21-22 years (T14)	7	-0.88	-1.38	0.50	[-2.13 ; 1.00]	1.000

*Mann-Whitney U compared to T4 (1-2 years post-implantation) with Bonferroni correction. A p-value of <0.05 is considered statistically significant. MRSE= manifest refraction spherical equivalent; N=number of eyes; pre-op=preoperative; min=minimum; max=maximum; D=diopters; IF-pIOL=iris-fixated phakic intraocular lens; T=time point

Table 3. Estimated time slopes for main interest variables

Main interest variable	β-time	95% CI	p-value*
MRSE post-implantation (D)	-0.029	[-0.035 ; -0.022]	<0.001
CDVA (logMAR)	0.000	[-0.001 ; 0.000]	0.634
UDVA (logMAR)	0.005	[0.003 ; 0.007]	<0.001
EC change (cells/mm^2)	-56.19	[-58.730 ; -53.645]	<0.001
Axial length (mm)	0.030	[0.023 ; 0.037]	<0.001

*Linear mixed model; a p-value of < 0.05 is considered statistically significant.
MRSE=manifest refraction spherical equivalent; CDVA=corrected distance visual acuity; UDVA=uncorrected distance visual acuity; EC=endothelial cell; CI=confidence interval; logMAR=logarithm of the minimum angle of resolution; D=diopters; β-time=regression coefficient of follow-up time in years; mm=millimeters

Table 4. Safety and efficacy index per follow-up period

Follow-up	N	Safety index [min ; max]	N	Efficacy index [min ; max]
1-2 years (T4)	236	1.19 [0.68 ; 2.18]	238	0.96 [0.17 ; 2.00]
3-4 years (T5)	163	1.17 [0.70 ; 2.28]	179	0.89 [0.08 ; 1.88]
5-6 years (T6)	116	1.17 [0.48 ; 2.47]	124	0.84 [0.08 ; 1.80]
7-8 years (T7)	85	1.21 [0.50 ; 1.96]	86	0.82 [0.08 ; 1.57]
9-10 years (T8)	85	1.21 [0.50 ; 1.96]	94	0.85 [0.10 ; 1.77]
11-12 years (T9)	105	1.20 [0.48 ; 1.83]	98	0.81 [0.07 ; 1.59]
13-14 years (T10)	108	1.17 [0.12 ; 1.97]	94	0.83 [0.08 ; 1.71]
15-16 years (T11)	56	1.17 [0.36 ; 2.48]	39	0.90 [0.10 ; 1.88]
17-18 years (T12)	35	1.15 [0.60 ; 1.52]	26	0.98 [0.20 ; 1.52]
19-20 years (T13)	19	1.20 [0.95 ; 1.71]	9	1.02 [0.43 ; 1.57]
21-22 years (T14)	7	1.10 [0.93 ; 1.25]	2	1.00 [0.75 ; 1.25]

T=time point; N=number of eyes; min=minimum; max=maximum

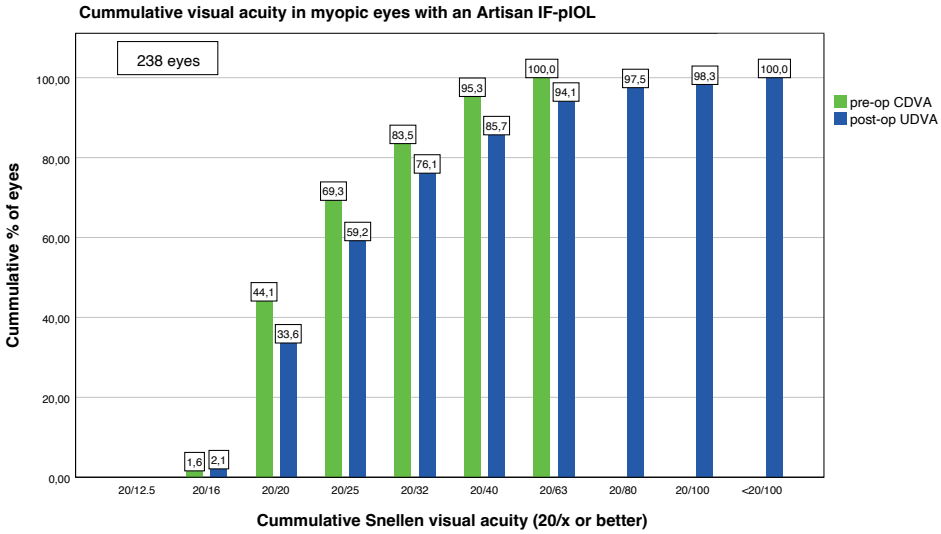

Figure 4. Efficacy post-implantation of an iris fixated phakic intraocular lens (IF-pIOL) in myopic eyes at T4 (1-2 years postoperative). The cumulative percentage of eyes with a preoperative corrected distance visual acuity (CDVA) (green bars) and postoperative uncorrected distance visual acuity (UDVA) (blue bars) is shown. Post-op=postoperative; pre-op=preoperative; %=percentage

Table 5. Details of uncorrected distance visual acuity in myopic eyes implanted with an IF-pIOL

Follow-up	N	Median UDVA logMAR (dec)	Percentile 25	Percentile 75	Range [min ; max]	p-value*
1 month (T1)	227	0.15 (0.71)	0.05	0.30	[-0.18 ; 2.00]	-
3 months (T2)	180	0.10 (0.79)	0.00	0.27	[-0.18 ; 2.00]	-
6 months (T3)	164	0.10 (0.79)	0.00	0.21	[-0.18 ; 0.80]	-
1-2 years (T4)	238	0.07 (0.85)	0.00	0.21	[-0.18 ; 1.00]	-
3-4 years (T5)	179	0.09 (0.81)	0.00	0.30	[-0.22 ; 1.30]	1.000
5-6 years (T6)	124	0.15 (0.71)	0.02	0.29	[-0.17 ; 1.31]	0.015
7-8 years (T7)	86	0.14 (0.72)	0.04	0.32	[-0.10 ; 1.30]	0.002
9-10 years (T8)	94	0.13 (0.74)	0.01	0.31	[-0.20 ; 1.30]	0.089
11-12 years (T9)	98	0.12 (0.76)	0.00	0.30	[-0.18 ; 1.52]	0.232
13-14 years (T10)	94	0.13 (0.74)	0.02	0.34	[-0.18 ; 1.22]	0.148
15-16 years (T11)	39	0.05 (0.89)	-0.05	0.28	[-0.18 ; 1.06]	1.000
17-18 years (T12)	26	0.00 (1.00)	-0.04	0.16	[-0.13 ; 0.70]	1.000
19-20 years (T13)	9	0.00 (1.00)	-0.06	0.10	[-0.18 ; 0.52]	1.000
21-22 years (T14)	2	0.11 (0.78)	0	0.22	[0.00 ; 0.22]	1.000

*Mann-Whitney U compared to 1-2 years postoperative period with Bonferroni correction. A p-value of <0.05 is considered statistically significant. UDVA= uncorrected distance visual acuity in logMAR, between brackets converted to decimal (dec); N=number of eyes; pre-op=preoperative; min=minimum; max=maximum; LogMAR=logarithm of the minimum angle of resolution; IF-pIOL=iris-fixated phakic intraocular lens; T=time point

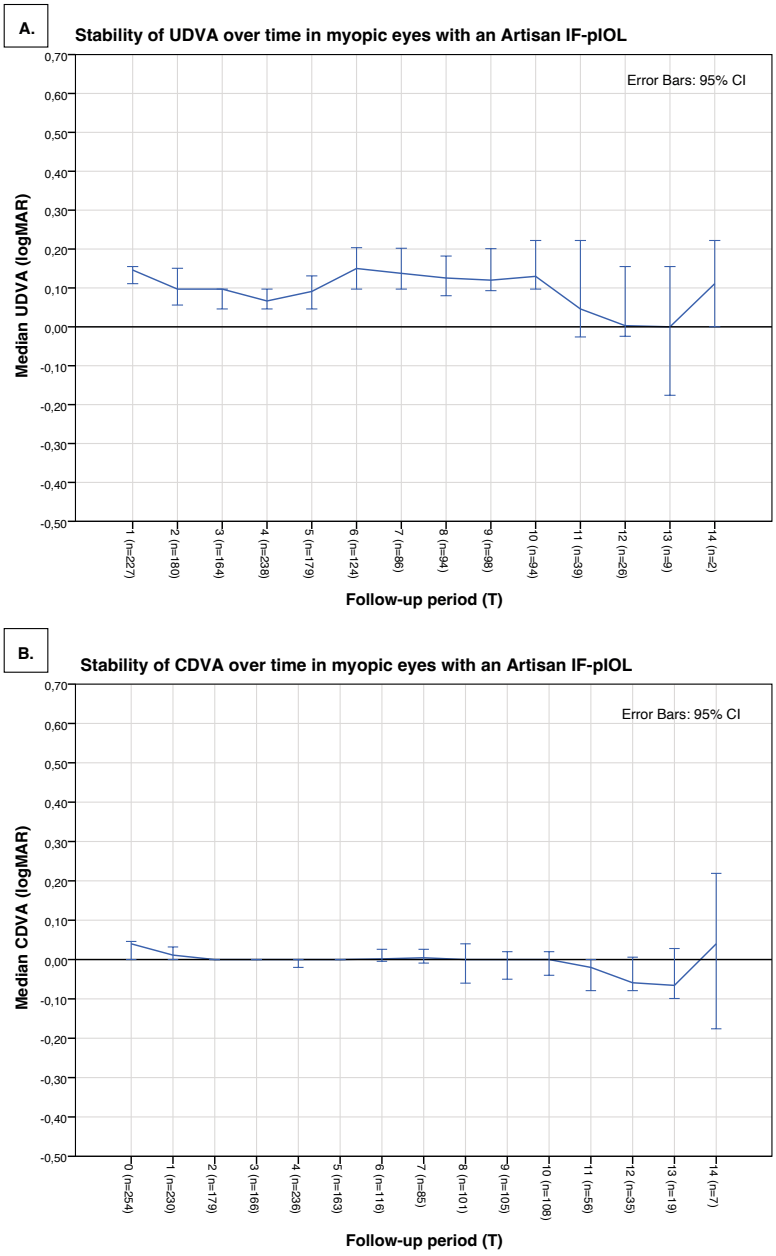

Figure 5. Stability over time of the A. uncorrected distance visual acuity (UDVA) and B. corrected distance visual acuity (CDVA) in myopic eyes implanted with an iris fixated phakic intraocular lens (IF-pIOL). logMAR=logarithmic angle of minimum resolution; CI=confidence interval; n=number of eyes; T=time-point; T0= preoperative; T1= 1 month, T2= 3 months T3=6 months, T4= 1-2 years, T5= 3-4 years, T6= 5-6 years, T7= 7-8 years, T8= 9-10 years, T9= 11-12 years, T10= 13-14 years, T11= 15-16 years, T12= 17-18 years, T13= 19-20 years, T14= 21-22 years

Table 6. Details of corrected distance visual acuity in myopic eyes implanted with an IF-pIOL

Follow-up period	N	Median CDVA logMAR (dec)	Percentile 25	Percentile 75	Range [min ; max]	p-value*
pre-op (T0)	254	0.04 (0.91)	0.00	0.16	[-0.18 ; 0.40]	<0.001
1 month (T1)	230	0.01 (0.98)	0.00	0.10	[-0.20 ; 0.37]	-
3 months (T2)	179	0.00 (1.00)	-0.07	0.05	[-0.18 ; 0.52]	-
6 months (T3)	166	0.00 (1.00)	-0.08	0.05	[-0.18 ; 0.30]	-
1-2 years (T4)	236	0.00 (1.00)	-0.08	0.03	[-0.18 ; 0.51]	-
3-4 years (T5)	163	0.00 (1.00)	-0.07	0.04	[-0.16 ; 0.40]	1.000
5-6 years (T6)	116	0.00 (1.00)	-0.05	0.09	[-0.19 ; 0.72]	0.166
7-8 years (T7)	85	0.00 (1.00)	-0.06	0.10	[-0.18 ; 0.54]	0.768
9-10 years (T8)	101	0.00 (1.00)	-0.09	0.10	[-0.30 ; 0.58]	1.000
11-12 years (T9)	105	0.00 (1.00)	-0.09	0.09	[-0.22 ; 0.70]	1.000
13-14 years (T10)	108	0.00 (1.00)	-0.09	0.08	[-0.24 ; 1.30]	1.000
15-16 years (T11)	56	-0.02 (1.01)	-0.10	0.11	[-0.24 ; 0.44]	1.000
17-18 years (T12)	35	-0.06 (1.14)	-0.08	0.05	[-0.18 ; 0.30]	1.000
19-20 years (T13)	19	-0.07 (1.18)	-0.10	0.03	[-0.18 ; 0.31]	0.626
21-22 years (T14)	7	0.04 (0.91)	-0.06	0.10	[-0.18 ; 0.22]	1.000

*Mann-Whitney U compared to 1-2 years post-operation with Bonferroni correction. A p-value of <0.05 is considered statistically significant. CDVA=corrected distance visual acuity in logMAR, expressed as a decimal number in parentheses (dec); N=number of eyes; pre-op=preoperative; min=minimum; max=maximum; LogMAR=logarithm of the minimum angle of resolution; IF-pIOL=iris-fixated phakic intraocular lens; T=time point

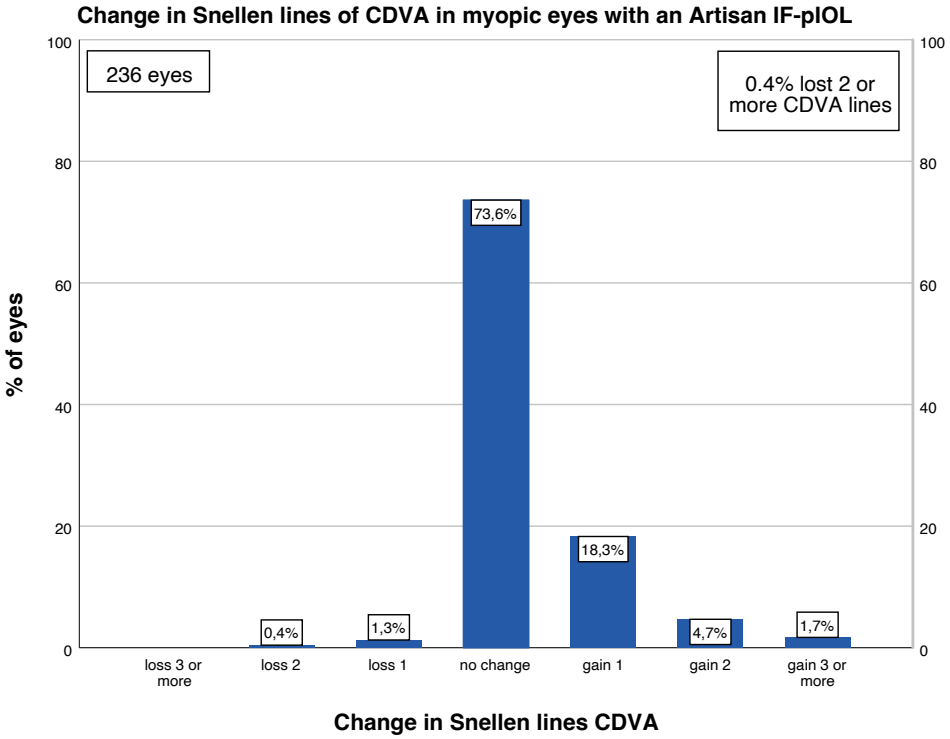

Figure 6. Bar graph demonstrating the change in Snellen lines of corrected distance visual acuity (CDVA) T4 (1-2 years postoperative) compared to T0 (preoperative) in myopic eyes implanted with an iris fixated phakic intraocular lens (IF-pIOL). One Snellen line change in CDVA equals 0.10 logarithmic angle of minimum resolution (logMAR).

Complications

Cataract

In 43 eyes (15.8%), cataract was sufficiently clinically significant to perform phacoemulsification with IOL implantation after a mean time of 11.76 ± 5.90 years (range 1.15 - 21.10). The mean age by then was 56.04 ± 9.77 years (range 30.32 - 79.73). In 15 eyes (5.5%), a minimal degree of cataract was noted pre-implantation. Six (2.2%) of these eyes progressed to visually significant cataract for which phacoemulsification was performed after 4.73 ± 2.93 years (range 1.15 - 8.45). In 2 eyes (0.7%) of 1 patient, anterior capsule cataract was first described 7 years post-implantation. There was no evidence of intermittent touch between the crystalline lens and the IF-pIOL during slit lamp examination and anterior segment imaging. The ACDs (from the corneal endothelium to the anterior pole of the crystalline lens) were 3.02 and 3.11 mm, and surgery was recorded as having been uncomplicated. Nineteen years post-operation, the IF-pIOLs

were still in situ, although the anterior capsule cataract had slowly progressed for which phacoemulsification was scheduled. There were still no signs of intermittent lens touch upon examination.

Endothelial cell change

Figure 7 displays the EC density change for all eyes during the different follow-up periods. Paired comparisons between pre- and postoperative EC values are listed in Table 7. There is a statistically significant change from preoperative EC count from T4 onwards. Linear regression analysis showed a significant effect of follow-up time on EC loss, indicating a decline in EC count of 56.2 cells/mm^2 per year (Table 3). At the final patient follow-up visit, 30 eyes (of 21 patients) (11%) had an EC density of <1500 cells/mm^2 after a mean time of 10.79 ± 3.88 years (range 3.71 - 20.57). At 5, 10, 15 and 22 years of follow-up, the percentage of eyes that had reached this EC density of <1500 cells/mm^2 was 1.1% (3 eyes), 4.0% (11 eyes), 10.3% (28 eyes) and 11% (30 eyes), respectively. There was no baseline difference in implanted IF-pIOL power (p=0.721), axial length (p=0.924), mean keratometry (p=0.376), EC density (p=0.221) or gender (p=1.000) between the eyes with an EC density above 1500 cells/mm^2 and eyes with an EC density below 1500 cells/mm^2. There did seem to be a difference between these two groups at baseline with respect to ACD and age; the eyes with an EC density of <1500 cells/mm^2 seemed to have a slightly shallower ACD and a slightly higher age at implantation, but statistics failed to meet significance. For details, see Table 8. In 25 out of 30 eyes, IF-pIOL implantation was performed between 1997-2001. There was a statistically significant difference between the groups of eyes implanted with an IF-pIOL before and after 2001 (p=0.049) with respect to the percentage of eyes reaching an EC density below 1500 cells/mm^2 (Appendix 8). In 17 eyes (6.2%), EC loss was the main reason for IF-pIOL explantation after a mean time of 13.94 ± 7.82 years (range 6.01 - 20.98 years). The mean age at explantation was 58.79 ± 7.82 years (range 40.47 - 72.30 years).

Retinal complications

In 3 eyes (1.1%), retinal detachment occurred, of which 1 eye (0.4%) required vitrectomy with concomitant phacoemulsification and IF-pIOL explantation, 1 eye (0.4%) was treated with scleral buckling surgery, and 1 eye (0.4%) was treated with retinal laser coagulation. In 3 eyes (1.1%), a retinal hole developed which was treated with retinal laser coagulation. In 2 eyes (0.7%), a macular neovascularization developed. In 3 eyes (1.1%), a macular hole developed. In 3 eyes (1.1%), a macular pucker developed.

Pigment dispersion and inflammation

Formation of posterior synechiae was noted in 2.6% of the eyes (7 eyes of 5 patients). Several degrees of inflammation and pigment dispersion with concomitant posterior synechiae formation were observed. Three eyes (1.1%) had an excessive inflammatory reaction with synechiae formation within the first month after surgery: 1 eye developed progressive pigment dispersion with synechiae formation directly after an IF-pIOL exchange which led to explantation of the IF-pIOL 4 years after initial IF-pIOL implantation; in 1 eye (0.4%), the IF-pIOL was initially malpositioned but the inflammation subsided after having been repositioned; one eye (0.4%) had an inflammatory reaction with synechiae formation 1 month after implantation which subsided with topical therapy. Four other eyes (1.5%) developed synechiae in a clinically uninflamed eye between 11-14 years post-implantation.

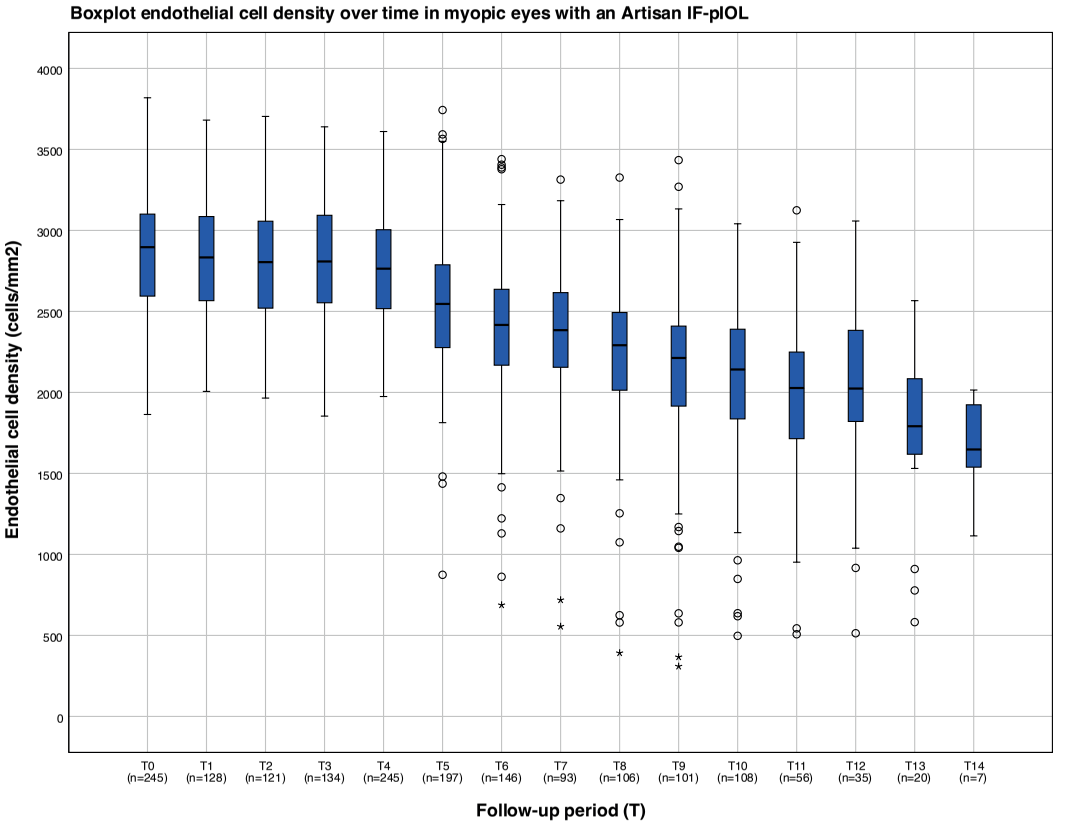

Figure 7. Boxplot of endothelial cell density change over time in myopic eyes with an Artisan IF-pIOL. IF-pIOL = iris-fixated phakic intraocular lens; T=time-point; T0= preoperative; T1= 1 month, T2= 3 months T3=6 months, T4= 1-2 years, T5= 3-4 years, T6= 5-6 years, T7= 7-8 years, T8= 9-10 years, T9= 11-12 years, T10= 13-14 years, T11= 15-16 years, T12= 17-18 years, T13= 19-20 years, T14= 21-22 years

Table 7. Paired endothelial cell counts in myopic eyes with an IF-pIOL

Follow-up period	N	Mean pre-op ECD ± SD	Mean post-op ECD ± SD	p-value*	Yearly rate of loss (%)
1 month (T1)	117	2861 ± 349	2843 ± 363	1.000∞	-
3 months (T2)	106	2817 ± 351	2809 ± 386	1.000∞	-
6 months (T3)	123	2880 ± 351	2819 ± 396	0.249∞	-
1-2 years (T4)	218	2878 ± 351	2753 ± 357	<0.001∞	2.48
3-4 years (T5)	176	2867 ± 337	2574 ± 415	<0.001	2.75
5-6 years (T6)	131	2848 ± 361	2398 ± 453	<0.001	2.76
7-8 years (T7)	82	2882 ± 363	2325 ± 479	<0.001	2.42
9-10 years (T8)	97	2761 ± 343	2231 ± 484	<0.001	1.96
11-12 years (T9)	89	2869 ± 362	2191 ± 493	<0.001	1.99
13-14 years (T10)	92	2831 ± 362	2044 ± 531	<0.001	2.04
15-16 years (T11)	54	2893 ± 373	1993 ± 486	<0.001	1.95
17-18 years (T12)	33	2950 ± 363	2043 ± 533	<0.001	1.74
19-20 years (T13)	17	2986 ± 292	1794 ± 508	0.004	2.03
21-22 years (T14)	7	2814 ± 238	1672 ± 314	0.251	1.96

*Wilcoxon signed-rank test with Bonferroni correction; ∞ Paired *t*-test with Bonferroni correction. IF-pIOL=iris-fixated phakic intraocular lens; ECD=endothelial cell density (cells/mm^2); SD=standard deviation; N=number of eyes

Table 8. Difference between myopic eyes implanted with an iris-fixated phakic intraocular lens with endothelial cell densities below and above 1500 cells/mm² at final patient follow-up visit

	Eyes with ECD <1500 cells/mm²	**Eyes with ECD >1500 cells/mm²**	**p-value**
N	26	219	0.221∞
Median pre-op ECD [range] (cells/mm²)	2819 [1997 ; 3819]	2915 [1864 ; 3664]	
25th percentile ; 75th percentile	2607 ; 3039	2595 ; 3132	
N	30	243	0.065*
Mean pre-op ACD [range] (mm)	3.53 [3.20 ; 4.40]	3.76 [2.86 ; 4.70]	
25th percentile ; 75th percentile	3.38 ; 3.79	3.51 ; 3.91	
N	30	243	0.376∞
Median pre-op Kmean [range] (D)	44.13 [41.87 ; 48.88]	43.81 [39.94 ; 49.19]	
25th percentile ; 75th percentile	43.13 ; 44.49	42.75 ; 44.81	
N	30	243	0.057∞
Median pre-op age [range] (years)	40.61 [23.53 ; 57.91]	38.46 [17.97 ; 61.18]	
25th percentile ; 75th percentile	37.20 ; 45.69	30.34 ; 45.82	
N	30	243	0.721∞
Median IF-pIOL power [range] (D)	-12.5 [-22.0 ; -7.0]	-12.0 [-23.5 ; -5.5]	
25th percentile ; 75th percentile	-14.5 ; -10.5	-15.0 ; -10.0	
N	30	243	0.924∞
Median axial length [range] (mm)	27.85 [25.20 ; 30.90]	27.68 [23.69 ; 37.27]	
25th percentile ; 75th percentile	26.70 ; 29.35	26.49 ; 29.06	

∞Mann-Whitney U test; *Independent-samples *t*-test; a p-value of 0.05 is considered statistically significant. ECD=endothelial cell density (cells/mm²); ACD=anterior chamber depth in millimeters; Kmean=average keratometry; D=diopters; IF-pIOL=iris-fixated phakic intraocular lens; mm=millimeters; pre-op=preoperative

Other complications
Ocular hypertension necessitating topical therapy occurred in 13 eyes (4.8%). In 3 eyes (1.1%), glaucoma developed. In five eyes (1.8%), miotic eye drops were used due to glare/halo complaints.

Secondary Surgical Interventions
Repositioning
In 13 eyes (4.8%), the IF-pIOL was exchanged due to undercorrection or exchanged for a toric IF-pIOL. In 3 eyes (1.1%), the IF-pIOL was repositioned to enlarge the iris enclavation site so as to prevent lens dislocation. In 2 eyes (0.7%), the lens was repositioned due to postoperative iris prolapse (1 eye) and incorrect positioning (1 eye). In 2 eyes (0.7%), the wound was reconstructed due to early postoperative undesired astigmatism.

Explantation
IF-pIOL explantation with concomitant phacoemulsification and posterior chamber IOL implantation was performed after a mean of 11.94 ± 5.50 years (range 0.06 - 21.10 years) in 69 eyes of 46 patients (25.3%) (see Figure 8). A total of 43 eyes were explanted (15.8%) due to clinically significant cataract after a mean time of 11.76 ± 5.90 years (range 1.15 - 21.10 years), 17 IF-pIOLs (6.2%) were explanted due to EC loss after a mean time of 13.94 ± 4.08 years (range 6.01 - 20.98 years). In 3 eyes (1.1%), the IF-pIOL was explanted during vitreoretinal surgery (2 retinal detachments, 1 macular pucker peeling) after 0.06, 14.46 and 6.68 years, respectively; in 2 eyes (0.7%) due to pigment dispersion after 4.05 and 12.67 years, respectively, and in 1 eye (0.4%) due to dislocation after trauma after 13.39 years. In 3 eyes (1.1%), the main reason for explantation was unknown. The median survival time (i.e. until 50% of the IF-pIOLs were explanted) was 19.99 years (95CI 18.96 - 21.03). Figure 9 shows the Kaplan Meier survival curve of the Artisan myopic IF-pIOL of our study cohort.

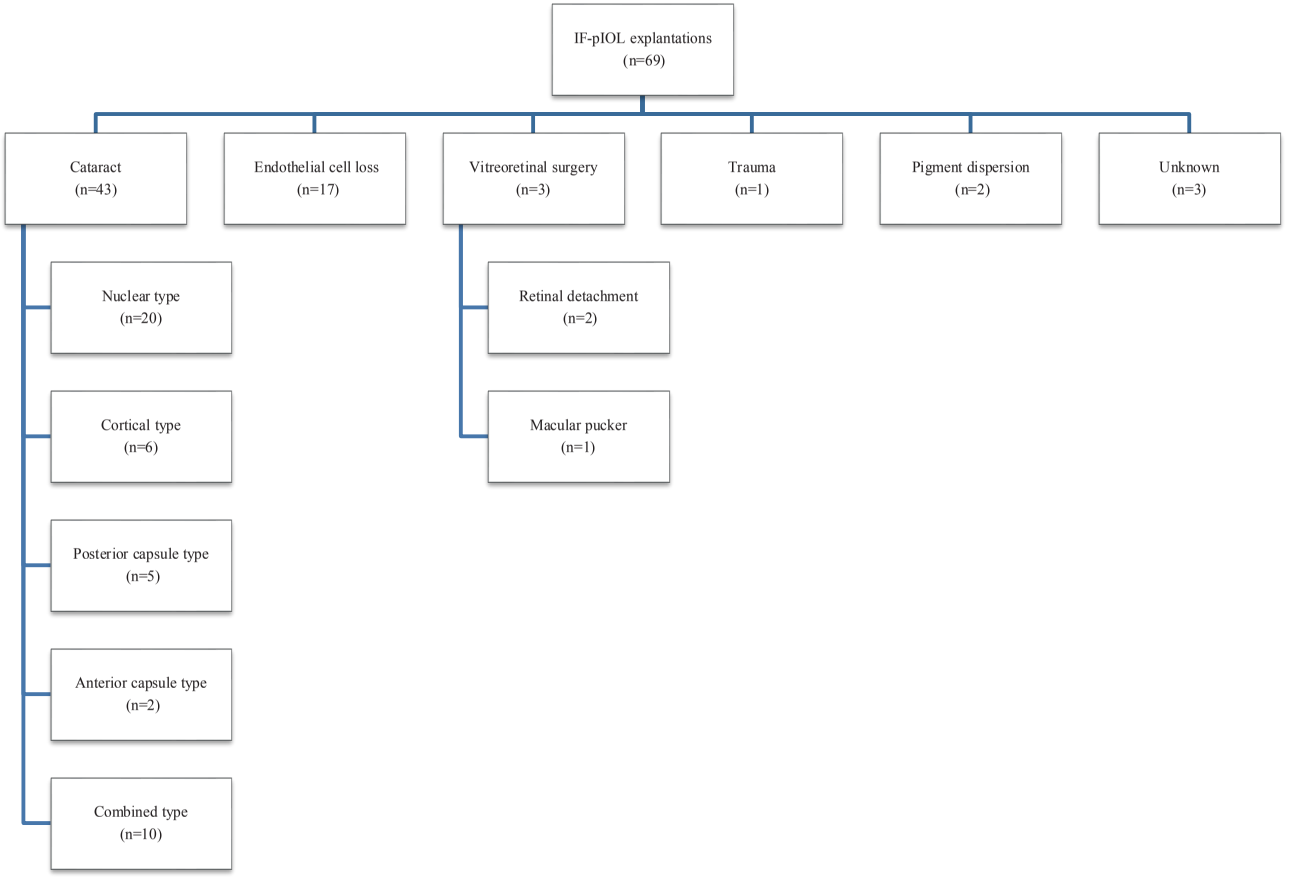

Figure 8. Reasons for explantation. IF-pIOL=iris-fixated phakic intraocular lens; n=number of eyes

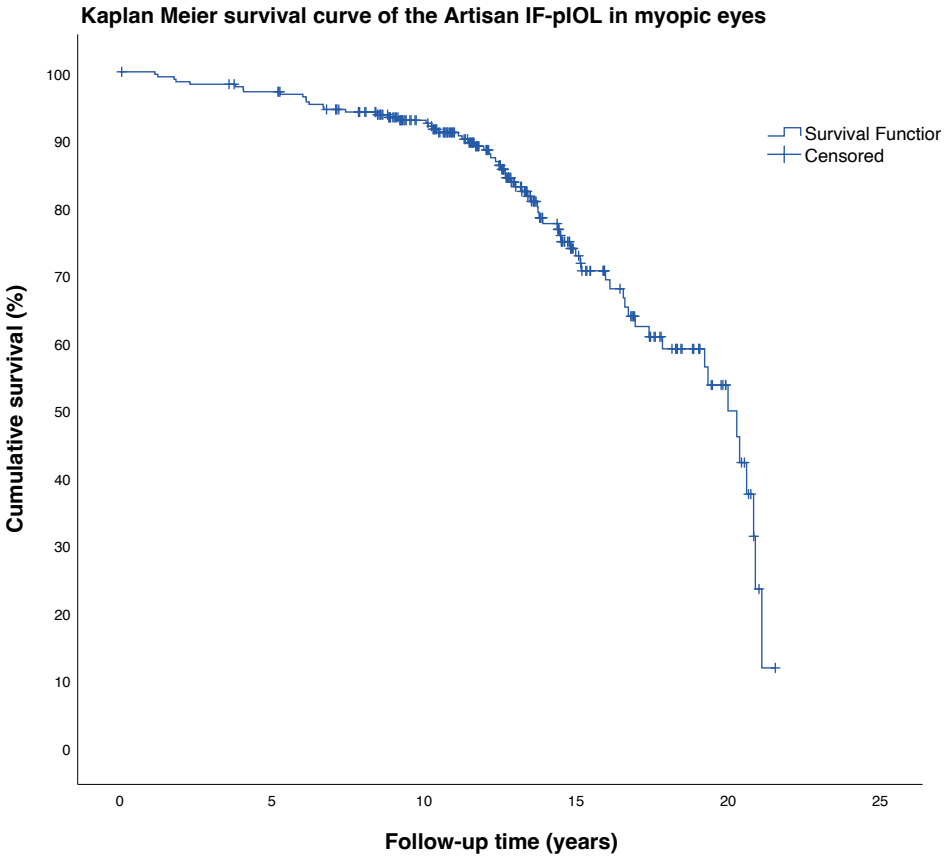

Figure 9. Kaplan Meier survival curve. Reasons for iris-fixated phakic intraocular lens (IF-pIOL) explantation before 10 years; cataract (n=12), endothelial cell loss (n=4), retinal detachment (n=1), pigment dispersion (n=1), unknown (n=1) Reasons for IF-pIOL explantation after 10 years; cataract (n=31), endothelial cell loss (n=13), retinal pathology (n=2), pigment dispersion (n=1), trauma (n=1), unknown (n=2)

DISCUSSION

In this paper, we report the results of 273 myopic eyes implanted with an Artisan IF-pIOL with a follow-up of up to 22 years. This is the first study to report such long-term results for the correction of myopic refractive error with an Artisan IF-pIOL.

The refractive predictability was comparable with previously published results with 86% of eyes having a post-implantation MRSE within 1.00 D of emmetropia.[38] Most eyes resulted in being slightly undercorrected compared to the intended correction, which may be considered an advantageous outcome since we clinically experience myopic patients to be more satisfied with a slightly myopic MRSE postoperative outcome compared to a slightly hyperopic outcome. We found a small but statistically significant myopization of -0.030 D per year. A plausible reason for this minor myopization might be the slight but statistically significant increase in axial length over time. In our study of Gaurisankar et al., we performed an in-depth longitudinal analysis of axial length over a mean time of 12 years in a subset of myopic and hyperopic eyes implanted with an IF-pIOL. Here we also found significant elongation over time within the same order of magnitude, being 0.04 mm per year, in the myopic eyes implanted with an IF-pIOL, whereas the axial length did not change in the hyperopic eyes implanted with an IF-pIOL.[39]

Visual results after myopic IF-pIOL implantation were very good. There was a significant gain in CDVA after IF-pIOL implantation compared to pre-implantation. We found a stable CDVA throughout our follow-up of 22 years, with all mean safety indices being above 1.10. In 9 eyes (3.5%), a decrease in CDVA of more than 2 Snellen lines compared to pre-implantation occurred at the final patient follow-up visit. The loss of more than 2 lines of CDVA seems to be unrelated to IF-pIOL implantation; the myopic nature and normal aging of these eyes are likely to be the reasons for this observed CDVA loss. The main reason for a loss in CDVA was cataract. Long-term, population-based follow-up studies have provided evidence to support that myopic eyes may have an increased risk of cataract development compared to emmetropic eyes.[40] Although cataract formation after IF-pIOL implantation has been documented before, the relationship between cataract development and IF-pIOL implantation has not clearly been shown.[41-43] Earlier cataract development in myopic eyes implanted with the IF-pIOL lens compared to un-operated myopic eyes may be related to a variety of factors, such as the material of the IF-pIOL itself, metabolic effects, the use of postoperative topical medication, intermittent touch or close approximation of the pIOL to the crystalline lens, or sterile intraocular (subclinical) inflammation processes. Clinically significant cataract formation occurred in 15.8% of the total study population and was the main reason for IF-pIOL explantation. Comparable with other papers, most cataracts were of nuclear

sclerotic type.[41-44] In a study of Jonker et al., 17% of rigid (toric) IF-pIOLs were explanted due to cataract formation after a mean time of 168 months. The mean age of 56 years at the time of IF-pIOL explantation is almost identical to the mean age at explantation in our population.[45] Moreover, shorter-term papers also report a comparable age at the time of cataract extraction, ranging between 47 and 62 years.[24,42,43] The majority of the explantations in our study, however, were performed after 10-year follow-up. The median survival time (i.e. until 50% of the IF-pIOLs were explanted) was 19.99 years, which is somewhat better than the median survival time of 15.25 years reported by others.[45] This difference may be explained by a variation in explantation criteria applied by the treating ophthalmologist in consultation with the patient.

We found a comparable estimated overall EC decline of 56.2 cells/mm^2 per year to previously published data.[46,47] Our result, with a cumulative loss of 18.8% at T8 (9-10 years post-operation), is within the range of the cumulative EC loss reported in previously published papers, being up to 22.5% at 10-year follow-up.[34,47-49] A lower threshold of 1500 cells/mm^2 is recommended by the AFSSAPS (French Health Products and Safety Agency) for IF-pIOL explantation because it is assumed that this is a safe EC density for pIOL explantation and cataract surgery without compromising the corneal endothelium in the long run.[50] Few studies have described this threshold as an 'endpoint' in their results. Jonker et al. describe 0.8% and 3.9% of eyes reaching this point at 5 and 10 years, respectively[47], which is comparable to our results. Additionally, we report that after 15 and 22 years post-implantation, 10.3% and 11.0% of eyes, reached this point, respectively. It should be considered that a significant majority of eyes reaching an EC density below 1500 cells/mm^2 were implanted in the early years of the IF-pIOL when safety criteria were still in the developmental phase and thus scarcely defined. Long-term studies evaluating well-defined modern safety criteria might find fewer eyes reaching this threshold.

In the early postoperative period (up to 6 months), no statistically significant EC loss was detected compared to the preoperative EC. We did, however, find a statistically significant EC loss 1 to 2 years post-implantation. We hypothesize that there was no surgically induced damage to the central corneal endothelial cells but that there may have been surgically-induced loss of ECs at the incisional sites and that this is only noticed in the later postoperative period due to reshuffling. EC loss, however, continues at a more or less steady rate of around 2% per year during the postoperative follow-up period. Is this the ongoing result of EC reshuffling? Or are there other underlying factors that play a role in EC decline, such as intermittent IF-pIOL touch to the endothelium, eye-rubbing, subclinical inflammation, or something that is still unknown? It could be speculated that, with increasing age, a shallower ACD might lead to accelerated EC loss as a result of the IF-pIOL being closer to the corneal endothelium. Our results,

however, do not indicate an acceleration of EC loss over time. Nor have we found a correlation between EC loss and ACD in eyes with an EC density below 1500 cells/mm^2, though statistics just failed to meet significance. Unfortunately, we are only able to report on central EC changes as this is a long-term retrospective study in which only central EC counts were historically performed. It would be of great value if future studies could focus on the behavior of the ECs in relation to their location relative to the surgical incisional sites and relative to the smallest distance points from the corneal endothelium to the IF-pIOL with the use of EC mapping.

It should be considered that a selection bias as well as variations in examination protocols, materials and technicians may have influenced the results of the outcome variables due to the long follow-up and retrospective nature of this study. Especially changes in equipment and analysis methods pose a threat and are a weakness of long-term (retrospective) studies. For EC analysis, measurements acquired with different corneal specular microscopes (CSMs) are prone to interchangeability variability, as we discovered with our own CSMs. In our case, the interchangeability concern was caused by erroneous calibration and software imprecision and led to a difference in EC density of up to 500 cells/mm^2. We incorporated a method to increase the reliability of our EC analysis, which we have described in detail elsewhere.[51] Using this method, we were able to (retrospectively) calculate a correction factor for EC density measurements performed by different specular microscopes for the purpose of longitudinal comparison.

Generally speaking, patients with an IF-pIOL are relatively young, socially and economically active, and tend to move jobs and homes and forget their regular check-ups when they have no complaints. This may explain the relatively high loss to follow-up and incomplete data at the follow-up time points, which might have resulted in an overestimation of complication rates in this study. Even so, life-long yearly follow-up visits are a mandatory safety requirement, and patients should be carefully counselled preoperatively on this safety requirement.

In conclusion, the visual and refractive results after IF-pIOL implantation to correct myopic refractive error were positive up to 22 years post-implantation, with no clinically relevant changes. Cataract development was the main reason for IF-pIOL explantation, followed by EC loss. An estimated annual EC loss of 56.2 cells/mm^2 was found in our study. Annual EC check-ups are considered mandatory with an IF-pIOL in place. Prospective long-term studies using up-to-date safety criteria and an in-depth analysis of the corneal endothelium in relation to anterior chamber dimensions would be of great value for the future.

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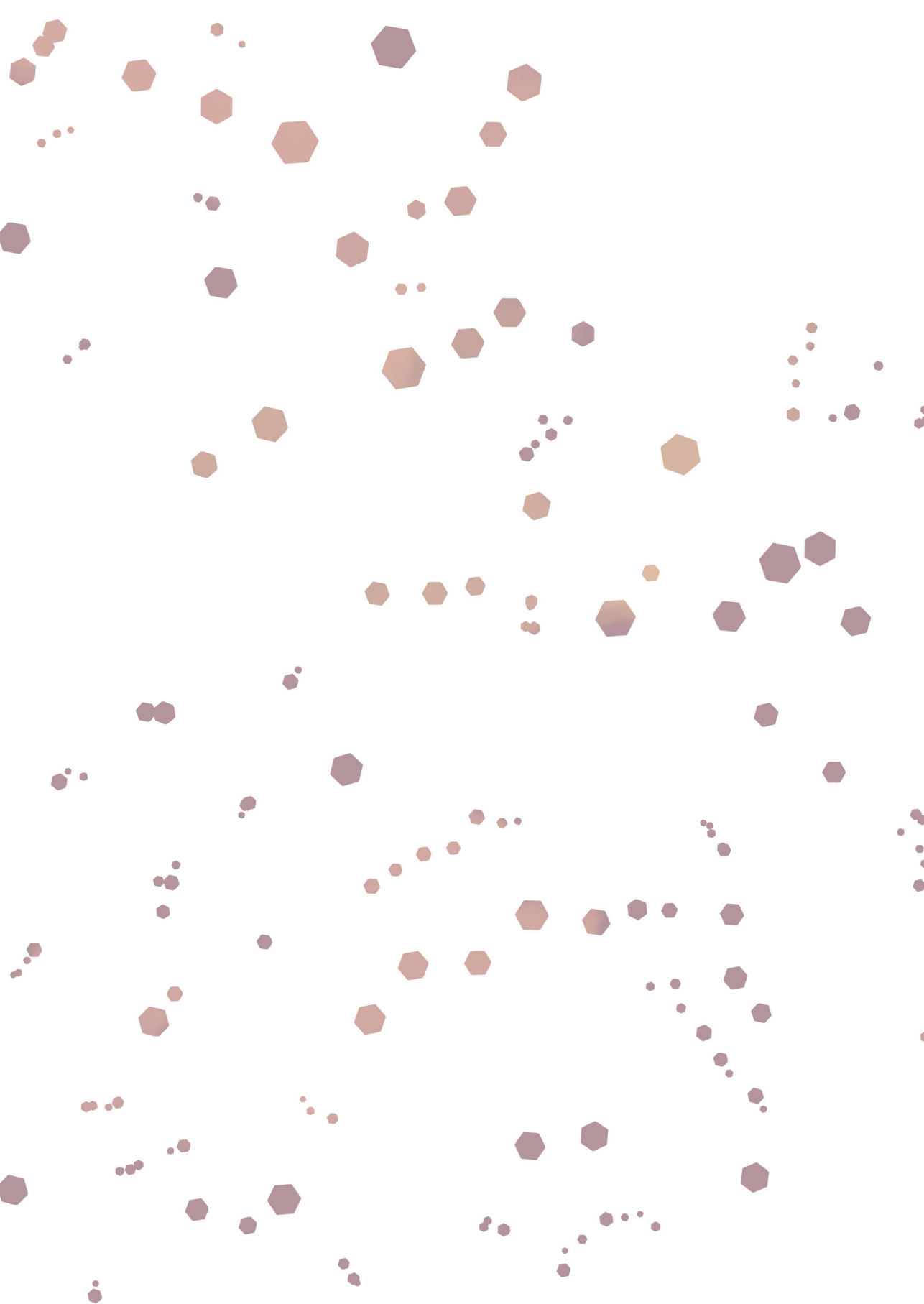

Chapter 5

Implantation of a Phakic Intraocular Lens in 3 Patients with Oculocutaneous Albinism

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INTRODUCTION

Albinism refers to a group of autosomal recessive melanin disorders in which pigmentation is reduced compared with pigmentation in others of the same ethnic and racial backgrounds.[1] Melanin is a chromophore with various biological functions including photoprotection, antioxidant defense, camouflage, drug-binding metal-ion chelation, and thermoregulation.[2] In the eye, it is found in the uveal melanocytes derived from the neural crest and in the retinal pigmented epithelium derived from the neuroectoderm. Melanin is also present in the posterior iris- pigmented epithelium and in the phagocytic clump cells within the iris stroma.

Ocular involvement is characteristic in albinism. Sole eye involvement is referred to as ocular albinism; in oculocutaneous albinism, the eyes in combination with the skin and hair may be simultaneously affected. Common ocular findings include refractive errors (primarily astigmatism and hyperopia,[3] iris transillumination due to reduced pigmentation, nystagmus, absence of stereopsis, foveal hypoplasia, fundus hypopigmentation, and misrouting of optic nerve fibers at the chiasm; all leading to reduced visual acuity).[1,4] Oculocutaneous albinism type 1A, the most severe form of oculocutaneous albinism, is associated with the highest rate of hyperopia and the poorest visual acuity compared with the other subtypes.[3]

Studies of iris-fixated phakic intraocular lenses (pIOLs) for the correction of high refractive errors in healthy eyes have shown good levels of safety and efficacy.[5–8] This has raised the possibility that an iris-fixated pIOL might be a good option for the treatment of high refractive errors commonly found in albinism. However, the presumed fragility of the iris and supposedly high risk for decentration or dislocation of the pIOL may deter surgeons from implanting an iris-fixated pIOL. We describe 3 patients with oculocutaneous albinism type 1A who had successful iris-fixated pIOL implantation in both eyes with an 8- to 14-year follow-up.

CASE REPORTS

An overview of the clinical data of the 3 cases is shown in Table 1.

Case 1

A 41-year-old male schoolteacher with clinical phenotype oculocutaneous albinism 1A presented to us in February 1998 due to increasing visual disturbances caused by unstable positioning of rigid contact lenses from a pendular nystagmus. The corrected distance visual acuity (CDVA) was 20/400 with -11.25 -5.00 x 17 in the right eye and 20/1200 with -9.75 -4.00 x 160 in the left eye. Slitlamp examination revealed a total diaphanous iris with no sign of iridodonesis, and fundoscopic eye examination showed retinal hypopigmentation. The anterior chamber depth (ACD) from the corneal epithelium was 3.5 mm in the right eye and 3.7 mm in the left eye. Because of the nystagmus, no reliable endothelial cell density (ECD) measurement could be performed.

Later in 1998, a -14.5 diopter (D) Artisan pIOL (Ophtec) was implanted according to protocol (Appendix 9) in each eye under general anesthesia in 2 consecutive sessions. (Toric IOLs were not used as they were not available until April 2001.)

Six months after implantation, the CDVA had improved to 20/200 in both eyes. The pIOLs were well centered with good enclavation bites, and the intraocular pressure (IOP) was within normal limits. At 5 and 10 years, the CDVA remained stable at 20/200 in both eyes. The ECD was successfully measured at the 5-year follow-up and remained stable up to 10 years. At the last examination, 14 years after implantation, the ECD was 3075 cells/mm^2 in the right eye and 2842 cells/mm^2 in the left eye, indicating a mean yearly decline of 0.33% and 1.13%, respectively, over 9 years. The CDVA was 20/400 in the right eye and 20/200 in the left eye. A clear crystalline lens was observed, and the pIOLs were stable and well centered with no signs of atrophy at the enclavation sites (Figure 1A). During the past 4 years, recurrent corneal erosions due to epitheliopathy have caused discomfort, problems with reading, and a slight decrease in the CDVA in the right eye. Regular follow-up visits at our clinic are scheduled. Although some residual astigmatism and slightly increasing hyperopia remain, the patient is satisfied with the result of the implantation and continues to work as a schoolteacher.

Case 2

A 45-year-old woman with clinical phenotype oculocutaneous albinism 1A, who was a first-degree relative of the Case 1 patient, visited our clinic in 2002 because she was dissatisfied with her visual acuity with spectacles and suffered from contact lens intolerance. The CDVA was 20/200 with -3.50 -3.75 x 6 and -3.00 -3.00 x 13 in the

right eye and left eye, respectively, with a pendular nystagmus. Biomicroscopy of the anterior segment revealed a total diaphanous iris without iridodonesis. Fundoscopic eye examination showed hypopigmentation of the fundus (Figure 2). The ACD was 3.4 mm in the right eye and 3.26 mm in the left eye.

In 2002, an Artisan toric pIOL of -5.00 -3.50 x 8 was implanted in the right eye according to protocol. Three weeks later, a toric pIOL of -3.50 -3.00 x 13 was implanted in the left eye. Both procedures were performed under general anesthesia. Throughout the 10-year follow-up, the CDVA remained stable around 20/200 in both eyes and the IOPs remained within normal limits. The endothelium in both eyes showed a mean yearly decline of 1.75% in the right eye and 1.12% in the left eye throughout the follow-up. The pIOLs remained in central and stable positions with no signs of iris atrophy or inflammation in the anterior chamber (Figure 1B). The patient remains pleased with the outcome.

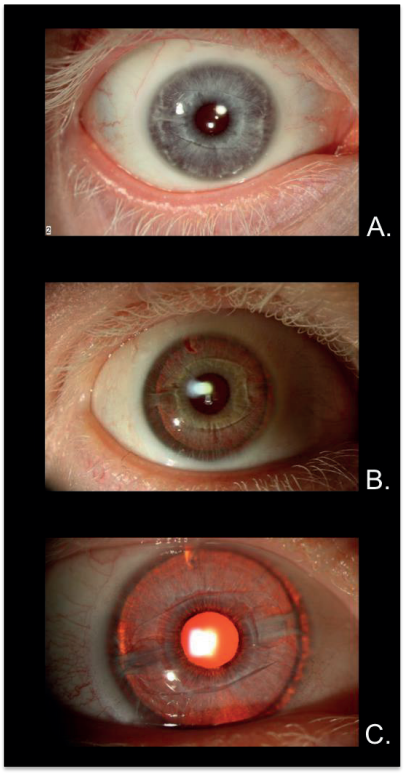

Figure 1. Right eye in Case 1 (A), Case 2 (B), and Case 3 (C) 14, 10, and 8 years, respectively, after implantation of the iris-fixated pIOL. Note the translucent iris tissue, the intact enclavation bites, and the central positioning of the pIOLs.

Table 1.

	Right Eye					
Exam Period	**UDVA**	**Sphere**	**Cylinder**	**CDVA**	**IOP**	**ECD**
Case 1						
Pre-op	-	-11.25	-5.0	0.05	14	*
Post-op (y)						
0.5	0.1	1.5	-2.25	0.1	12	*
5	0.1	1.25	-2.75	0.1	18	3170
10	0.1	2	-2.5	0.1	13	3247
14	0.05	2	-1.75	0.05	14	3075
Case 2						
Pre-op	-	-3.5	-3.75	0.1	16	*
Post-op (y)						
1	0.1	-0.25	-1.5	0.1	9	3312
5	0.1	-0.75	-2.25	0.1	14	*
10	0.1	0.25	-2.25	0.1	14	2790
Case 3						
Pre-op	-	-10.5	-2	0.08	16	*
Post-op (y)						
1	0.1	-0.25	-1.5	0.2	15	2967
8	0.16	0.75	-0.75	0.16	13	2825

CDVA = corrected distance visual acuity; ECD = endothelial cell density (cells/mm^2); IOP = intraocular pressure (mmHg); UDVA = uncorrected distance visual acuity

Case 3

A 40-year-old man with clinical phenotype oculocutaneous albinism 1A presented in 2003 because of progressive contact lens intolerance. The CDVA was 20/250 with -10.50 -2.00 x 34 in the right eye and 20/200 with -9.50 -1.25 x 133 in the left eye. On examination, a pendular nystagmus, a complete diaphanous iris without signs of iridodonesis, and an absence of the macular reflex were noted. A convergent strabismus of the right eye was observed. An initial ECD could not be performed because of the nystagmus. The ACD was 3.4 mm in the right eye and 3.45 mm in the left eye.

Left Eye					
UDVA	**Sphere**	**Cylinder**	**CDVA**	**IOP**	**ECD**
-	-9.75	-4.0	0.02	14	*
0.1	1	-1.75	0.1	12	*
0.1	2.5	-2.75	0.1	16	3165
0.1	2.75	-3.25	0.1	13	3106
0.1	4	-2.75	0.1	14	2842
-	-3	-3	0.1	14	*
0.1	-0.75	-0.5	0.16	9	3063
0.16	-1	-1	0.16	14	*
0.1	-0.25	-0.25	0.1	14	2755
-	-9.5	-1.25	0.1	16	*
0.1	0.5	-1.75	0.2	14	2347
0.16	1	-1.25	0.16	13	2086

*Missing data; failed ECD because of presence of nystagmus or because it was impossible to recount due to poor quality of endothelial cell photographs

In 2004, a -12.5 D Artisan iris-fixated pIOL was implanted in each eye under local anesthesia. At the 1-year follow-up, the CDVA had improved to 20/100 in both eyes and successful endothelial cell counts of 2967 cells/mm^2 in the right eye and 2347 cells/mm^2 in the left eye were obtained. At the last follow-up in 2012, the CDVA was 20/ 125 in both eyes. Throughout the 8-year follow-up, the pIOLs were well centered and remained in stable positions with no signs of iris atrophy around the enclavation sites (Figure 1C). The IOP remained within normal limits. At the last follow-up, the ECD was 2825 cells/mm^2 in the right eye and 2086 cells/mm^2 in left eye, indicating a mean yearly endothelial cell loss of 0.68% and 1.59%, respectively. The patient is very satisfied with the result and will continue regular follow-ups at our clinic.

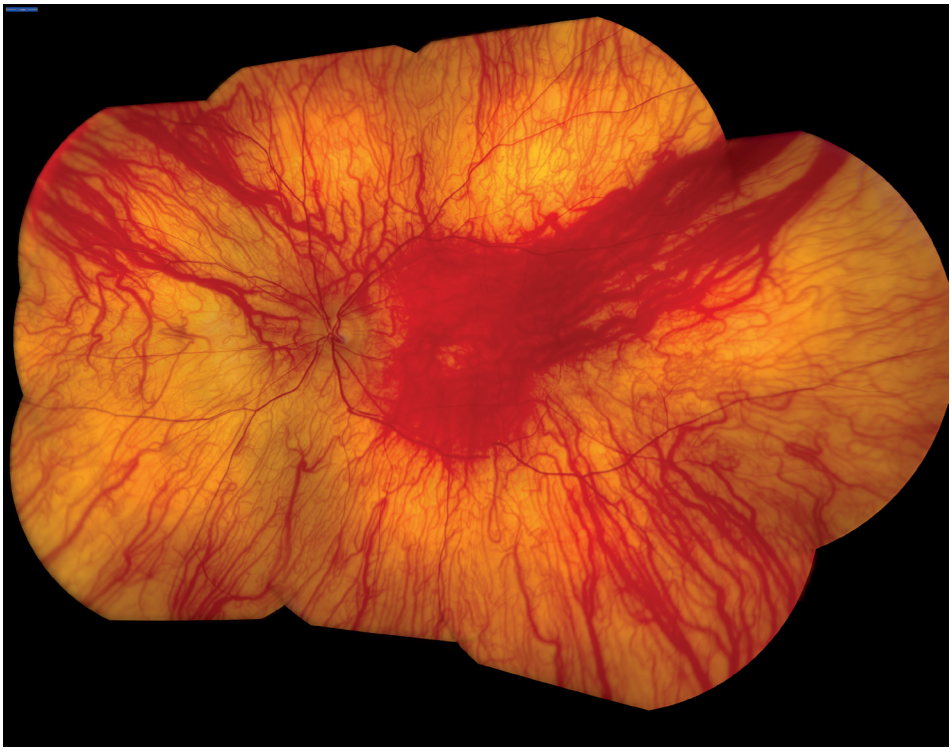

Figure 2. Fundus showing hypopigmentation and an absence of the macular reflex in oculocutaneous albinism type 1A.

DISCUSSION

High refractive errors are a common finding in patients with albinism. Often, the visual correction with spectacles is inadequate. Correction with contact lenses can be disappointing due to intolerance or lens instability caused by nystagmus. For these patients, refractive surgical correction, such as the iris-fixated pIOL, may be a good option to maximize visual acuity, although determining an accurate refraction may not be easy in patients with oculocutaneous albinism because of low visual acuity in combination with high astigmatism and nystagmus. Subjective improvement with less disturbing vision was reported in our 3 cases, and postoperative visual acuity increased. In Case 1, a spherical equivalent of around zero was achieved initially but slightly increasing hyperopia was seen in the long-term follow-up. In the other cases, mainly astigmatism remains. The patients are satisfied with the refractive results even though some rest-refractive error remains. To our knowledge, no literature currently describes the stability of refractive errors over time in patients with oculocutaneous albinism, but we do not have any reason to doubt that the stability might be different from that in normal eyes.

Strict preoperative criteria have to be met before iris-fixated pIOLs can be implanted to minimize the risk for endothelial cell loss and other complications in healthy eyes. Reliable endothelial cell analysis is known to be difficult to perform. Besides the measurement device, the skills of the technician, and the location on the cornea, the quality of the endothelial image accounts for a great deal in performing reliable endothelial cell analysis. In our cases, all endothelial cell photographs were acquired from the central region of the cornea with 2 noncontact specular microscopes. To correct for the use of 2 specular microscopes, although manufactured by the same company, the endothelial cell images were imported and manually recounted in external software, as described in Appendix 10. In our 3 cases, the acquired endothelial cell images were of fair to poor quality due to the presence of nystagmus. Preoperative endothelial cell photographs were acquired but were impossible to analyze because of the extremely poor image quality. As noted by McCarey et al.,[9] the number of visible and countable endothelial cells is greatly affected by the image quality. Endothelial cell density estimation will become more accurate with larger image samples and more cells counted per image. Physiological central corneal endothelial cell loss is reported to be approximately 0.6% per year.[10] In our cases, endothelial cell loss varied from 0.33% to 1.75% per year. The rate of endothelial cell loss does not seem to differ from the rate reported in normal eyes implanted with an iris-fixated pIOL.[5,8] However, reliability of the reported ECDs is limited because of the low quality of the analyzed images. We believe that the difference

in ECD between the 2 eyes in Case 3 may have been preexistent as it was visible at the first reliable ECD measurement at the 1-year follow-up and both surgeries and direct postoperative history were unremarkable.

In patients with albinism, the iris might not be suitable for iris-fixated pIOLs. A thin iris may be too fragile to allow satisfactory enclavation of the IOL. The normal iris is characterized by 5 layers of tissue: an anterior layer of chromatophores containing melanocytes with a genetically determined density of melanin pigment granules, a well-vascularized stroma containing a dense collection of fibroblasts and radially oriented collagen fibers and glycosaminoglycans, sphincter and dilator muscle fiber layers, and the iris-pigmented epithelium. Although a translucent iris, as may be observed in oculocutaneous albinism, appears fragile, absence or lack of pigmentation does not appear to decrease the mechanical strength of the iris and thus is not likely to increase the risk for dislocation of an iris-fixated IOL. We were unable to find any mechanical strength properties attributed to melanin in the literature. A plausible theory is that rather than pigment, other components of the iris are responsible for the mechanical strength of the tissue, such as the muscular structures or the heavily vascularized stroma.

Melanin is proposed to have proinflammatory properties.[11] This suggests that less inflammation is to be expected after surgery in eyes that contain a small amount or no melanin than in eyes that contain melanin, i.e., normal eyes. In our 3 cases with oculocutaneous albinism 1A, no extraordinary inflammatory response was observed after pIOL implantation.

The 3 cases demonstrate successful Artisan pIOL implantation in patients with oculocutaneous albinism 1A. No complications, particularly no dislocation or luxation, were observed. The obtained refractive results were satisfactory to the patients. The visual acuity improved in all 3 cases after implantation, and the endothelial cell counts remained acceptable throughout follow-up. Regular visits of the patients to continue ECD follow-ups at our clinic will be maintained.

Although studies with greater numbers of eyes must be performed, these 3 cases suggest that iris-fixated pIOLs can be considered a safe treatment option for patients with albinism and high refractive errors.

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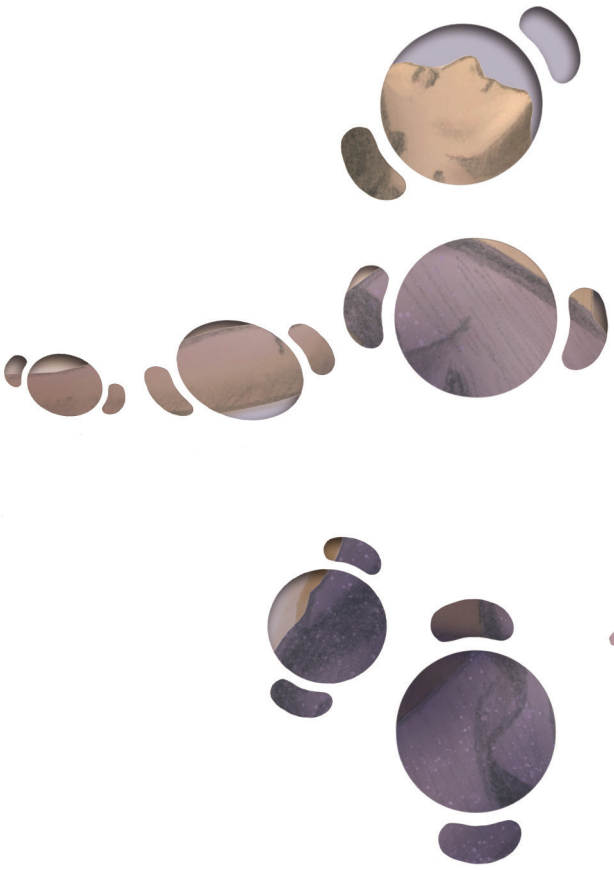

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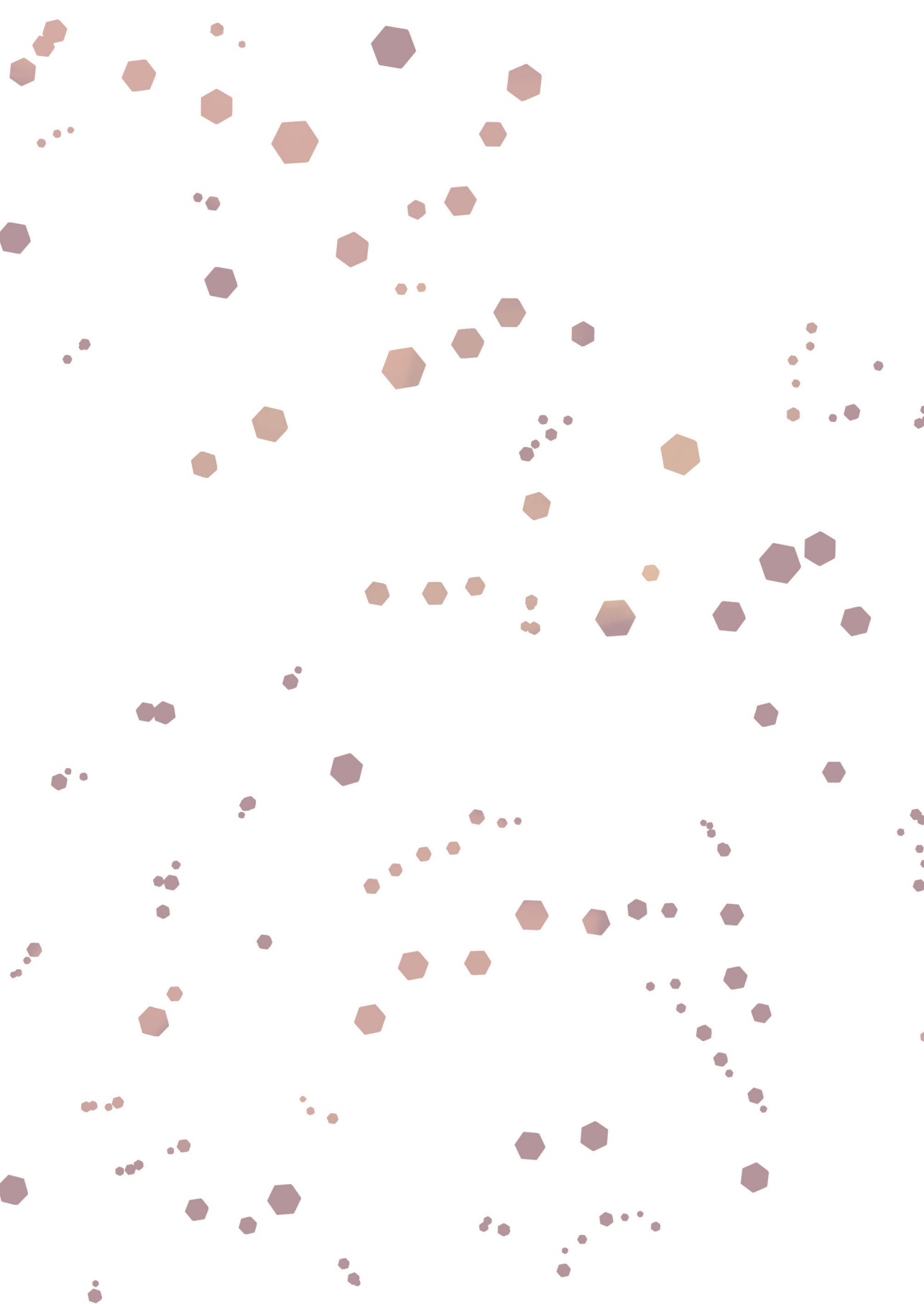

Chapter 6

Magnetic Resonance Compatibility of Intraocular Lenses Measured at 7 Tesla

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ABSTRACT

Purpose

To determine whether intraocular lenses (IOLs) are compatible with magnetic resonance imaging (MRI) at a magnetic field strength of 7 Tesla, the highest field strength at which clinical MRI scans are performed.

Methods

A set of 23 intraocular lenses was selected based on the presence of dyes and metals and different geometric shapes. MR compatibility was evaluated in a high-field 7 Tesla MRI scanner according to the American Standard Test Method (ASTM). The magnetically induced displacement was measured via the angular deflection method. The degree of magnetic susceptibility artifact formation was evaluated by positioning the IOLs in a phantom gel for scanning, using a three- dimensional gradient echo (GRE) sequence. All images were visually inspected to determine the spatial extent of any signal voids. Fiber-optic temperature probes were deployed to measure radio-frequency (RF) heating using a GRE sequence with powers 10 times higher than clinical settings.

Results

No significant displacement was detected with any of the tested IOLs. A significant magnetic susceptibility artifact was caused by the small platinum component of the Worst Platinum Clip IOL. None of the other 22 IOLs caused measurable susceptibility artifacts. Measurements on RF induced heating showed no significant temperature rise (<0.25°C) of the tested IOLs.

Conclusions

MRI did not induce movement or RF heating of any of the IOLs. We conclude that all the tested intraocular lenses are considered safe for MRI up to and including 7 Tesla. One IOL, the Worst Platinum Clip IOL, caused a significant imaging artifact.

INTRODUCTION

Magnetic Resonance Imaging (MRI) relies on the principle of nuclear magnetic resonance and involves the patient being placed in a strong static magnetic field, with the image being formed using short pulses of low-frequency (kHz range) magnetic field gradients and high-frequency (hundreds of MHz) radio-frequency (RF) pulses. Clinical MRI scans of the eye are currently performed at a field strength of either 1.5 or 3 Tesla.

With the arrival of higher (7 Tesla) commercial MRI systems, a higher signal-to-noise ratio can be achieved in the image, which can also be utilized for improved spatial resolution. High-resolution, high-field MRI scans may become an important tool for imaging the structures of the eye and retina, since conventional imaging methods like ultrasound imaging, partial coherence interferometry, and optical coherence tomography are limited by optical distortions or depth visualization, and have limited penetration through ocular structures such as the iris and sclera.[1–4] MRI provides depth visualization of the entire eye in any desired anatomic plane. Moreover, MRI does not obstruct binocular vision and enables research of accommodating structures of the eye.[3]

Prior to undergoing an MR examination, every patient should be screened in order to ensure safety and, in a broader sense, confirm that any implants present are MR compatible. The term "MR compatibility" indicates that an object or a device, when used in the MR environment, does not significantly reduce the quality of the diagnostic information via the formation of image artifacts, and that its operation will not be detrimentally affected by the MR device (i.e., it is MR safe). In this sense, safety is defined as the lack of potential injury to the individual and is determined by evaluating whether physical movement or heating of the implant is induced during MR imaging.[5] Knowledge of specific types of implants is essential for screening patients before MRI. All tested implants are considered safe up to a field strength in which they were tested. For higher field systems, all objects and devices should be retested for safety and compatibility prior to screening patients because of the shorter RF wavelengths involved.

Cataract surgery with IOL implantation is the most commonly performed surgery, and incidence is still increasing.[6–8] Because millions of people undergo cataract and refractive surgery with intraocular lens (IOL) implantation worldwide, testing IOLs at a high magnetic field strength MRI is essential in order to warrant the patient's safety. Keizer and Strake tested a selection of IOLs in a magnetic field strength of 1.0 Tesla.[9,10] To our knowledge no testing of IOLs at a field strength of 7 Tesla has been performed.

There are a variety of IOLs on the market, some containing different colors, such as blue-blocking IOLs or IOLs made with colored haptics. In addition, specific older types of IOLs contain metal. The different elements and the composition of an IOL, for example, the presence of dyes or metal, may cause movement and/or heating during an MR procedure. To illustrate the significance, stents, vascular clips, and other implants containing metal elements are being thoroughly tested for MR compatibility as they may be subject to movement or heating.[11] Furthermore, dyes based on iron oxide, as seen in permanent makeup and decorative tattoos, are notorious for causing burning of the skin during an MR procedure.[12–14]

Our hypothesis was that scanning IOLs containing either metal or dyes would cause a higher rise in temperature on or near the IOL due to RF heating, in comparison to clear IOLs. To test this hypothesis, clear and colored IOLs with various geometric shapes, as well as an IOL containing metal, were exposed to a 7 Tesla MR field and examined for magnetically induced movement, heating, and artifact formation. The purpose of this study was to ascertain whether the presence of an IOL, when performing an MR examination at a field strength of 7 Tesla, can influence the image quality or cause damage to the eye as a result of heating or movement.

METHODS

The IOLs tested were obtained from various manufacturing companies (see Table 2). A set of 23 IOLs was selected, based on the presence of dyes or metal and different geometric shapes. MRI compatibility of the IOLs was evaluated according to American Standard Test Methods (ASTMs) F2052-06 and F2182-09 for magnetically induced displacement and radio frequency–induced heating.[15,16] The formation of magnetic susceptibility–induced image artifacts was also evaluated. MR was performed on an Achieva whole body 7 Tesla MR system (Philips Healthcare, Best, The Netherlands), which is used for clinically related research at Leiden University Medical Center.

Phantom Formulation

A phantom (gel) was formulated with tissue mimicking conductivity and permittivity for imaging the IOLs and heating tests, according to ASTM protocol. The gel consisted of 1.55 g/L sodium chloride (NaCl) and 31 g/L hydroxyethylcellulose (HEC) in water. To obtain a gel free of air bubbles, suitable for imaging the IOLs, the following procedure was used: A container was positioned in an ultrasound bath. NaCl was added to the water and stirred manually for 20 minutes until completely dissolved. Thereafter, the gel was slowly stirred using an electric stirrer for a period of at least 3 hours until a uniform gel was formed. Finally, the gel was positioned in the 7 Tesla scanner room for at least 24 hours prior to testing, to obtain a transparent gel that was free of bubbles and at room temperature.

Magnetically Induced Displacement

The magnetically induced displacement was measured via the angular deflection of the IOL, using a protractor mounted on a stand with the zero-degree mark at the "6 o'clock position." The first step was to determine the position along the longitudinal axis of the magnet that gives the maximum deflection angle. To perform this measurement, a slightly ferromagnetic object was hung on a 0.1 mm diameter nylon string. The protractor stand was placed at the center of the patient table in the left-right direction, and the reference position corresponding to maximum deflection was determined by incrementally moving the tabletop into the magnet. Subsequently, the angular deflection from the vertical was measured for all IOLs with the protractor placed at the reference position. During all these measurements, the air circulation in the scanner bore was switched off. In the case where the deflection angle equals 45°, the pulling force exerted by the magnet equals that of gravity. Magnetic forces are considered significant only when the deflection angle is greater than 45°.[15]

Radio Frequency Induced Heating

Radio-frequency heating tests were performed with a 6 cm diameter transmit/receive surface coil, which is used for imaging the eye at 7 Tesla. The surface coil is segmented by four equal-value capacitors, to reduce the conservative electric field from the coil. A pi network is used to impedance match the coil to 50Ω. The IOLs were placed in a small chamber formed within an acrylic sheet, which was filled with the formulated gel. An MR-compatible fiber-optic temperature sensor (Opsens, Quebec, Canada) was positioned using a 1 mm diameter groove, which bisected the chamber so that its tip was positioned within 2 mm of the IOL (Figure 1). A separate reference measurement, without an IOL present, was performed with the same set-up to determine the temperature rise of the gel itself. The position of the temperature probe was checked prior to and immediately after scanning, for correct and stable positioning. The air circulation was switched off, and the surface coil was placed on top of the chamber, with a 5 mm thick spacer between the chamber and the RF coil. In order to present the "worst case scenario", the coil was placed off-center with respect to the IOL, so the electric field close to the IOL was at its maximum value. The temperature was monitored during a conventional multi-slice gradient echo (GRE) sequence used for imaging the eye, with power settings above the regulatory clinical scanning parameters. By manipulating the flip angle, repetition time, and allowable maximum RF amplifier, the time-averaged specific absorption rate (SAR) was increased by a factor of 10. This resulted in an averaged SAR of approximately 5 W/kg - well above the value that would be used in any clinical study, which in normal operating mode is limited to 2 W/kg. A period of between 2 and 5 minutes was allowed after placing the set-up in the magnet before temperature data acquisition began in order to allow thermal equilibrium to be established; the criterion for this was a temperature change of no more than 0.1°C over 1 minute. Measurements were performed at least in duplicate per IOL and spread over three sessions. For each session, the test assembly was rebuilt, and a minimum of three reference measurements were taken.

Evaluation of Image Artifacts

In order to measure any magnetic susceptibility–induced image artifacts, the IOLs were suspended from a nylon string and placed in a box filled with the formulated gel. Image artifacts were evaluated by performing a three-dimensional (3-D) spoiled GRE sequence with TR/repetition time/echo time (TR/TE) =50/30 ms, flip angle 10°, spatial resolution of 0.22 x 0.22 x 0.22 mm, 105 slices, and field of view 115 x 115 mm. In post-processing, multi-planar reformats were made to reconstruct images parallel and perpendicular to the IOL. All images were visually inspected to determine the presence of any signal voids, and the spatial extent of the voids was determined using the measuring tool as provided by the manufacturer.

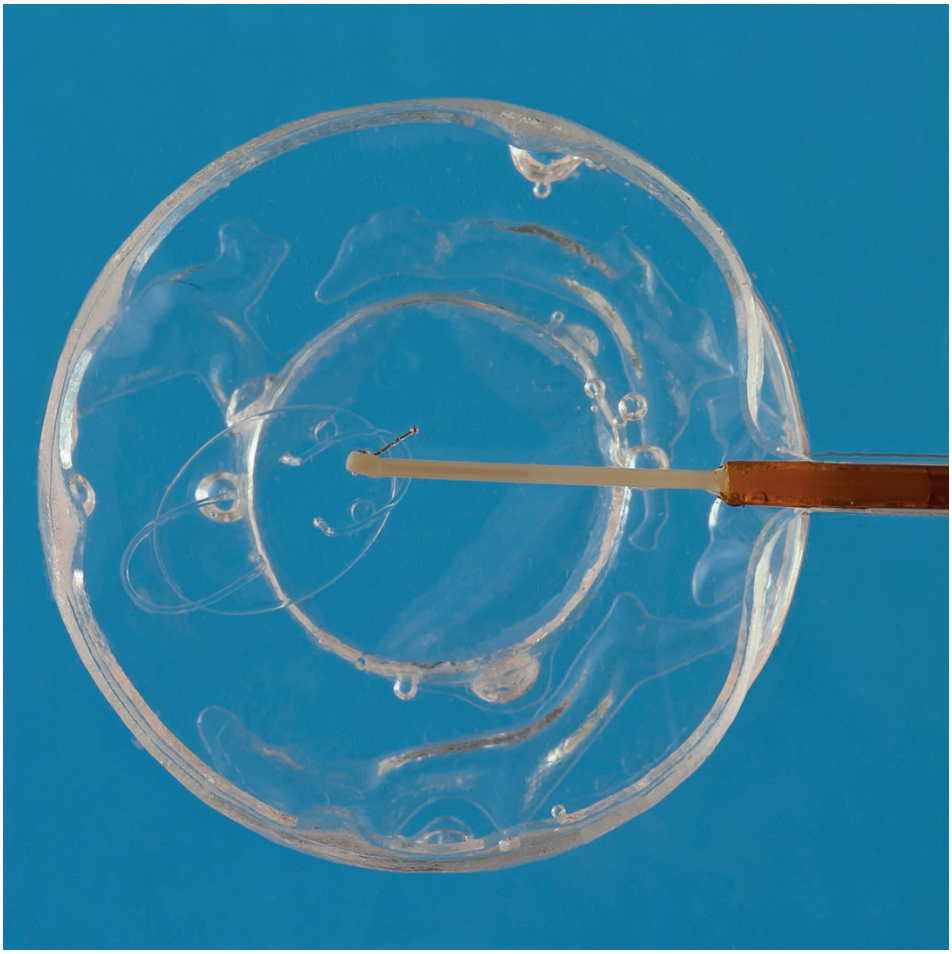

Figure 1. For evaluation of radio-frequency heating, IOLs were individually placed in a small chamber. A fiber-optic temperature sensor (Opsens) was positioned as close to the IOL as possible. Temperature was monitored during a multi-slice GRE sequence with high power settings.

RESULTS

An overview of results per group (clear, dyed, and metal- containing IOLs) is shown in Table 1. An overview of individual details for IOL properties and measurement results is shown in Table 2.

The capsular tension ring (Ophtec, Groningen, The Netherlands) was excluded from the deflection tests because the weight of the capsular tension ring was insufficient to pull the string straight down. All other IOLs had sufficiently significant weight to pull the nylon string vertically. A maximum of 1° of deflection was observed during the magnetically induced displacement tests. This is well under the 45° that is considered the threshold for significant deflection. Temperature rises of 0.05°C ± 0.08°C, 0.07°C ± 0.07°C, and 0.07°C ± 0.06°C were observed for the clear, dyed, and metal-containing IOL groups, respectively (Table 1), compared with the control gel. The difference between groups was not statistically significant (ANOVA, $p = 0.856$). A maximum temperature rise of 0.25°C was measured. The values are essentially identical to that measured in the control gel in the absence of any IOL, suggesting no extra contribution to temperature rise was invoked by the presence of the IOL. The relative mean temperature rise of RF heating, per tested IOL, is shown in Figure 2.

A susceptibility artifact of 4 x 5 x 4 mm (width x length x depth) was observed as a signal void at the position of the platinum component of the Worst Platinum Clip IOL (Figure 3). None of the other 22 IOLs caused measurable susceptibility artifacts (Figure 4).

Table 1. Overview of results per group

Group IOL	Temperature Rise		Artifact Formation	Deflection
Clear	0.05 ± 0.08°C	Max 0.18°C	No	< 0.5°
Dyed	0.07 ± 0.07°C	Max 0.25°C	No	< 1°
Metal	0.07 ± 0.06°C	Max 0.15°C	Yes	< 0.5°

Table 2. Overview of properties and results of the tested intraocular lenses.

Type IOL	Manufacturing Company	Characteristic	Artifact	Deflection	Mean Temperature Rise
Verisyse	Advanced Medical Optics USA	clear	no	0°	0.135
Akreos Adapt AO	Bausch&Lomb USA	clear	no	< 0.5°	-0.016
Microincision Lens MI60	Bausch&Lomb USA	clear	no	0°	0.06
Artisan Model 206	Ophtec the Netherlands	clear	no	0°	-0.02
Capsular Tension Ring	Ophtec the Netherlands	clear	no	-	-0.05
Artiflex Model 401	Ophtec the Netherlands	clear	no	0°	0.024
Quadrimax pc 545	Ophtec the Netherlands	clear	no	0°	0.1
CT Aspina 409M	Carl Zeiss Germany	clear	no	< 0.5°	0.180
Acrysof IQ SN60WF	Alcon, USA	dyed	no	0°	0.15
MN60ac 210	Alcon, USA	dyed	no	< 0.5°	0.045
Acrysof MA60 ac 210	Alcon, USA	dyed	no	< 1°	0.245
Z9002	Advanced Medical Optics USA	dyed	no	< 0.5°	-0.01
ZA9003	Advanced Medical Optics USA	dyed	no	0°	0.045
Crystalens HD	Bausch&Lomb USA	dyed	no	0°	0.07
AF-1 imics1 NY-60	Hoya Lens Japan	dyed	no	0°	0.015
Model 410	Ophtec the Netherlands	dyed	no	0°	-0.009
Model 430	Ophtec the Netherlands	dyed	no	<0.5°	0.096
PC-440Y Orange series,	Ophtec the Netherlands	dyed	no	0°	0.04
PC 530 Trimax	Ophtec the Netherlands	dyed	no	0°	0.133
Lentis LS-312-1Y	Ophtec the Netherlands	dyed	no	< 1°	0.065
C-loop 3-piece L402	Oculentis Germany	dyed	no	0°	0.045
Lentis LS-313-1Y	Oculentis Germany	dyed	no	< 1°	0.041
Worst Platinum Clip	Ophtec the Netherlands	metal	yes	< 0.5°	0.07

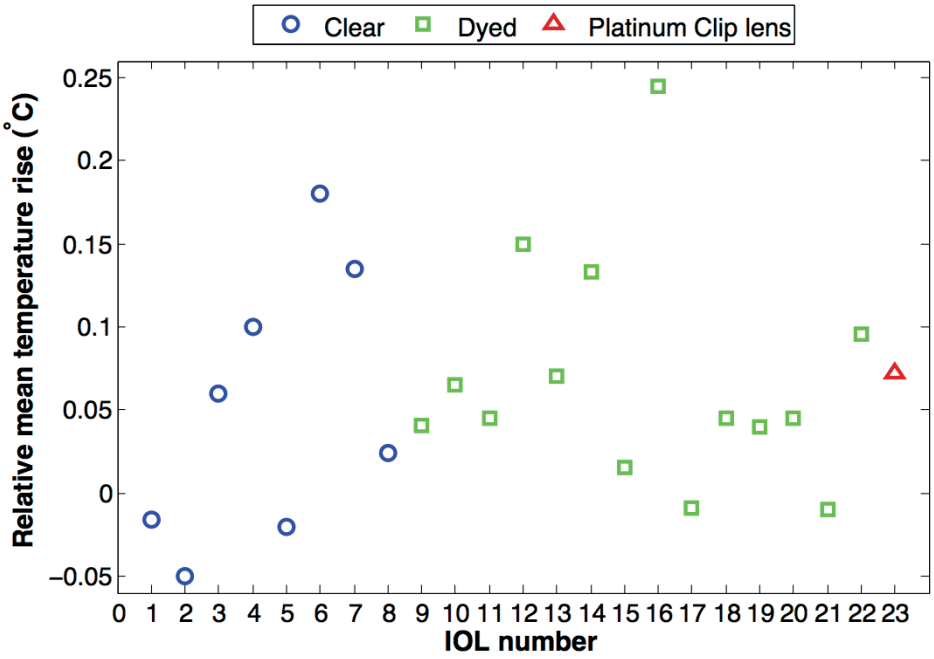

Figure 2. Graph showing the relative mean temperature rise per tested IOL. Different colors correspond with clear IOLs (blue), dyed IOLs (green), and a metal-containing IOL (red).

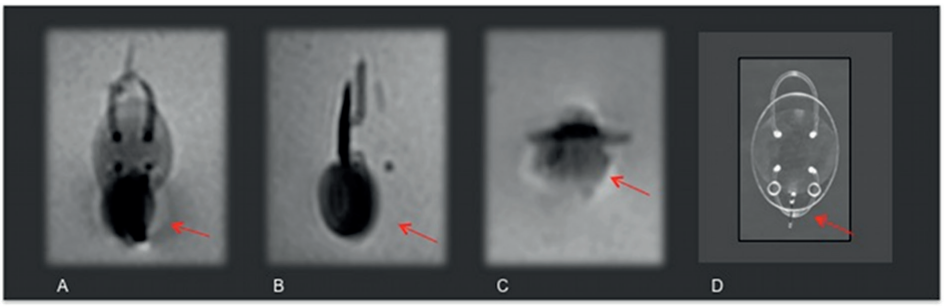

Figure 3. Reconstructed images showing an artifact around the platinum pin of the Worst Platinum Clip IOL. IOLs were reconstructed in (A) coronal, (B) sagittal and (C) transverse planes and visually inspected for signal voids. The red arrow indicates an artifact of 4 x 5 x 4 mm (width x length x depth). (D) Photograph of Worst Platinum Clip IOL with red arrow indicating the platinum component.

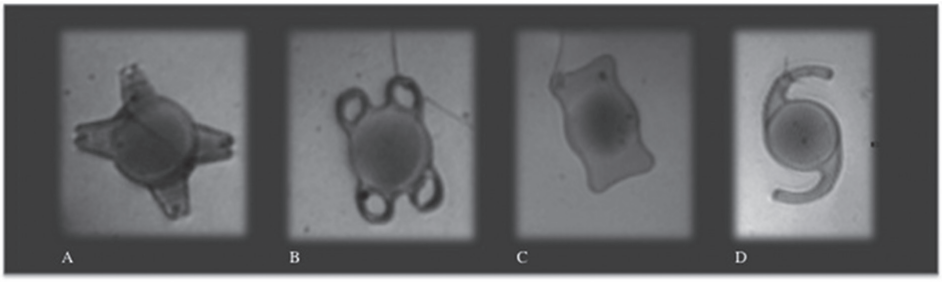

Figure 4. Examples of reconstructed MR images in coronal plane of (A) Micro Incision Lens (Bausch & Lomb, Rochester, NY), (B) Quadrimax (Ophtec, Groningen, The Netherlands), (C) CT Aspina 409 M (Carl Zeiss, Jena, Germany), and (D) LS 312-1Y (Oculentis, Berlin, Germany). No artifact formation is observed.

DISCUSSION

Various objects used in ophthalmology have been evaluated for safety at various field strengths during an MR procedure.[10,17–22] De Keizer and Te Strake tested IOLs at a field strength of 1.0 Tesla.[9] Testing of eyelid implants has been performed at a magnetic field strength of 7 Tesla by Schrom et al.[24] The Ex-PRESS glaucoma shunt has been tested at a field strength of up to 4.7 Tesla.[18] To our knowledge, this is the first time IOLs have been tested at a 7 Tesla magnetic field strength for compatibility during an MR procedure. Testing was done according to ASTM protocol for magnetically induced displacement and radio frequency–induced heating. The formation of magnetic susceptibility-induced image artifacts was also evaluated.

The first safety concern is that an IOL might contain magnetic components, which could experience a force from the static magnetic field (and the gradient in the static magnetic field when the patient is slid into the magnet), which in turn could cause physical movement of the implant and thus damage to the eye. Physical movement of the IOLs was evaluated by measuring the magnetically induced displacement. According to the ASTM standard testing method for magnetically induced displacement, the weight of the nylon string should be no more than 1% of that of the tested devices for the deflection experiment in order for the weight of the string to be considered negligible. In this study, this criterion did not meet strict ASTM standards because of the lightness of the IOLs. We conclude that, within measurement error, there is effectively 0° of deflection, meaning no displacement of the IOLs resulting from the magnetic forces exerted by the static magnetic field. Furthermore, taking into consideration that in vivo resistance is provided by ocular tissue, a maximum deflection angle of 1° due to the magnetic field is highly unlikely to result in any movement of the IOLs in vivo; thus the risk of displacement caused by the magnetic force is smaller than the risk that is imposed by normal daily activity in the Earth's gravitational field.

During MRI, high-frequency pulses of radio-frequency energy are used to excite the protons. Depending on the material properties, size, and shape of an implant, an electric current may be formed or (part of) the object or device may act as an antenna, causing heating, which may lead to serious burning of the surrounding tissue.[25] Problems of excessive heating and the induction of electric currents are typically associated with implants that have elongated configurations and/or are electronically activated. Furthermore, the presence of dyes may cause heating, as is seen in metal-based dyes used in tattoos and permanent makeup.[12–14] RF temperature measurements are complex to perform and multi-parameter dependent. Conditions such as room temperature and ventilation, positioning of the test assembly in the bore, and the

position of the temperature probe to the IOL were carefully monitored during the study. Nevertheless, five IOLs showed a minimal negative temperature rise compared with the control gel. This can be explained by physiological fluctuations in room temperature and by the complexity and multi-parameter dependence of the measurement method. We measured a maximum temperature rise of 0.25°C with MR power levels much above regulatory limits. Based on safety standards for MR systems published by the International Electrotechnical Commission (IEC), for healthy subjects with a normal core body temperature of 37°C, the spatially localized temperature limit of the head is set at 38°C.[23] This indicates a maximum temperature rise of the head of 1°C during normal MR operation modes. The maximum temperature increase we observed is well below the value set by the IEC, meaning no safety issues. Furthermore, measurement in vitro of temperature rise is likely to overestimate the actual temperature rise for an implant in situ, since natural convection in wet tissue will also reduce temperature rise when these conditions are present at or near the implant.[16] Between the clear, dyed, and metal-containing IOL groups, no statistical difference in temperature rise was found. Hence, we conclude that there is no additional safety risk for RF heating for the tested dyed and metal-containing IOLs compared with the clear IOLs.

Finally, in order to help clinicians make a decision about the appropriateness of a given MRI scan for a patient with an implant, a statement about image artifact formation of a given object or device should be determined. If an IOL induces a susceptibility artifact, this may lead to diagnostic misinterpretation and/or it may mistakenly be apportioned to pathology if not recognized as such. It is known that platinum can cause low-level susceptibility artifacts.[26] Schrom et al. observed an artifact of platinum-containing eyelid implants.[24] In accordance with their findings, an artifact was observed at the position of the platinum component of the Worst Platinum Clip IOL. Although the artifact we observed around the platinum pin of the Worst Platinum Clip IOL is quite small in terms of size (4 x 5 x 4 mm), it would cover a relatively large part of the field of view, hampering 7 Tesla eye imaging. No other IOL showed any measurable image artifact.

In conclusion, all tested IOLs are considered safe for MR imaging at a field strength of up to and including 7 Tesla. Further testing of other surgical materials and implants used in ophthalmology should be performed as well, in order to ensure a patient's safety.

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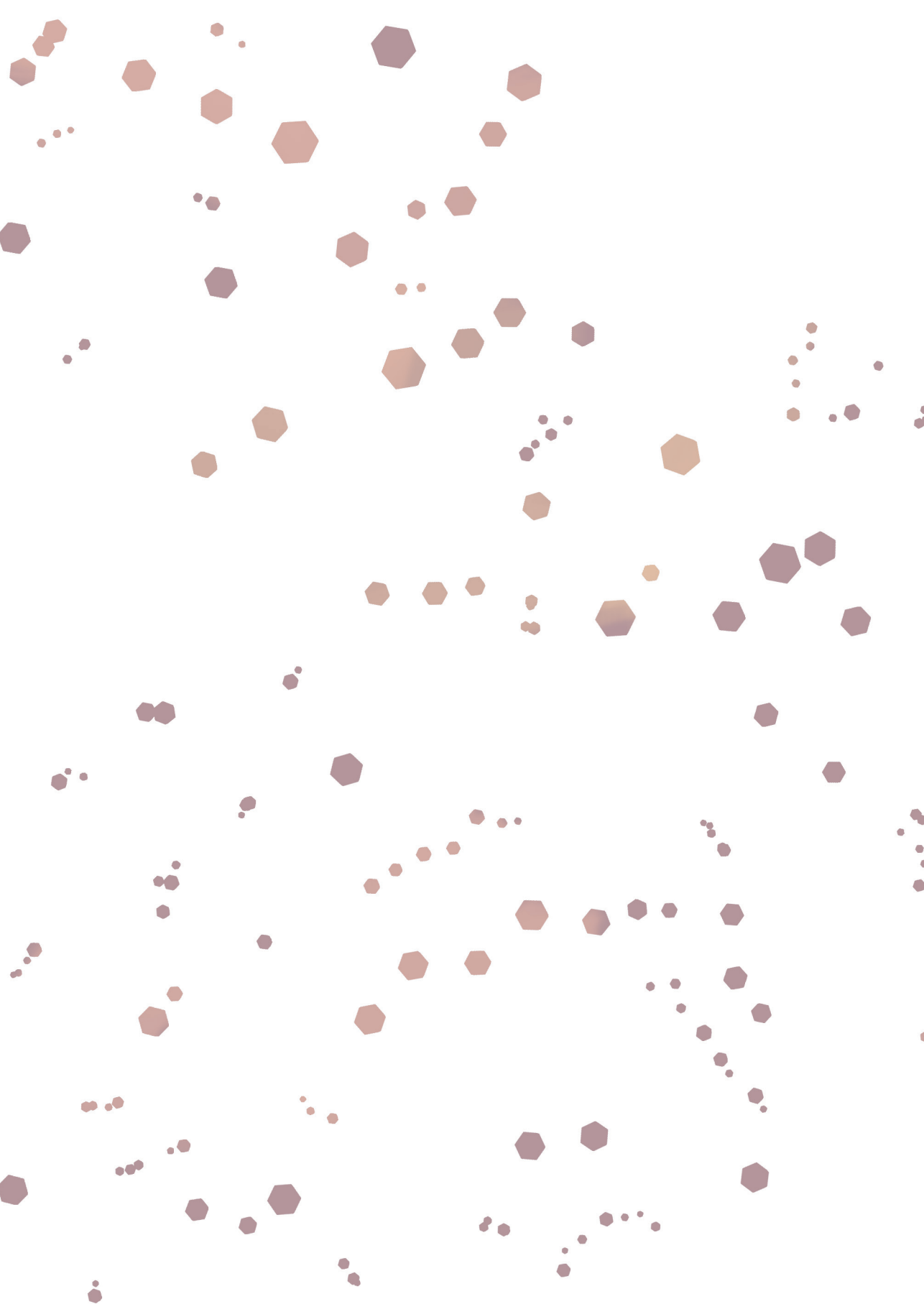

Chapter 7

Improved Interchangeability with Different Corneal Specular Microscopes for Quantitative Endothelial Cell Analysis

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ABSTRACT

Introduction

During our clinical practice and research, we encountered an interchangeability problem when using the SP-2000P and SP-3000P Topcon corneal specular microscopes (CSMs) (Topcon Medical Systems, Tokyo, Japan) regarding the endothelial cell count (ECC). We describe a method to improve interchangeability between these CSMs.

Methods

Five consecutive good-quality endothelial cell photographs were obtained in 22 eyes of 11 subjects. An ECC comparison between the two CSMs was performed after (I) gauging and calibration by the manufacturer, (II) adjustment of the magnification, (III) correction after external horizontal and vertical calibration.

Results

There was a statistically significant difference between the ECC of the SP-2000P and SP-3000P at the start. The SP-2000P counted an average of 500 cells/mm^2 more than the SP-3000P ($p=0.00$). After correction for magnification and determining a correction factor based on external calibration, the difference between the ECC of the SP-2000P and the SP-3000P was then found to be 0.4 cells/mm^2 and was not statistically significant ($p=0.98$).

Discussion

We propose a method for improving interchangeability, which involves checking magnification settings, re-checking magnification calibration with external calibration devices, and then calculating correction factors. This method can be applied to various specular or confocal microscopes and their associated endothelial cell analysis software packages to be able to keep performing precise endothelial cell counts and to enable comparison of ECCs when a CSM needs to be replaced or when results from different microscopes need to be compared.

INTRODUCTION

Corneal specular microscopy (CSM) can provide non-invasive quantitative and qualitative analysis of the most inner layer of the cornea, the endothelium. Specular reflection refers to the viewing of objects that occurs when light is reflected from the interfaces of materials with different refractive indices. A specular microscope (SM) captures the image that is reflected from the optical interface between the corneal endothelium and the aqueous humor. The endothelial cells (ECs) can be imaged because the refractive index of the ECs exceeds the refractive index of the aqueous humor.[1] When the angle of incident light equals the angle of reflection, an image occurs in a mirror-like fashion and can be captured by the eye or a camera. This principle was first described by Vogt in 1920.[2]

In modern specular microscopic endothelial analysis, software is responsible for quantitative EC analysis. This is also referred to as endothelial cell density (ECD) or endothelial cell count (ECC) in cells per square millimeter (cells/mm^2). The only way for the software to correctly assess the ECC is when it is attached to only one adequately calibrated and gauged CSM. This is important since every individual CSM has its own magnification and calibration settings.

Various specular microscopes have been developed by a number of companies. Different CSMs and image analysis methods have been evaluated for comparability and are usually not interchangeable.[3-8] To be able to reliably compare longitudinal ECC measurements, it is therefore wise to use the same CSM and analysis system for all measurements. However, when instruments wear out, it is often no longer possible or even desirable to replace it with the same previous type. This may pose a problem, as we discovered when we needed to replace the old CSM at our department. Although we selected its newer version, manufactured by the same company, we still encountered an interchangeability issue.

Amongst other indications, the CSM is actively used at our department to evaluate the corneal endothelium for preoperative assessment and follow-up visits after implantation of iris-fixated phakic intraocular lenses (IF-pIOLs). Evaluation of the corneal endothelium is a key safety parameter after implantation of IF-pIOLs and other anterior chamber pIOLs. Since quantitative EC analysis is the most accepted and commonly used parameter for evaluating the corneal endothelium after various types of intraocular surgery and there is a need for reliable ECCs to assess the long-term safety [9-12], we would like to propose an effective way to deal with interchangeability concerns arising from the use of different types of CSMs, such as when an instrument needs to be replaced.

METHODS

We will describe the method used for comparing two individual CSMs in the SP-series of Topcon (Topcon Medical Systems, Tokyo, Japan): our newer SP-3000P model and our older SP-2000P model.

With each specular microscope, five consecutive good-quality endothelial cell photographs were obtained in 22 eyes of 11 subjects. In accordance with the Declaration of Helsinki and approval of the medical ethical committee of the Leiden University Medical Center, each participating patient signed an informed consent form. Photographs of the central corneal ECs were acquired by one experienced operator. ECCs were determined by semi-automated "corrected endothelial cell count" using the IMAGEnet software, i.e. the software-defined cell borders were manually corrected prior to quantitative calculations (also known as re-traced method) as described by Cheung et al.[13] The maximum possible cell area was selected for semi-automated corrected endothelial cell counts. All ECCs obtained were recorded in a database (Microsoft Excel 2010), and statistics were performed in SPSS (IBM SPSS version 23 for Windows). Mixed models and Bland Altman plots were used for analysis and graphical visualization of the acquired data.

An ECC comparison between the two CSMs was performed after each of the following steps:

1. Both CSMs were checked, calibrated and gauged by the manufacturer, and the associated Topcon IMAGEnet software was updated to version 3.10.5.
2. Manual adjustment of magnification factor.
   The "true mask slit width", meaning the distance between the tick marks on an EC photograph, is close to 0.2 mm but differs in each microscope. The exact individual value can be displayed on the instrument by pressing the "cancel" and "delete" buttons simultaneously before turning it on. The magnification is reported for each endothelial cell image as "pixel size", as shown in Figure 1. Usually, it is set at a default value of 0.00115, which is the standard, pre-programmed magnification value in the IMAGEnet software assuming a true mask slit of 0.2 mm. To optimally gauge the instrument to its analysis software, the magnification factor was re-calculated using the true mask slit according to the formula: Magnification = (True mask slit width/0.2) * 0.00115 [14,15] and, if necessary, the magnification factor was in turn manually adjusted accordingly in the IMAGEnet software, see Appendix 11. ECCs were subsequently re-analyzed with the re-traced method ("corrected endothelial cell counts") within the IMAGEnet software.

3. External calibration.
   An external calibration micro-ruler tool was photographed both horizontally and vertically with both CSMs. To obtain a clear photographic image of the calibration micro-ruler, an experimental set-up was created with the micro-ruler positioned where normally the investigated eye would be. To obtain a clear photograph without using the internal flash of the CSM, a filter was placed in front of the CSM and a light source was placed behind the micro-ruler. To minimize distortion effects, the calibration micro-ruler was photographed five times both horizontally and vertically. Photographs were taken by two technicians, each time with a slight positional change of the experimental set-up. Photographs were only taken if the light reflex was or approximated a perfect circle. A minimum of two measurements was performed per photograph and the mean of all measurements was reported as the true distance; see Figure 2.

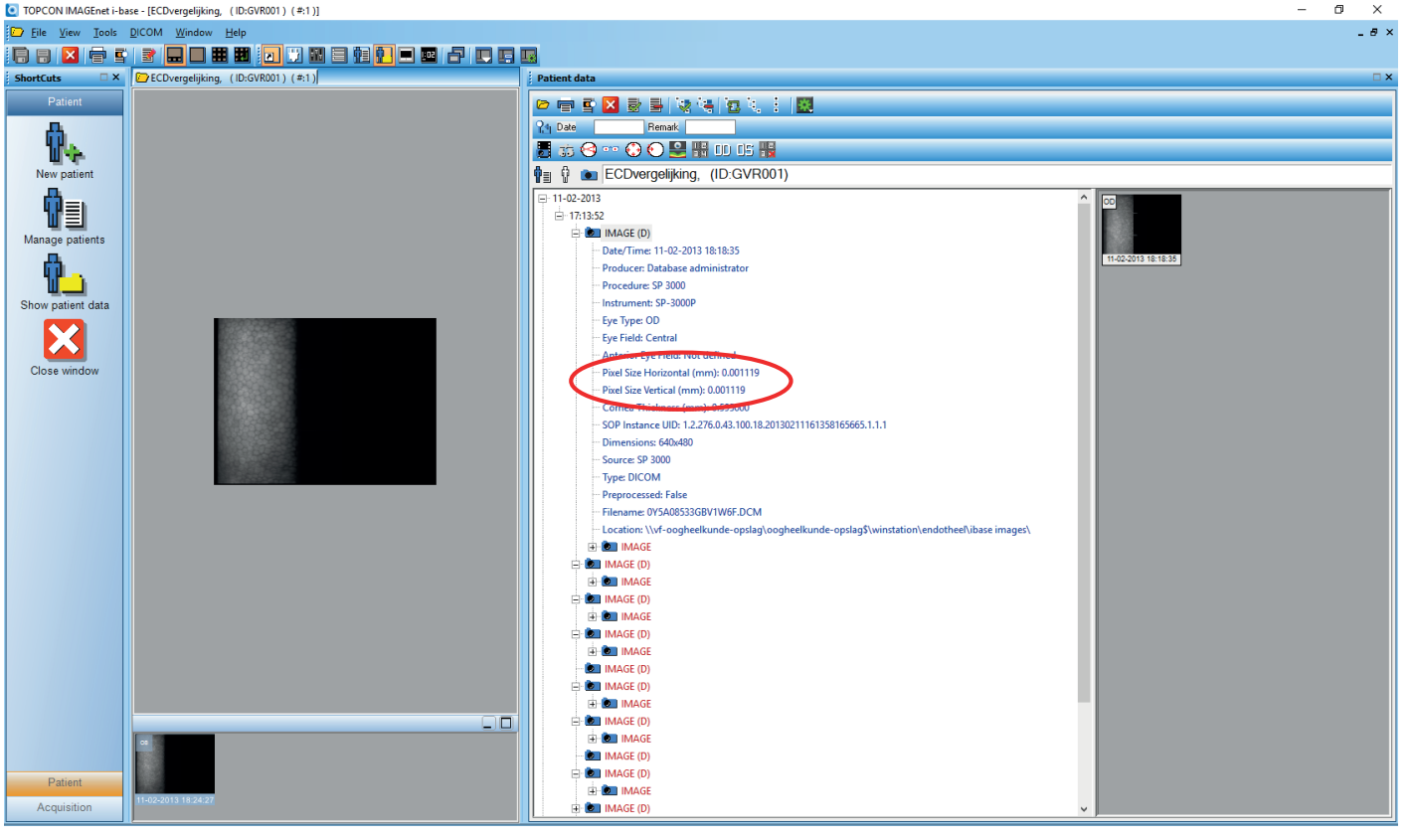

Figure 1. Print-screen of IMAGEnet software for endothelial cell analysis. The red circle indicates where to find the parameter for magnification referred to as “pixel size”.

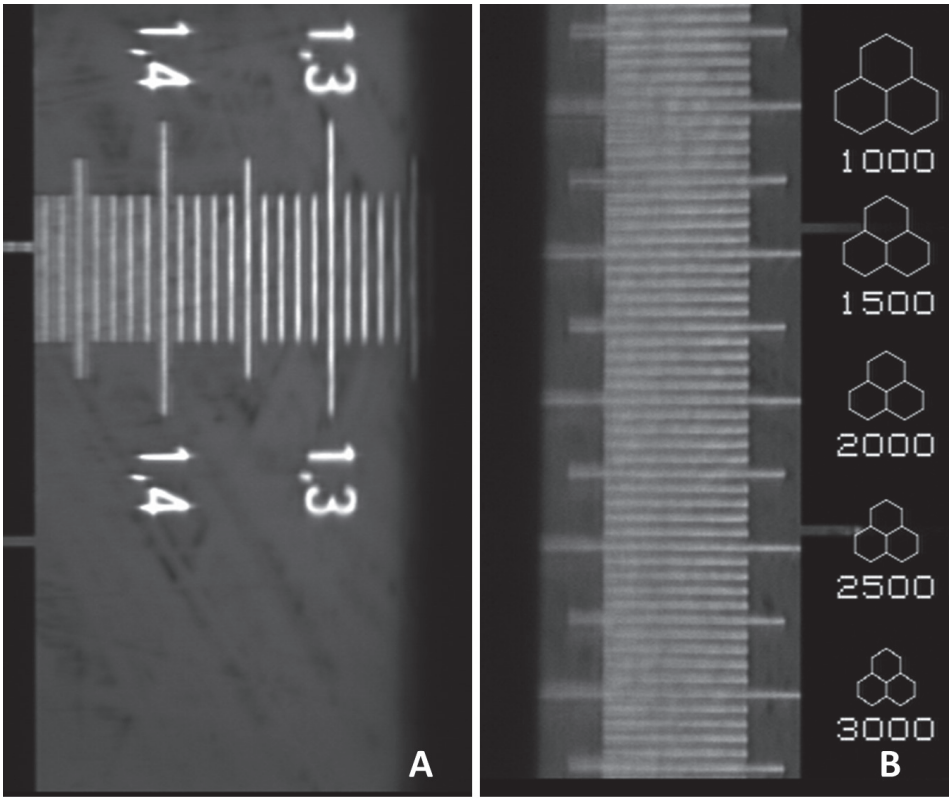

Figure 2. Picture of the micro-ruler used for external calibration, photographed with our specular microscopes.

A. Image of horizontal external calibration made with the SP-3000P
B. Image of vertical external calibration made with the SP-2000P

RESULTS

1. There was a statistically significant difference between the ECC of the SP-2000P and SP-3000P. The SP-2000P counted an average of 500 cells/mm^2 more than the SP-3000P (p=0.00); see Table 1 and Figure 3.
2. Manual adjustment of magnification factor.
    - SP-2000P: The true mask slit width was 0.1891 mm. The magnification was perfectly set to (0.1891/0.2) * 0.00115 =0.001087. In the IMAGEnet software, we discovered that the magnification was set to the factory default 0.00115 and we also encountered a situation where the magnification was not set at all.
    - SP-3000P: The true mask slit width was 0.1946 mm. The magnification was perfectly set to (0.1946/0.2) * 0.00115= 0.001119. The magnification was correctly set in the IMAGEnet software.
    - After adjusting to the correct pixel size and doing a recount of ECC, a statistically significant difference of 245 cells/mm^2 (p=0.00) remained between the two CSMs; see Table 2 and Figure 4.
3. External calibration.
   Based on the horizontal and vertical calibration with the micro-ruler tool, a slight asymmetry was detected between horizontal and vertical measurements. This slight distortion of the cell count area led to an over- or underestimation of the ECC, as shown in Figure 5.
    - SP-2000P: An underestimation in cell count area resulted in an overestimation in ECC of 8.1%.
    - SP-3000P: An overestimation in cell count area resulted in an underestimation in ECC of 1.4%.

A correction factor, based on the remaining difference in surface area after external calibration, was computed for both CSMs, and ECCs were re-determined. The difference between the ECC of the SP-2000P and the SP-3000P was then found to be 0.4 cells/mm^2 and was not statistically significant (p=0.98); see Table 3 and Figure 6.

Table 1. Difference in endothelial cell count per specular microscope IMAGEnet

Specular Microscope	Mean ECC (cells/mm²)	Difference (cells/mm²) (SD) (p)
SP-2000P	3058.7	500.2 (SD 150.4) (p<0.05)
SP-3000P	2558.5	

*ECC= endothelial cell count; SD = standard deviation; p = significance level linear mixed model

Table 2. Difference in endothelial cell count per specular microscope corrected for magnification factor

Specular Microscope	Mean ECC (cells/mm²)	Difference (cells/mm²) (SD) (p)
SP-2000P	2802.7	244.5 (SD 110.9) (p<0.05)
SP-3000P	2558.2	

*ECC= endothelial cell count; SD = standard deviation; p = significance level linear mixed model

Table 3. Difference in endothelial cell count per specular microscope after external calibration correction

Specular Microscope	Mean ECC (cells/mm²)	Difference (cells/mm²) (SD) (p)
SP-2000P	2593.6	0.4 (SD 88.7) (p=0.98)
SP-3000P	2594.0	

*ECC= endothelial cell count; SD = standard deviation; p = significance level linear mixed model

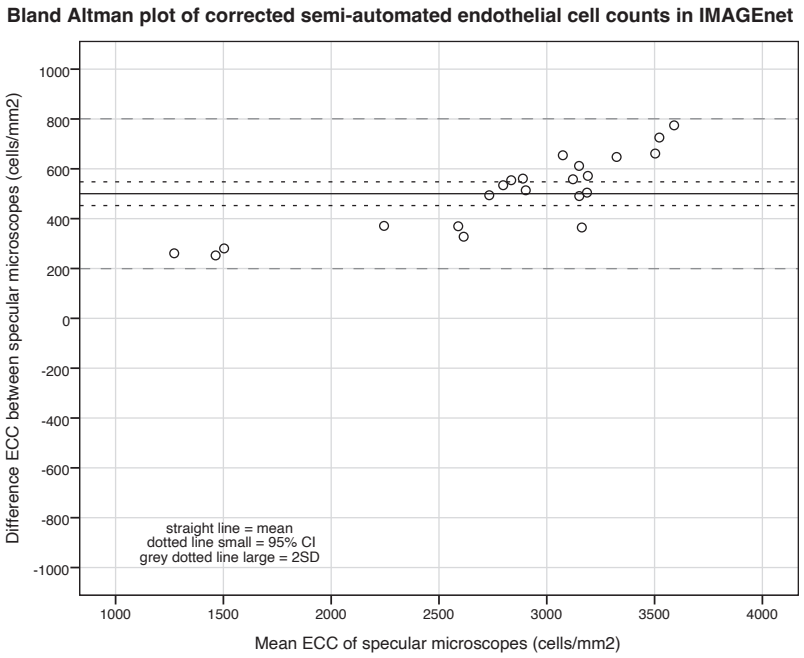

Figure 3. Bland Altman plot of corrected endothelial cell counts (re-traced method) in IMAGEnet

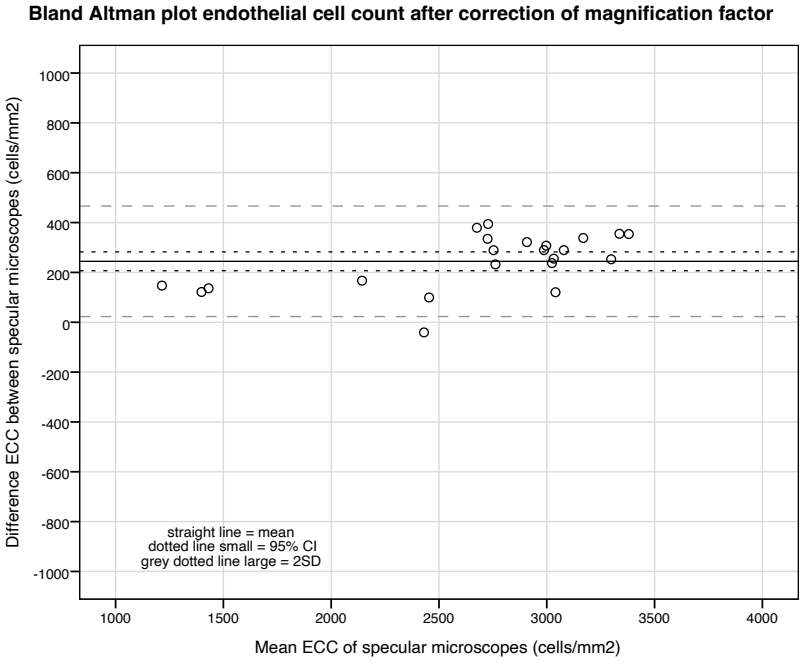

Figure 4. Bland Altman plot of endothelial cell count after correction of magnification factor

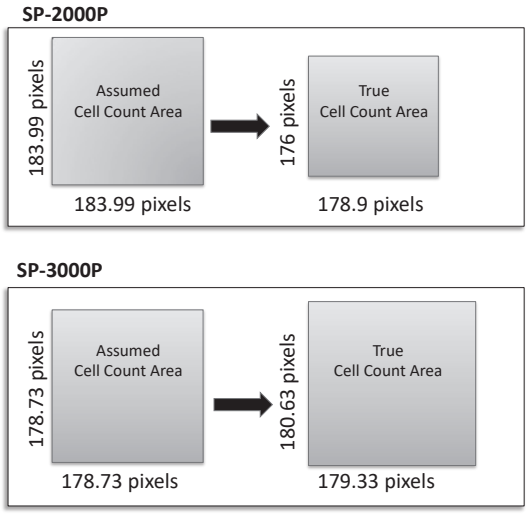

Figure 5. Based on external calibration, a difference in "true cell count area" versus "assumed cell count area" was found. Moreover, a slight asymmetric distortion of the postulated square surface area was noted. A correction factor was calculated, based on the difference in surface area.

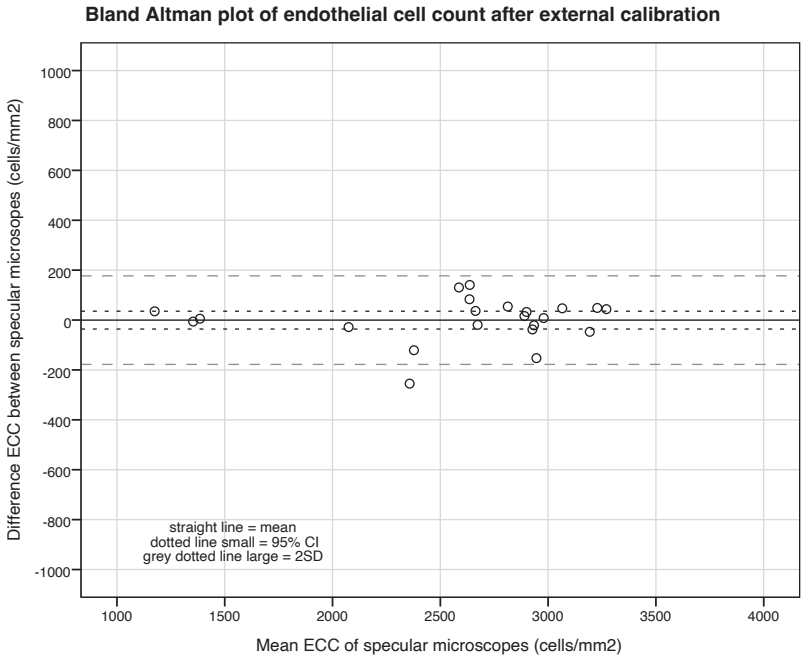

Figure 6. Bland Altman plot of endothelial cell count after external calibration

DISCUSSION

Various authors describe that different types of CSMs, manufactured by different companies, are not interchangeable.[3-8,16] During our clinical practice and research, we also encountered an interchangeability problem when using different CSMs. In our research involving longitudinal ECC analysis after Artisan IF-pIOLs, we discovered a significant difference in ECCs when we replaced our "old" SP-2000P CMS with the newer SP-3000P version; see Figure 7. In this paper, we discuss an interchangeability problem between two CSMs, the Topcon SP-2000P and SP-3000P, manufactured by the same company (Topcon Medical Systems). The interchangeability concern in our case was caused by software imprecision and erroneous calibration.

We solved this problem by 1) checking and, where necessary, correcting the magnification settings in both instruments and in the analysis software, 2) re-checking the magnification, using an external (micro-)calibration tool, and 3) calculating a correction factor so that the ECC results obtained with both instruments from the same eyes no longer showed a systematic difference.

Accurate and reliable endothelial cell analysis is not easy to perform. Known reasons for imprecise measurement are (1) the accuracy of operator-software interaction, (2) software precision, (3) specular reflection limitations leading to the generation of a low-quality image, (4) versatility in acquiring endothelial mosaic images, and (5) sampling processes.[17] Even when one technician is responsible for acquiring and analyzing an endothelial cell image, a ± 2-5% variability is described.[18] The quality of the acquired image largely determines the accuracy of the analysis.[19] Identifying cell borders in a specular micrograph can be difficult, and poor recognition of cell borders can result in the erroneous omission of cells or double entry of cells during analysis. Omitting one single cell during analysis can lead to errors ranging from 0.5% to 1.1%, depending on the size of the omitted cell and cell density per surface area.[18] We aimed to avoid these possible errors by having one experienced operator generating and analyzing the consecutively acquired images.

The reliability of the evaluation of the corneal endothelium seems to be a recurrent topic for discussion.[3-8,14,16] Software imprecisions within the Topcon SP-series have been previously described by Cheung et al. They found significant differences in ECC of the SP2000P from the semi-automated ECC IMAGEnet counts compared to the re-traced ECC. They recommend that re-traced analysis is necessary.[13] We also noticed that the semi-automated border recognition was not optimal with both the SP-2000P and SP-3000P, thus accordingly, we adjusted cell borders using the re-traced method.

Attempts to optimise cell border recognition are ongoing.[20] Regarding software-instrument accuracy, Van Schaik et al. report unchecked pre-set factory values, leading to substantial errors in ECC of up to 9% with the SP2000P and IMAGEnet2000 software.[14] We discovered an identical situation with our CSM and associated IMAGEnet software, where we encountered multiple (inaccurate) magnification values. Unfortunately, we were unable to determine the reason for these. We hypothesize that software updates might have been the cause. But even after re-tracing endothelial cell borders and adjustment of the settings with correct magnification factors, the two CSMs continued to show a significant difference in ECC. An asymmetric distortion in the photographs taken was revealed by external horizontal and vertical calibration. This distortion in EC counting area resulted in an underestimation in ECC of 1.4% in the SP-3000P and an overestimation in ECC of 8.1% in the SP-2000P. To the best of our knowledge, this distortion in images is a matter that has not previously been described in literature. After creating a correction factor for the over- or underestimation in cell count area, the two CSMs showed no significant difference in EC counts. External calibration seems to be the only way to correct this distortion.

We propose a method for improving interchangeability concerns when using different CSMs and to continue obtaining precise endothelial cell counts when a CSM needs to be replaced. The method we describe for externally calibrating our specular microscope is not restricted to the Topcon specular microscopes and can be directly applied to other specular or confocal microscopes and their associated analysis software packages. We advise to implement these steps prior to using an CSM and its software, especially in multicenter trials or long prospective studies where the corneal endothelium is a key safety outcome measure. It is noteworthy, however, that retrospective correction of interchangeability issues with ECCs is possible.

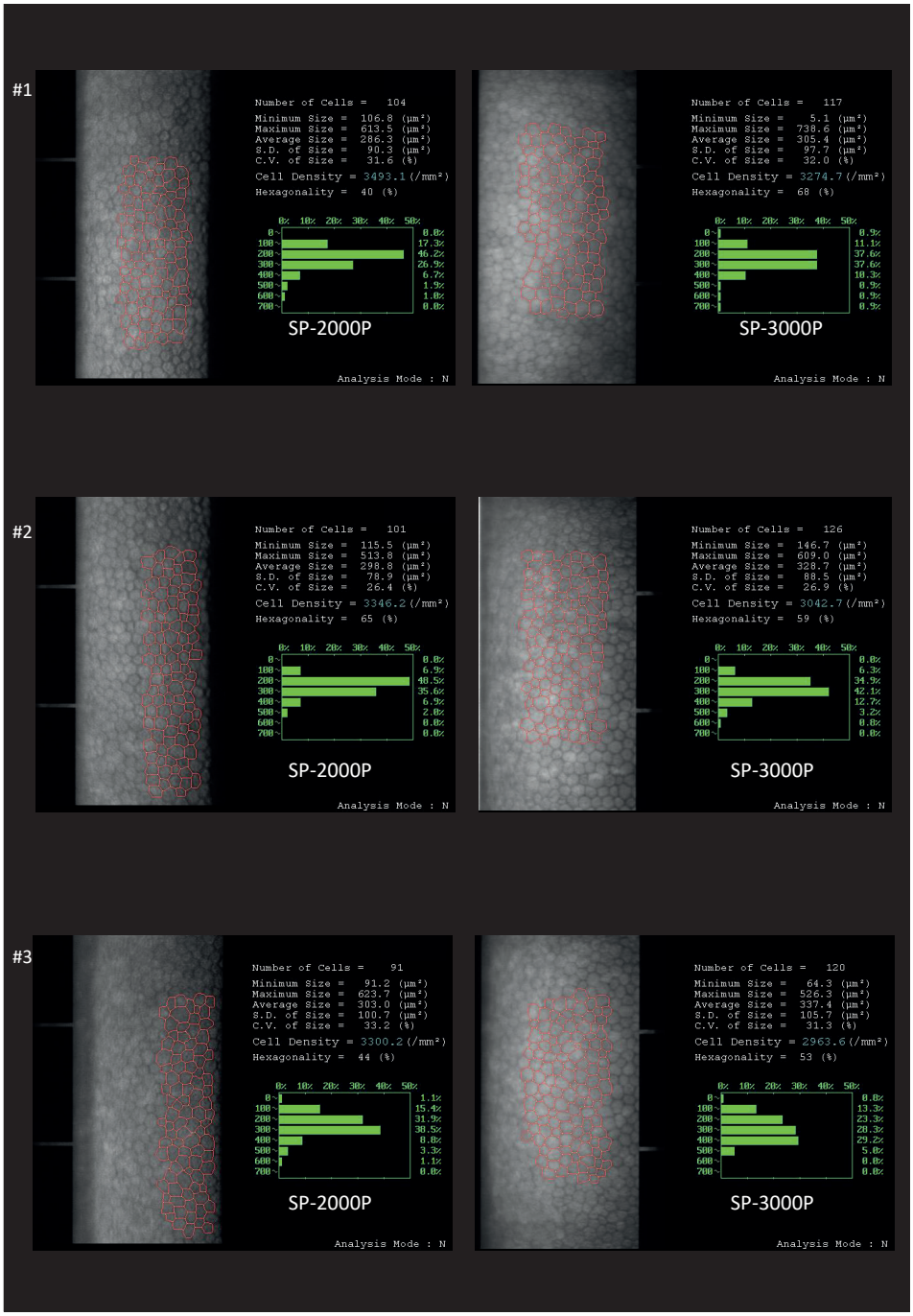

Figure 7. Endothelial cell photographs showing a systematic difference in endothelial cell count between the Topcon SP-2000P corneal specular microscope (left) and the Topcon SP-3000P corneal specular microscope (right).

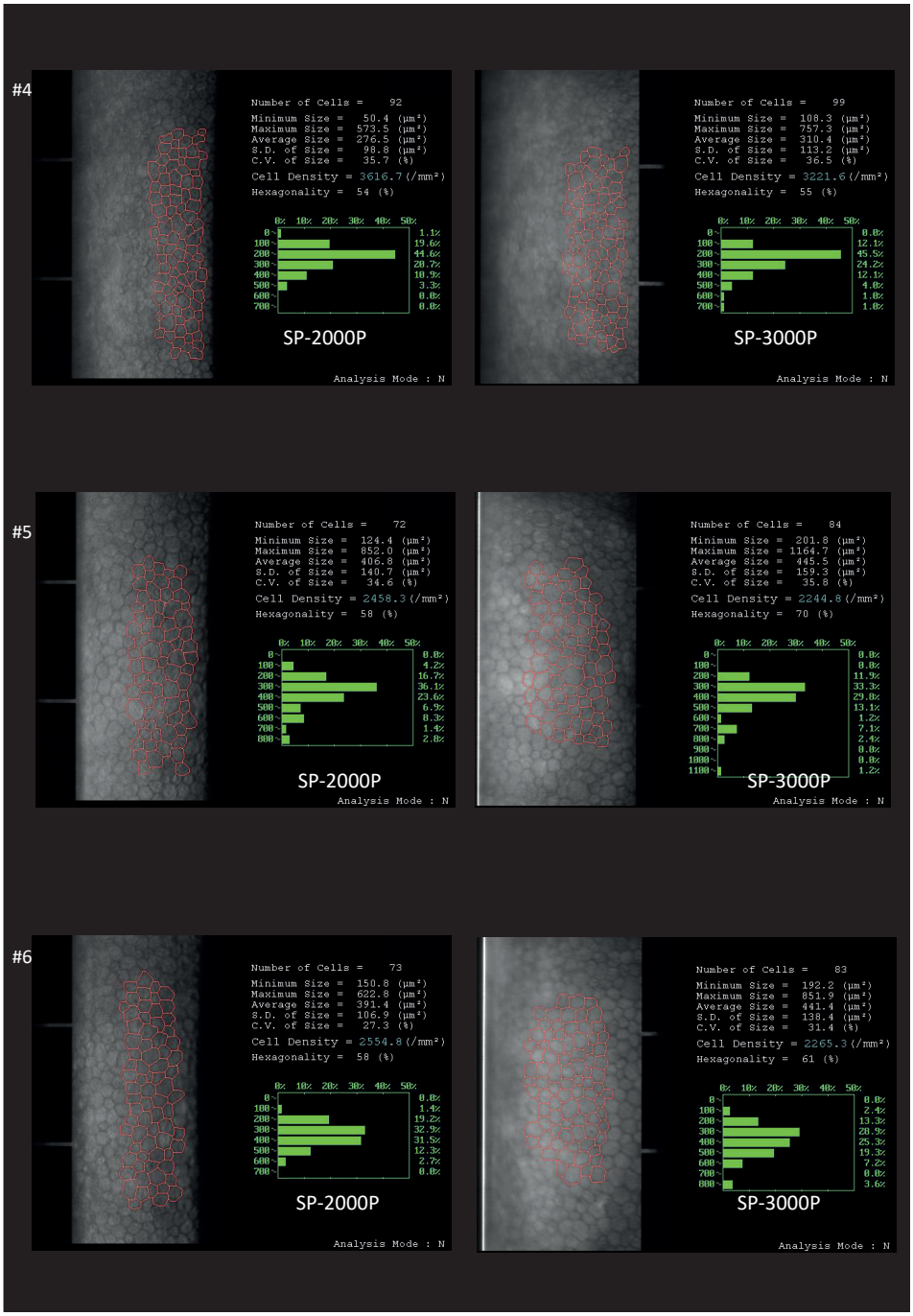

Figure 7. Continued.

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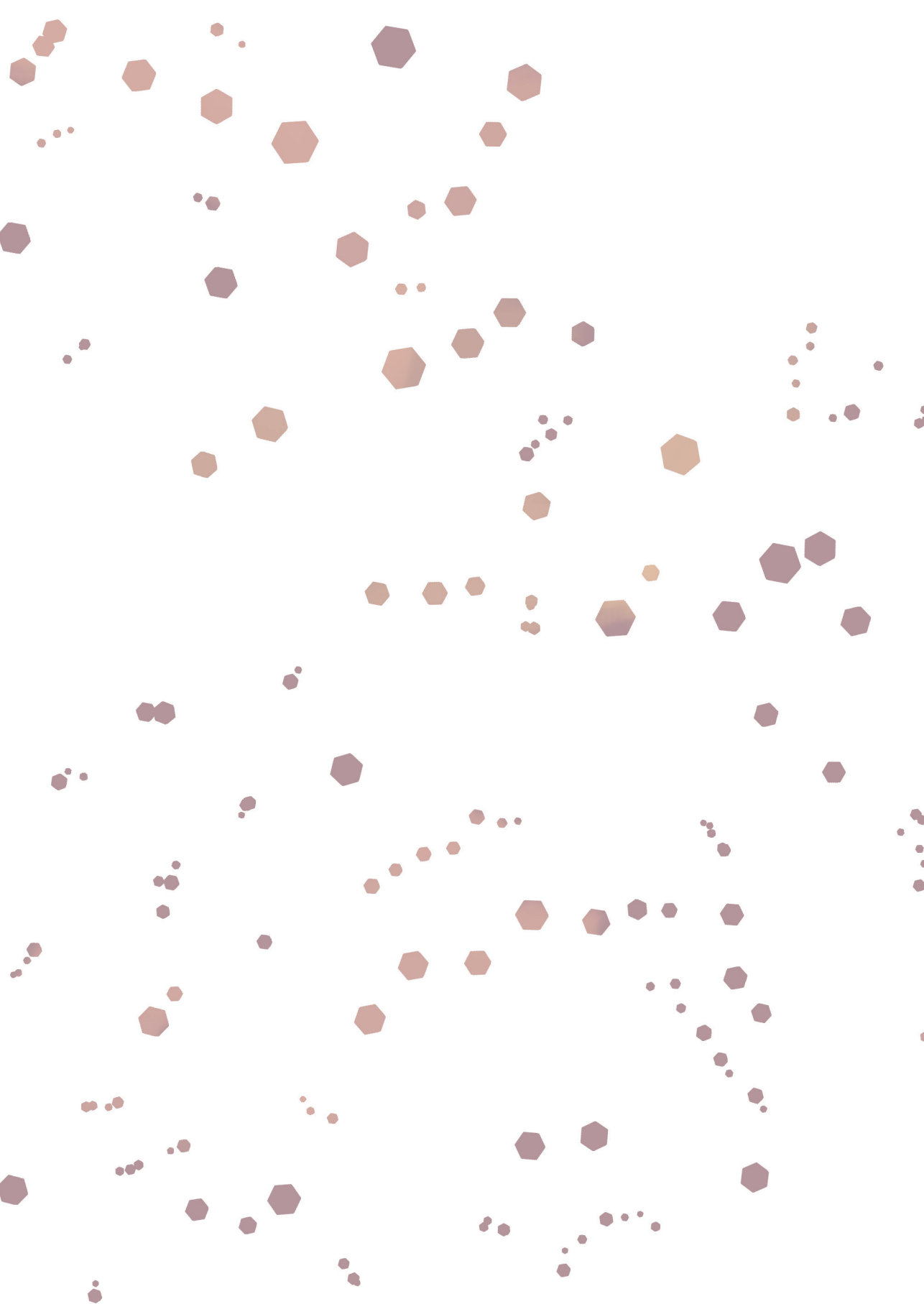

Chapter 8

Differences between Scheimpflug and Optical Coherence Tomography in Determining Safety Distances in Eyes with an Artisan Iris-Fixated Intraocular Lens

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Accepted for publication

ABSTRACT

Purpose

To investigate the agreement and reliability of anterior segment optical coherence tomography (AS-OCT) and Scheimpflug imaging in measuring the distance from the anterior edge of an iris-fixated phakic intraocular lens (IF-pIOL) to the corneal endothelium.

Methods

Anterior segment configuration was assessed in a total of 62 eyes of which 25 hyperopic and 37 myopic eyes, all corrected with an IF-pIOL. Measurements were performed by two independent observers using AS-OCT (Visante, Model 1000, Carl Zeiss Meditec Inc.) and Scheimpflug imaging (Pentacam HR, Oculus Optikgerate). The distance from the anterior edge of the pIOL to the endothelium was measured in five different positions using both modalities with their corresponding pIOL software. The measurements as well as the inter- and intra-observer reliability of the two imaging modalities were then compared.

Results

Distance measurements for all positions performed by AS-OCT were found to be significantly larger than those performed by Scheimpflug imaging, with mean differences ranging from 0.11 to 0.22 mm. Both instruments exhibited good inter- and intra-observer reliability.

Conclusion

Anterior pIOL edge to endothelium distance measurements by AS-OCT and Scheimpflug imaging have good intra- and inter-observer reliability. However, as AS-OCT provides larger measurements, these two modalities cannot be used interchangeably. Correction of this difference might be essential for proper decision-making during preoperative screening for pIOL implantation and postoperative safety monitoring.

INTRODUCTION

Phakic intraocular lens (pIOL) implantation has proven to be safe and effective for the correction of a broad range of ametropia.[1,2] The Artisan lens (Ophtec BV, Groningen, the Netherlands) is an iris-fixated (IF) pIOL that has been used successfully to correct moderate to high myopia, hyperopia and astigmatism since 1991. The outcomes after Artisan implantation have found to be predictive and stable over time.[1,3,4]

To establish the long-term safety of IF-pIOL and to prevent complications, an extensive preoperative evaluation in combination with long-term postoperative follow-up is required. One of the most feared and important potential complications of any type of anterior segment surgery, is accelerated endothelial cell (EC) loss, especially in the case of IF-pIOL. As this risk has been shown to be negatively correlated to the anterior chamber depth, the position of an IF-pIOL in the anterior chamber is one of the main safety parameters in both preoperative screening and follow-up.[1,4-9]

Monitoring of the anatomical relationship with an IF-pIOL in the eye can be performed at the slit lamp. However, accuracy between the distance of the pIOL to the corneal endothelium is subject to subjective interpretation and is thus limited in accuracy. To objectively measure the distance between the central and peripheral pIOL edge to the corneal endothelium, several clinical techniques may be used, including ultrasound biomicroscopy (UBM), Scheimpflug imaging, and anterior segment optical coherence tomography (AS-OCT). UBM delivers images of excellent quality but has several limitations, such as the fact that it is technically challenging, with a risk of distorting true anterior chamber dimension, time-consuming to perform and possibly uncomfortable for the patients.[10] The non-contact AS-OCT and Scheimpflug imaging techniques both provide high resolution images of the anterior chamber on which the pIOL position can be determined with provided software.[11-13,14-16]

To minimize the risk of increased cell loss, Baïkoff introduced in 2006 the 'minimum (or 'critical') safety distance': a minimum distance between the central edge of the optical zone of the pIOL and the endothelium.[11] Based on the clinical results of Pérez-Santonja et al. and de Sousa et al., he proposed a minimum distance of 1.5 mm to prevent accelerated EC loss.[17,18] Later studies confirmed the importance of the central distance between the anterior surface of the pIOL and the endothelium, showing a yearly increase in EC loss with smaller distances.[13,15,16,19] Doors et al.

described an average EC loss of 0.15%, 0.98% and 1.80% per year for a minimum central distance between the anterior surface of the pIOL and the endothelium of 1.59 mm, 1.37 mm and 1.15 mm, respectively.[13] In addition to the central distances and a smaller ACD, Jonker et al. found smaller distances between the peripheral pIOL edge and endothelium to also be a significant risk factor for accelerated EC loss.[19]

The aim of this study is to compare the AS-OCT and Scheimpflug imaging in measuring pIOL-to-endothelium distances and to assess the inter- and intra-observer variability of these measurements.

METHODS

In this cross-sectional study, we examined 62 phakic eyes that had undergone pIOL implantation, of which 25 eyes (13 patients) were corrected for hyperopia and 37 eyes (20 patients) for myopia. All the eyes were implanted with an Artisan IF-pIOL by the same experienced eye surgeon at the Leiden University Medical Center (LUMC), Leiden or Erasmus Medical Center, Rotterdam; Artisan lens model 203 was implanted for hyperopia and model 206 for myopia, with the available refractive powers ranging from +1.0 to +12.0 diopters and -1.0 to -23.5 diopters respectively, in 0.5 diopter steps. The study was approved by the Medical Ethical Committee of the LUMC and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients before they were examined. Anterior segment scans were made with two different imaging modalities: the AS-OCT and Scheimpflug imaging. All images were made under the same dim light conditions in an unaccommodated state.

The Visante OCT (Visante, Model 1000, software version 3.0.1.8, Carl Zeiss Meditec Inc.) is a time domain system that uses infrared light (1310 nm) to image the anterior segment. For this study, all measurements were performed in high-resolution mode, which provides a detailed image with a field of view of 10 mm width by 3 mm. In this mode, the Visante performs 512 scans to assess the anterior segment area in 0.25 seconds. Axial and transverse resolutions are 18 and 60 μm, respectively.

The Pentacam HR system (Pentacam HR, software version 1.12r24, Oculus Optikgerate) uses the Scheimpflug imaging technique for anterior segment evaluation. A 360-degree, rotating, non-contact camera uses a monochromatic slit light source to reconstruct a three-dimensional map of the anterior segment of the eye. Such a scan is performed in two seconds and yields images with a clear visualization of the pIOL. For assessing the pIOL position, a 3-D pIOL-simulation software module is provided.

The acquired images were subsequently analyzed using the vendors' software. With AS-OCT, the distance from the pIOL to the corneal endothelium is measured by manually placing a pIOL template on the anterior segment image by computer mouse selection and dragging and drawing a measurement vector using the vendor's software (Figure 1a, b). In the case of Scheimpflug imaging, the software automatically calculates the minimum distance between the pIOL and the corneal endothelium after the 3-D pIOL template is manually added to the image (Figure 1c, d). When present, the iris image is used for better precision of the pIOL template position. On both types of anterior segment scans, the pIOL-to-endothelium distance was measured in five standard positions along the 180-degree horizontal axis (at "3 o'clock" and "9 o'clock" positions) (Figure 1b, d):

- Central
- At 2.5 mm nasal from the center
- At 2.5 mm temporal from the center
- At 4 mm nasal from the center
- At 4 mm temporal from the center

To determine the inter- and intra-observer variability, these analyses were performed separately by two independent, trained observers (ZSG, GAR). Both observers repeated the measurements at another time point, at least three months from the first measurements and without knowledge of the earlier results. To test the agreement between the two imaging modalities, the average of all four measurements was used for analysis.

Statistical Analysis

All statistical analyses were performed using SPSS statistics software version 25 (SPSS Inc., IBM, Somers, NY).

To assess the agreement between tomographers, a paired sample *t*-test was applied and Bland Altman analysis was performed, and 95% limits of agreement (LoA) were estimated by the mean difference ± 1.96 x standard deviation (SD) of the difference.[20] To exclude potential cofounding factors (right or left eye, hyperopic or myopic eye, time interval between pIOL implantation and examination date), a linear mixed model was used where these factors were taken into account to test their significance. A p-value of < 0.05 was considered to be statistically significant.

Inter- and intra-observer reliability was assessed by calculating the intraclass correlation coefficients (ICC) using a multilevel (hierarchical) linear mixed model to adjust for the possible correlation between measurements within the same eye and between the two eyes within the same patient. In this model, intra-observer reliability was evaluated by correlating each observer's first measurement by AS-OCT and Scheimpflug imaging with the same observer's second measurement. Inter-observer reliability was assessed by correlating measurements of one observer with the corresponding measurements of the other observer. The ICC was interpreted according to the Cohen's kappa classification.[21]

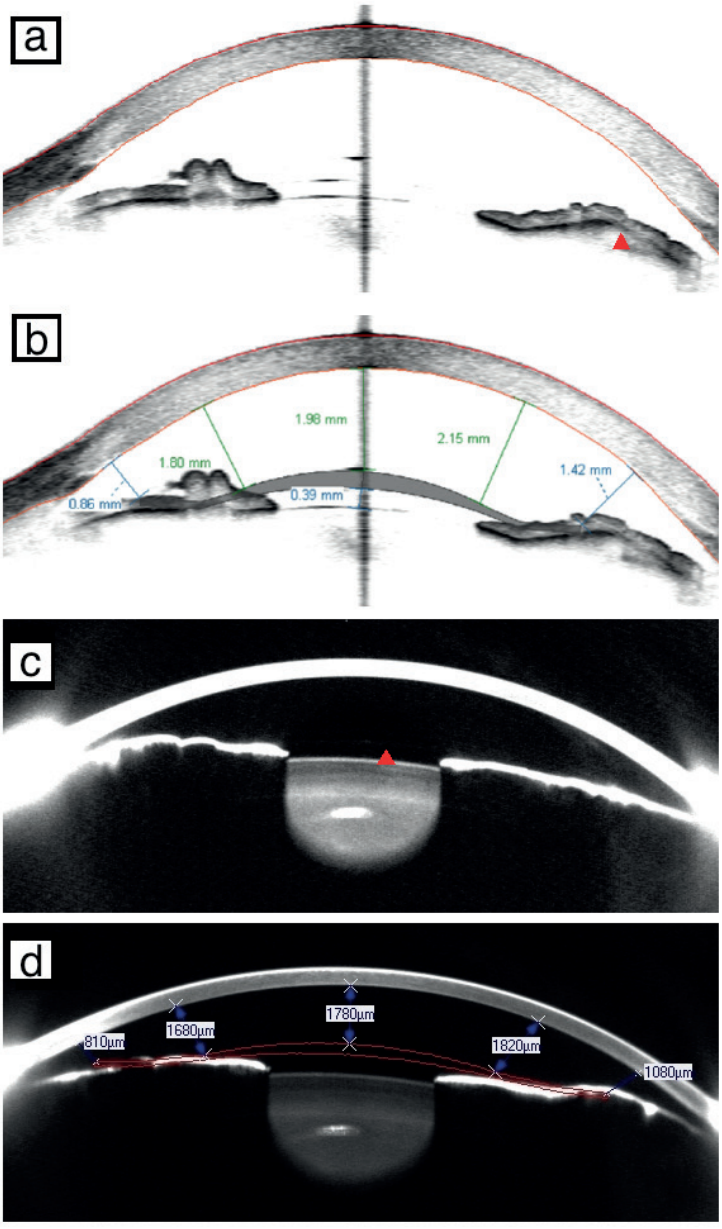

Figure 1. Anterior segment scan image acquired with the Visante anterior segment optical coherence tomography (AS-OCT) before (a; *red arrow*: phakic intraocular lens (pIOL) enclavation site) and after placement of the pIOL template using the pIOL analysis software (b). Similar images acquired with Scheimpflug imaging before (c; *red arrow*: edge of pIOL) and after placement of pIOL template (d; contrast of scan was adjusted). All four scans represent the left eye of the same subject on a 180° - 0° axis. (Please note the differences in clearance distances given by the Pentacam compared to the Visante.)

RESULTS

Patient Characteristics

Sixty-two phakic eyes of 34 subjects including 11 males and 23 females between the age of 24.9 to 76.6 years, with a mean (SD) of 49.6 (11.2) years, were examined. The power of the Artisan lenses implanted ranged from +12.00 to -23.50 diopters. The mean time interval between pIOL implantation and the first anterior segment analysis was 9.7 (4.7) years. For more details, see Table 1.

Inter- and Intra-Observer Reliability

The overall *inter*-observer ICC was 0.99 with a 95% confidence interval (CI) of 0.99-0.99 for both AS-OCT and Scheimpflug imaging. The overall *intra*-observer ICC was 0.99 with a 95% CI: 0.99-0.99 for AS-OCT and 0.98 with a 95% CI: 0.98-0.98 for Scheimpflug imaging. The ICCs per position measurement of each instrument are shown in Table 2. All correlations were 'very good' for both AS-OCT and Scheimpflug imaging according to the Cohen's kappa classification[21], showing that a single measurement is reliable irrespective of observer or measurement occasion.

Agreement Between Instruments

The distance from the anterior edge of the pIOL to the endothelium when measured by AS-OCT was consistently larger than when measured by Scheimpflug imaging, for all five separate positions, as listed in Table 3. The mean difference for all of the various positions was 0.161 (0.120) mm with a 95% LoA of -0.074 and 0.396 (paired t=23.74; p<0.001), see Figure 2 for the Bland Altman plot. The peripheral measurements showed similar results. Supplementary Figure 1 (Appendix 12) shows the Bland Altman plots for the differences in distance measurements at the 5 positions with the 95% LoA and 95% CIs. The mean difference between AS-OCT and Scheimpflug imaging for the central distance measurements was 0.150 mm (95% LoA, -0.014 and 0.314), for 2.5 mm nasal 0.189 mm (95% LoA, -0.020 and 0.398), for 2.5 mm temporal 0.114 mm (95% LoA, -0.102 and 0.330), for 4.0 mm nasal 0.218 mm (95% LoA, -0.045 and 0.481), and for 4.0 mm temporal 0.137 mm (95% LoA, -0.115 and 0.389). In a mixed model, distance measurements were not found to be significantly affected by age, sex, right or left eye, hyperopic or myopic eye, or the time interval between pIOL implantation and the examination date, so these factors were not included in further analyses.

Subsequently, a general estimating equations (GEE) model was developed. In this model, we used the average of four repeated analyses (each analysis was acquired twice by both the first and the second observer) of the different distances with the average AS-OCT measurements as the dependent variable and the average Scheimpflug

measurements as the independent variable. To assess the effect of the position of the measurement on this comparison, the same model was repeated with 'position' as the fixed factor. Following this model, the measurements of the two devices were correlated with the standardized regression coefficient (*r*) of 0.962 ($p<0.001$), with larger distances being measured by AS-OCT than by Scheimpflug imaging. Linear regression analysis yielded the following correlation (Equation 1: correlation of AS-OCT and Scheimpflug for pIOL-to-endothelium distance measurements):

$$D_{AS-OCT} = 0.962 \times D_{Scheimpflug} + 0.212\ mm$$

Equation 1.

D: pIOL-to-endothelium distance (in millimeters)

This relation is clearly visible in the scatter plot of Figure 3. To assess if this 'overall' regression coefficient accounts for all distance positions separately, each regression coefficient of a position was compared to the average regression coefficient of the other positions using linear regression. For every clearance distance position, the regression coefficient did not significantly differ from the others, indicating that there was no effect of the different 'distance position' slopes.

Table 1.

Variable
Eyes (count)
Sex (male:female) (%)
Age at examination ± SD (min-max) (years)
pIOL power ± SD (min-max) (D)
Time interval between pIOL implantation and anterior segment examination ± SD (min-max) (years)

Table 2. Intraclass correlation coefficients of anterior segment optical coherence tomography and Scheimpflug imaging show good reproducibility of analysis for both modalities.

4.0 mm nasal endothelium to pIOL					
2.5 mm nasal endothelium to pIOL					
central endothelium to pIOL					
2.5 mm temporal endothelium to pIOL					
4.0 mm temporal endothelium to pIOL					

AS-OCT= anterior segment optical coherence tomography; ICC= intraclass correlation coefficient; 95% CI= 95% confidence interval; pIOL= phakic intraocular lens

Table 3. Means and differences in distance measurements made by anterior segment optical coherence tomography and Scheimpflug imaging

Measurement to endothelium (mm) from
4.0 mm nasal of anterior edge of pIOL
2.5 mm nasal of anterior edge of pIOL
Center of anterior edge of pIOL
2.5 mm temporal of anterior edge of pIOL
4.0 mm temporal of anterior edge of pIOL
All five positions of anterior edge of pIOL

AS-OCT = anterior segment optical coherence tomography; 95% CI = 95% confidence interval; pIOL = phakic intraocular lens

Total	Hyperopic eyes	Myopic eyes
62	25 (12 right eyes)	37 (17 right eyes)
32:68	64:36	11:89
49.6 ± 11.2 (24.9 - 76.6)	52.6 ± 9.3 (24.9 - 67.4)	47.6 ± 12.0 (25.9 - 76.6)
9.7 ± 4.7 (0.0 - 18.0)	7.7 ± 2.6 (2.0 - 12.0)	-13.6 ± 4.6 (-23.5 - -13.6)
	9.8 ± 3.6 (0.0 - 14.0)	9.5 ± 5.5 (0.0 - 18.0)

AS-OCT ICC		Scheimpflug imaging ICC	
Inter-observer (95% CI)	Intra-observer (95% CI)	Inter-observer (95% CI)	Intra-observer (95% CI)
0.944 (0.908-0.966)	0.917 (0.882-0.942)	0.890 (0.813-0.935)	0.818 (0.740-0.873)
0.969 (0.949-0.982)	0.961 (0.944-0.972)	0.958 (0.928-0.976)	0.913 (0.875-0.939)
0.996 (0.994-0.998)	0.909 (0.835-0.949)	0.955 (0.910-0.976)	0.991 (0.987-0.994)
0.946 (0.911-0.968)	0.930 (0.901-0.951)	0.965 (0.940-0.979)	0.944 (0.920-0.961)
0.955 (0.910-0.976)	0.948 (0.926-0.964)	0.955 (0.920-0.974)	0.919 (0.884-0.944)

AS-OCT	Scheimpflug	AS-OCT versus Scheimpflug			
Mean ± SD	Mean ± SD	Difference (mean ± SD)	Range	95% CI	p-value
1.018 ± 0.249	1.509 ± 0.509	0.218 ± 0.135	0.30–1.52	0.184–0.253	< 0.001
1.652 ± 0.282	1.462 ± 0.251	0.189 ± 0.107	0.90–2.31	0.162–0.217	< 0.001
2.184 ± 0.361	2.034 ± 0.362	0.150 ± 0.084	1.17–2.78	0.129–0.171	< 0.001
1.760 ± 0.271	1.647 ± 0.261	0.113 ± 0.111	1.11–2.40	0.085–0.142	< 0.001
1.180 ± 0.280	1.043 ± 0.263	0.137 ± 0.128	0.46–1.89	0.104–0.170	< 0.001
1.509 ± 0.509	1.397 ± 0.517	0.161 ± 0.120	0.30–2.78	0.148–0.175	< 0.001

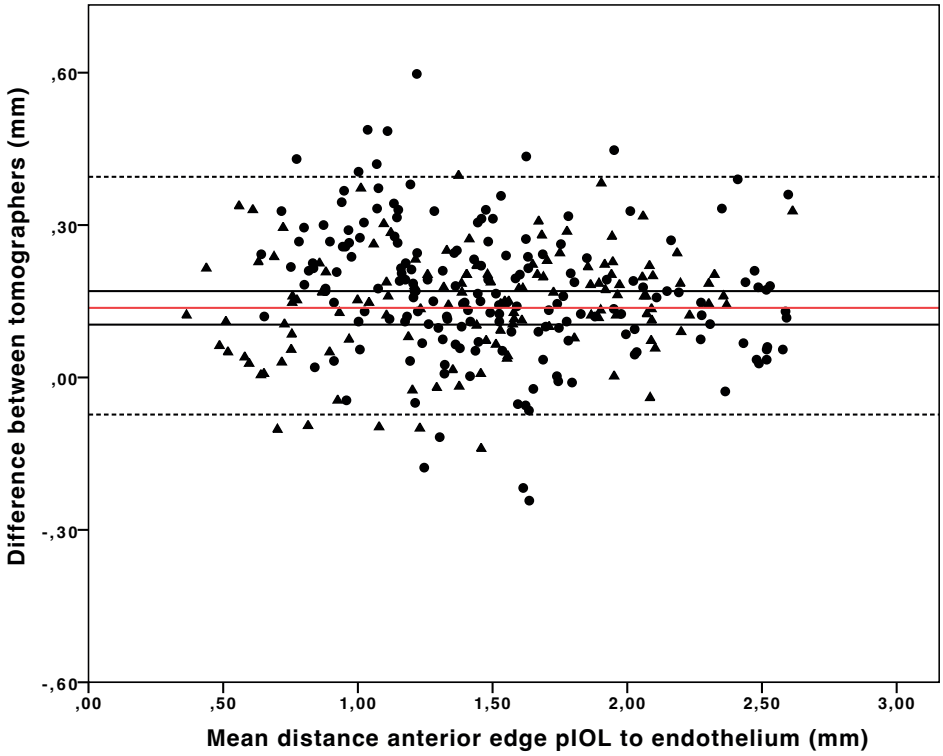

Figure 2. Bland Altman plot showing the difference in distance measurements between the anterior segment optical coherence tomography and Scheimpflug imaging modalities for all positions from the anterior phakic intraocular lens (pIOL) to the endothelium. The red line represents the mean, the black lines the upper and lower 95% confidence interval, the dashed lines the upper and lower 95% limits of agreement (LoA). *Triangles*: hyperopic eyes; *dots*: myopic eyes.

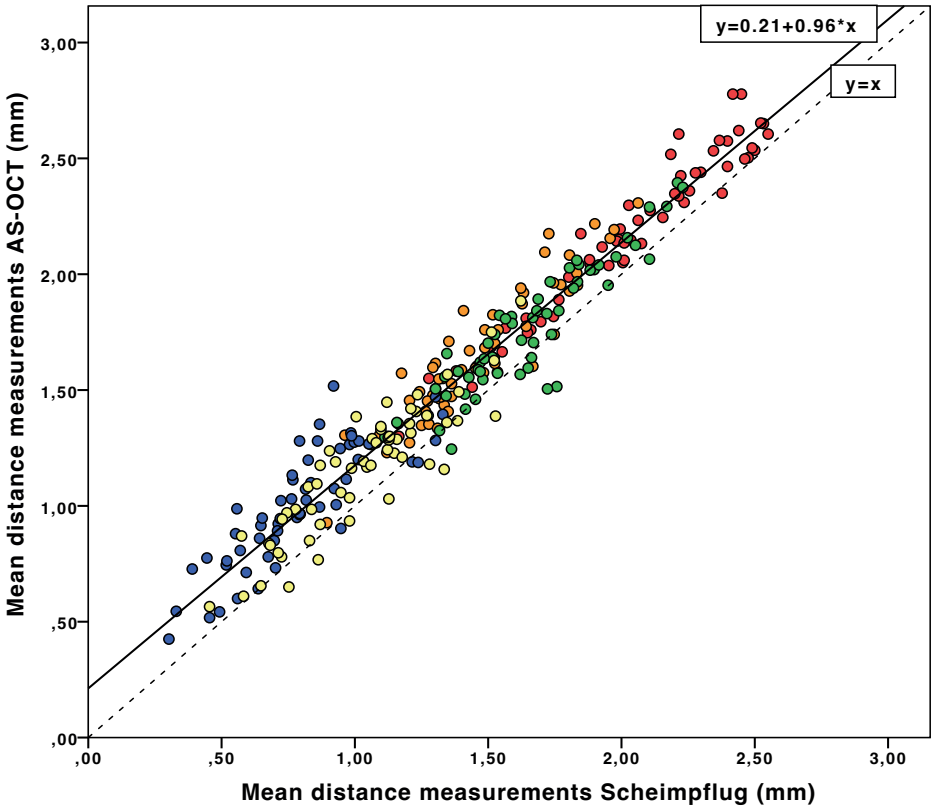

Figure 3. Scatter plot of the anterior segment optical coherence tomography (AS-OCT) measurements against Scheimpflug imaging measurements. The regression fit line (*black line*) following the relationship of the devices consistently shows higher measurements of AS-OCT compared to the *dashed line* which represents absolute agreement of the instruments. Dot colors represent the positions of distances from the pIOL to the endothelium: *red*: central; *green:* 2.5 mm temporal from the center; *orange:* 2.5 mm nasal from the center; *yellow:* 4.0 mm temporal from the center; *blue:* 4.0 mm nasal from the center.

DISCUSSION

Correct positioning of an IF-pIOL in the anterior chamber is of high importance to determine long-term safety, as a smaller ACD and smaller distance from the edge of the pIOL to the endothelium can cause accelerated EC loss, which could lead to the need for early pIOL removal.[19,22] Jonker et al. have recently reported a prevalence of IF-pIOL explantation due to excessive EC loss of up to 6.0% during five- and ten-year follow-up.[19] Today, both AS-OCT and the Scheimpflug imaging are used to measure the pIOL edge to endothelium distance before and after pIOL implantation.[11,13,15,18] The overall reproducibility of ACD biometry before and after pIOL implantation has been documented for both imaging modalities[23,24], and a comparison study for ACD has shown significant difference between the AS-OCT and Scheimpflug.[23] However, no reproducibility or comparison studies of the pIOL edge to endothelium distance measured with these two different imaging modalities have been performed. In this study, we demonstrate good inter- and intra-observer reproducibility for AS-OCT and Scheimpflug imaging when performing these measurements. A comparison between the two modalities, however, shows a significant difference in the measurement of the pIOL edge to endothelium distance, with the AS-OCT measurements being consistently larger than the Scheimpflug measurements.

Let us take a brief look at the aspects that differ between these instruments: the Pentacam HR, which uses Scheimpflug imaging, provides good images of the anterior segment. However, complex geometrical adjustments are performed to correct optical distortions caused by this modality.[25,26] With AS-OCT, these optical corrections do not need to be made for axial measurements. However, for peripheral measurements, refraction at the corneal surface will result in a systematic error.[27] Moreover, based on this study, similar differences between OCT techniques, such as spectrometer-based and swept-source OCT, are plausible as these use different optical setups which might result in similar systematic differences in apparent pIOL-to-endothelium distances.[28] Secondly, we need to consider the effect of the different software instructions to measure the pIOL-to-endothelium distance: With the Pentacam software, minimum pIOL-to-endothelium distances are *automatically* identified and visualized for different positions after aligning the 3-D pIOL template. By contrast, the OCT calculations are based on *manually* defined distances since both the pIOL template and all the different distances are manually dragged and drawn (vector tool) onto the 2-D anterior segment scan. Although this manual interaction could reduce the inter- and intra-observer reproducibility, especially for less trained operators, it cannot explain the systematic difference between both devices.

Different models and minimum ('critical') pIOL-to-endothelium distances are described in the literature for monitoring anterior chamber pIOL safety. Baikoff at first suggested a minimum safety distance between the pIOL and corneal endothelium of 1.5 mm, a distance based on Scheimpflug results from earlier studies.[11,17] Doors et al. evaluated pIOL clearances with the Visante OCT.[12,13] Ferreira et al. provided the clinicians with a new safety reference in 2014: a minimum *central* clearance distance of 1.7 mm, based on their Pentacam results.[22] Recently, Jonker et al. have demonstrated a 10.3% EC loss over five years and 20.5% over ten years with a mean distance between the central pIOL edge and endothelium of 2.17 mm using the Visante AS-OCT.[19] This risk showed a linear increase in EC loss with smaller distances.

For correct interpretation of the previously mentioned 'critical minimum pIOL-to-endothelium distance', including the risk of EC loss, the imaging modality used to obtain the pIOL-to-endothelium distance should be taken into account, as, according to our results, AS-OCT overestimates this distance compared to Scheimpflug. When using a Scheimpflug based minimum safety distance for a AS-OCT scan, we suggest the use of our conversion equation. For example, based on equation 1, the minimum safety distance should be 1.84 mm, instead of 1.7 mm as proposed by Ferreira, when using AS-OCT.[22] This difference of 0.14 mm is relevant for the follow-up of the patients, as it could explain increased EC loss. It is, however, important to realize that the found relation between both devices, and therefore also the modified safety distance, is not only vendor, but also potentially software version dependent.

In conclusion, measuring the distance from the anterior edge of a pIOL to the corneal endothelium with AS-OCT and Scheimpflug imaging are both accurate with good reproducibility, but the AS-OCT provides consistently larger measurements compared to Scheimpflug imaging. This difference is of great clinical importance for the follow-up of pIOL positioning in the anterior chamber. We therefore suggest not to use these two imaging modalities interchangeably for measuring the pIOL-to-endothelium distance during follow-up. Clinicians using a fixed minimum safety distance or predictive model for safety follow-up should be aware of the instrument used for measurement as conversion might be needed.

Key messages

- In eyes with a phakic intraocular lens (pIOL), a certain safety distance of anterior pIOL edge to corneal endothelium is important to prevent endothelial cell loss. Anterior segment optical coherence tomography (AS-OCT) and Scheimpflug imaging are the main imaging modalities to assess this distance.

- The distance of anterior pIOL edge to corneal endothelium measured with the AS-OCT, is consistently larger in comparison to Scheimpflug measurements.
- Interchangeability of these devices for measuring pIOL-to-endothelium distance is therefore not recommended, although a conversion between devices is possible if needed.

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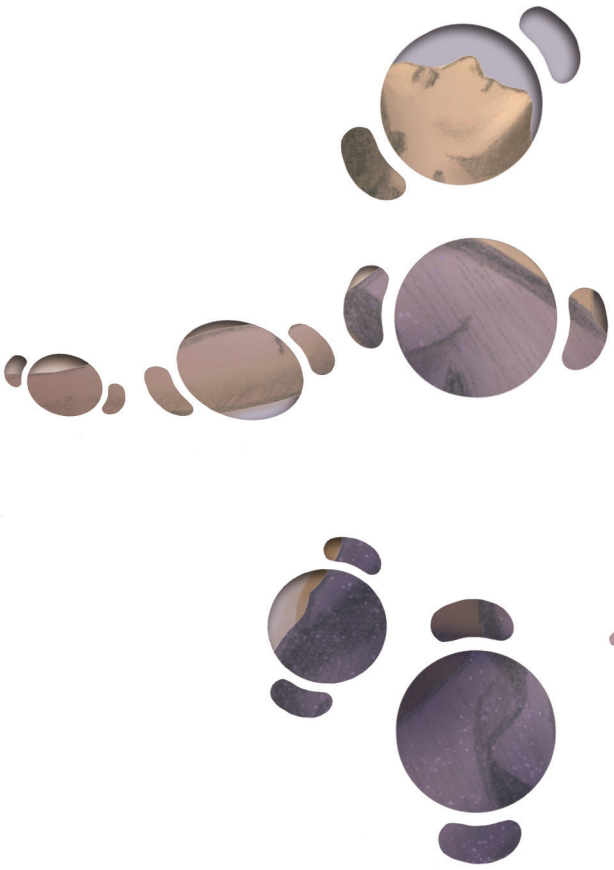

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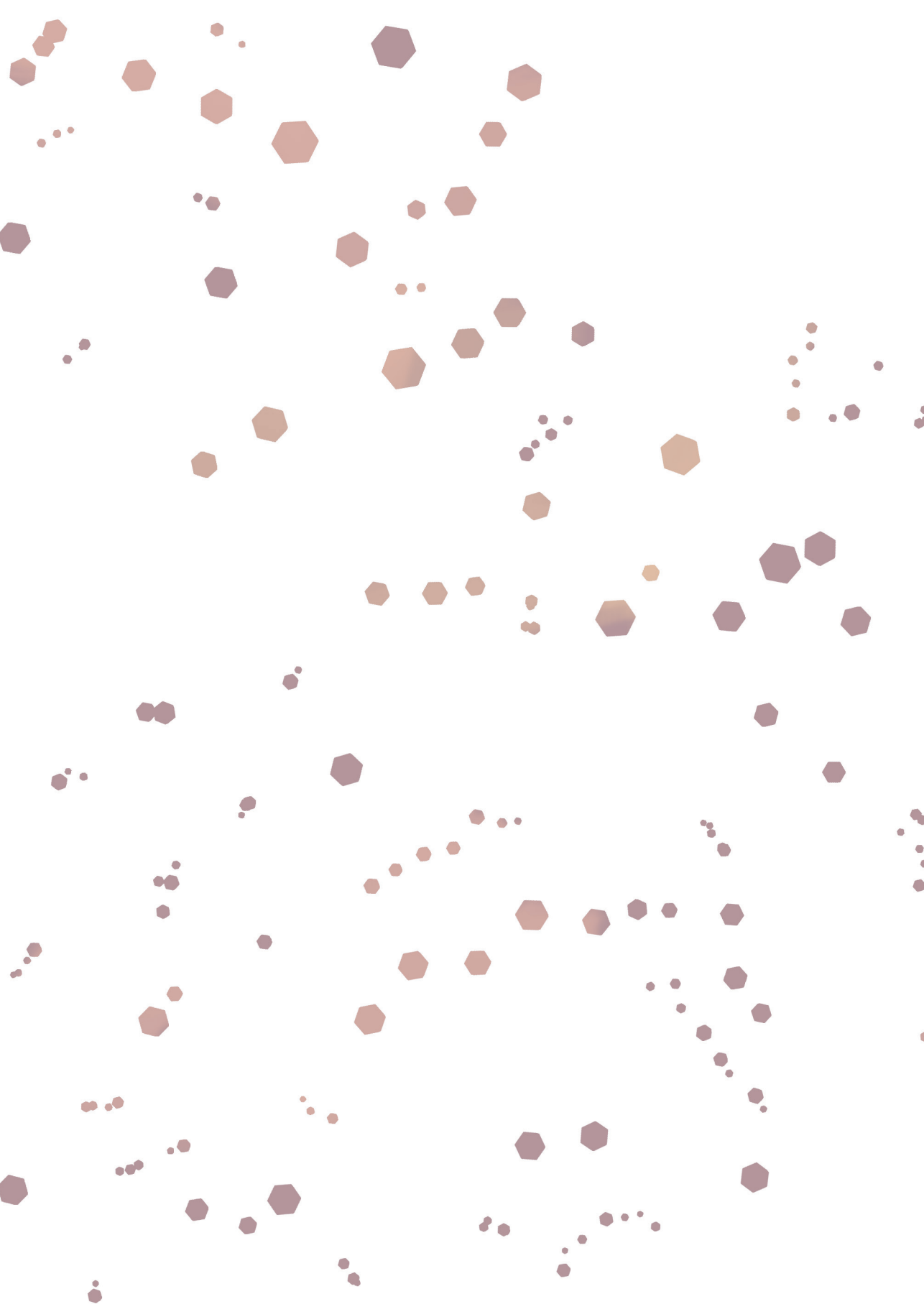

Chapter 9

General Discussion and Future Perspectives

GENERAL DISCUSSION

Individualized refractive correction, i.e. choosing the best available method for a particular patient, is one of the greatest challenges in refractive surgery. Choosing the appropriate refractive correction option should be based on the individual's risk-benefit profile. One should realize that patients with high refractive errors, such as myopia and hyperopia, are legally blind without the use of appropriate optical correction.[1] Optical correction of their refractive error can be achieved by non-surgical and surgical methods. Spectacle correction of myopia or hyperopia is the easiest, least invasive and safest option for optical correction. But image distortion in the peripheral visual field, the jack-in-the-box phenomenon, and aesthetic distortion of the face are disadvantages experienced by patients. Moreover, in young, active patients, dependency on spectacles may in some cases be problematic (for example, in physical professions such as those carried out by police officers, firefighters, gymnastic teachers, military officers, pilots, etc.). Contact lenses are an alternative in most cases, although with increasing ametropia, thicker contact lenses may lead to greater discomfort or intolerance. Moreover, the use of soft contact lenses is associated with the risk of developing infectious keratitis.[2] It is reported that laser refractive surgery is safer than soft contact lenses with regard to the risk of developing microbial keratitis and provides greater patient satisfaction.[3-5] But not all patients seeking optical correction are suitable for laser refractive surgery. Photorefractive keratectomy (PRK) and laser-assisted in situ keratomileusis (LASIK) of ametropia are considered safe in patients with myopia up to approximately -8 diopters (D) and hyperopia up to +4D. The introduction of small incision lenticule extraction (SMILE) has even broadened myopia treatment up to approximately -12D.[6,7] Nevertheless, a minimum corneal thickness is required. Other surgical options for patients seeking an alternative to the conservative optical correction methods, but who are unsuitable for laser refractive correction, may be phakic intraocular lens (pIOL) implantation or refractive lens exchange (RLE). PIOL implantation is a reversible surgical method, in contrast to laser refractive surgery and RLE. In younger patients, pIOL implantation is preferred to clear lens extraction to preserve accommodation. Additionally, RLE in younger patients and a long axial length are reported to lead to a higher risk of retinal detachment.[8]

Multiple pIOLs have been withdrawn from the market due to unacceptable risks.[9-11] The iris-fixated phakic intraocular lens (IF-pIOL) is one of the phakic anterior chamber IOLs that has passed the test of time, though modifications in lens design, the materials used and safety criteria have been made over the past decades. With progressive insight, eligibility criteria have been established, such as an age-dependent endothelial cell (EC) density, a minimum anterior chamber depth (ACD), a non-convex iris configuration and

a maximum pupil size. These eligibility criteria have been adjusted throughout the years to ensure greater safety of the IF-pIOL. Only recently the criterion for the minimum ACD had been adjusted: a minimum ACD of 3.0 mm as measured from the corneal endothelium is now recommended, whereas before the minimum recommended ACD was measured from the corneal epithelium.

In this thesis, we have attempted to provide an overview of the expected clinical benefits and risks after IF-pIOL implantation. Additionally, we have attempted to investigate the reliability of measurements performed for patient selection.

Benefits

The main outcome for patients undergoing any kind of refractive surgery is good and stable post-implantation visual acuity, preferably without the need for any other visual aids.

Short-term, medium-term and long-term visual and refractive results are consistently favorable after IF-pIOL implantation for the correction of hyperopia and myopia. (Chapters 2, 3 and 4). The visual outcomes are excellent. The safety indices for myopic and hyperopic IF-pIOL implantation are high. Corrected distance visual acuity (CDVA) can be expected to remain stable or even increase postoperatively. Refractive results are very favorable. There is good refractive predictability, and subjective refraction decreases significantly after IF-pIOL implantation, leading to a large proportion of patients achieving spectacle independence compared to pre-IF-pIOL implantation. Although manifest refraction may change over time due to (age-related) crystalline lens changes or due to elongation of the axial length, only a small, clinically insignificant change in subjective refraction was observed in myopic eyes.[12] (Chapter 4) Even so, a slight myopization is not necessarily a disadvantage, since with increasing age, presbyopia sets in, and slight myopia may delay the need for reading glasses (second sight).

The quality of life of these patients is reported to be excellent after IF-pIOL implantation.[13] (Own unpublished data) This reflects our own clinical experience during the follow-up period, where we see very satisfied patients.

One might question the suitability of the delicate iris tissue to fixate the haptics of a pIOL. Previous studies have shown that the iris-fixation principle of an IF-pIOL is stable.[14,15] Additionally, we have described that in eyes with oculocutaneous albinism, where the iris may appear fragile due to the lack of pigment, good enclavation of the IF-pIOL is achieved. (Chapter 5)

Risks

The risks of IF-pIOL implantation are mostly related to the underlying nature of the eye disease (i.e. high myopia and hyperopia), the evaluation of measurements and application of safety criteria for patient selection, and the skills of the refractive surgeon.

Cataract Formation

Cataract formation is a potential complication of any surgical intraocular procedure. Surgical trauma or intraocular lens (IOL) touch with the crystalline lens may lead to anterior capsule cataract. Fortunately, anterior capsule cataract is only very rarely reported after IF-pIOL implantation. (Chapters 2, 3 and 4)

Metabolic effects by altered aqueous flow have also been proposed as possible reasons for earlier cataract formation after IF-pIOL implantation. This hypothesis could not be confirmed by a computerized simulation study.[16]

On the other hand, myopia or hyperopia itself may be the reason for cataract development starting earlier than in emmetropic eyes.[17] Clinically significant cataract formation was the main reason for a loss in CDVA after IF-pIOL implantation. Most cataracts were of nuclear sclerotic type. (Chapters 2 and 3) In myopic eyes, cataract with the need for cataract extraction was the main reason for IF-pIOL explantation. (Chapter 4) The incidence of cataract seems higher in myopic eyes with an IF-pIOL compared to hyperopic eyes with an IF-pIOL, although this might be biased due to the smaller study group of hyperopic eyes compared to myopic eyes and the longer follow-up of the myopic study groups. It is still unclear whether cataract formation occurs sooner in eyes implanted with an IF-pIOL compared to the general (ametropic) population. It also remains unclear to which extent factors such as the following contribute to possible earlier cataract formation: the implantation procedure (complexity of the procedure and surgical experience), the IOL itself (material, metabolic effects and subclinical inflammation, intermittent touch), patient risk factors (trauma, medicine, other diseases, and genetic predisposition) and the (myopic or hyperopic) eye disease itself. Further research is required to clarify what factors contribute, and to what extent, to possibly earlier cataract development, especially in myopic eyes with an IF-pIOL.

IF-pIOL explantation and cataract extraction have been shown to be safe and effective.[18] Surgeons might experience simultaneous IF-pIOL explantation and phacoemulsification as a more complicated type of surgery. In our experience, the least complicated way to perform this combined type of surgery is to first perform the phacoemulsification underneath the IF-pIOL and to remove the IF-pIOL after the crystalline lens has been removed.[19] Our results are promising, but a randomized controlled trial should be performed to validate these findings.

Endothelial Cell Loss

The most feared complication after pIOL implantation is EC loss. Studies reporting EC densities have shown a wide variation of results. The extent of EC change ranges from a loss to a gain among short-, medium- and long-term studies. The general trend nevertheless demonstrates a decrease in EC density over time. (Chapter 2) There may be various reasons for the heterogeneity in results, such as surgeon experience and techniques, a difference in eligibility criteria for patient selection, differences among technicians, measurement devices and protocols, differences in geographical area and patient characteristics, location and timing of the operation, and the method of reporting outcomes. Researchers and clinicians should be aware of the difficulties and possible errors of EC analysis with specular microscopes. (Chapter 7) Care should be taken when reporting EC change from a single EC measurement, such as baseline, since this single measurement might be erroneous, as we experienced in our long-term studies. In our case, calibration errors led to erroneous EC densities with a difference of up to 500 cells/mm^2. Moreover, cell loss reported as a percentage of the previous measurement might overestimate actual cell loss since with lower EC counts, the loss of a single cell results in a higher percentage loss compared to when the EC count is high. In our opinion, absolute EC loss should be calculated by applying appropriate statistical methods to estimate a trend in EC change. In this way, it is possible to make full use of the data, and measurement errors are minimized.

One would expect a higher rate of EC loss in hyperopic eyes compared to myopic eyes due to a more crowded anterior segment. We found a comparable absolute annual EC decline of approximately 56 to 58 cells/mm^2 in myopic and hyperopic eyes. (Chapters 3 and 4)

An increase in EC loss is associated with a more shallow ACD[20,21] (Chapter 3), although in some other papers this cannot be statistically confirmed.[22-24] (Chapter 4) Presumably, a more reliable measurement might be the distance from the edge of the IF-pIOL to the corneal endothelium. It is expected that this is the first location where EC loss occurs due to intermittent touch of the edge of the pIOL since it is the smallest distance from the edge of the pIOL to the corneal endothelium. EC density 3 mm from the central cornea should be additionally measured during routine follow-up examinations. Previous studies have shown an association between a higher central EC loss and a smaller distance between the edge of the IF-pIOL and the corneal endothelium. Recommendations of a minimum clearance distance have been proposed, ranging from 1.0 to 2.0 mm.[24-28] However, none of these studies was a prospective longitudinal study, taking into account the age-related changes in anterior chamber morphometrics. Moreover, some studies were performed with anterior segment optical coherence

tomography (AS-OCT) whilst others were performed using Scheimpflug imaging. Recently, new and advanced software has become available to simulate age-related changes in anterior chamber morphometrics in relation to anterior chamber IOLs, using Scheimpflug imaging on the Pentacam (Oculus). To investigate the minimum required safe edge distance to the endothelium, a prospective longitudinal study in combination with "peripheral" EC analysis would be of great value for the future. In addition, specifying minimum safety criteria for each imaging method is recommendable due to statistically significant differences in anterior chamber measurements. (Chapter 8)

Another interesting future study could be to investigate whether there is a difference between loosely enclavated IF-pIOLs and more firmly enclavated IF-pIOLs. In glaucoma drainage devices, it has been suggested, among other hypotheses, that an altered aqueous flow might lead to a higher localized EC loss due to turbulence at the tip of the drainage device.[29] EC loss might also be partly related to the constant movement of the IF-pIOL during eye movement and blinking, depending on the tightness of IF-pIOL enclavation. This constant movement may lead to chronic mechanical irritation of the iris, leading to low levels of inflammation. Very tight enclavation, on the other hand, may result in a sandwich effect of the iris between the pIOL and the crystalline lens, also leading to mechanical irritation of the iris inducing an inflammatory response. Elevated levels of inflammatory cytokines could be a mechanism for loss of corneal clarity.[30] Previous work has attempted to study subclinical inflammation in IF-pIOLs.[31-33] Although we did not study inflammatory response, indirect evidence to reject this hypothesis might be the fact that we found a higher incidence of posterior synechiae formation in hyperopic eyes and a comparable EC loss in hyperopic and myopic eyes. Future work could include evaluation of morphological change in ECs with confocal microscopy in different IF-pIOL groups, or investigation of aqueous taps for the presence of inflammatory cells and cytokines.

More in-depth studies should be performed to unravel the reason(s) for a seemingly accelerated EC loss after IF-pIOL implantation. Mapping the entire corneal endothelium would lead to a greater understanding of the behavior of ECs after IF-pIOL implantation. To enable EC mapping of the entire cornea would be a breakthrough and give insights into many subfields of ophthalmology.

A central EC density of 1500 cells/mm^2 has been proposed as an endpoint to explant the IF-pIOL in order to maintain corneal clarity after phacoemulsification. To the best of my knowledge, evidence to support this guideline can not be found in literature. In light of clinical trials, endpoints should be defined to ensure comparability and safety for study subjects. In clinical practice, the endpoint of 1500 cells/mm^2 is not

always strictly adhered to; in my experience, the clinical endpoint is often around 1000 cells/mm^2. The decision to explant an IF-pIOL due to a drop in EC density in a relatively young patient, who is still able to accommodate and who is happy with optical correction with an IF-pIOL, may be undesirable. This situation may arise especially in young patients implanted in the early days of iris-fixated lenses since the minimum required EC density was 2000 cells/mm^2, irrespective of age. Thus, patients treated in the early days might reach this threshold relatively early in their lives. (Chapter 4) After careful consideration by the patient and physician, an IF-pIOL explantation could be postponed to until the patient loses their accommodative ability and has visually significant cataract with the need for cataract extraction. In this case, the patient has to be fully informed that corneal decompensation might occur due to the low EC density, and corneal endothelial cell transplantation might be necessary to maintain corneal clarity. On the other hand, in the light of a scarcity of donor tissue and possible shorter survival of the posterior lamellar corneal transplant in pseudo-phakic bullous keratopathy compared to other indications for corneal transplants, the question arises whether this is the best decision in the long run.[34] It remains unclear what central EC density cut-off point is safe to ensure enough (peripheral) EC reserve to repopulate the cornea after (future) phacoemulsification and IF-pIOL explantation.

At the same time, it is also our clinical experience that EC loss might stop or even be restored when the IF-pIOL is explanted. Is this due to patient factors, such as eye rubbing, re-shuffling of ECs or the removal of a foreign object that causes aqueous turbulence and/or subclinical inflammation? This is a question that is yet to be answered.

Retinal Detachment and Glaucoma

A high degree of myopia is associated with a higher risk of ensuing complications, such as retinal detachment, choroidal neovascularization and glaucoma. High hyperopia is associated with a higher risk of (angle-close) glaucoma development. Since the introduction of peripheral iridectomy/iridotomy, reports of pupillary block after IF-pIOL have become rare. Glaucoma is rarely reported after IF-pIOL implantation. (Chapter 2, 3 and 4) The risk of retinal detachment after pIOL implantation does not seem to increase after IF-pIOL implantation. (Chapters 2 and 4) The reason for this may lie in the fact that intraoperative changes during implantation of an IF-pIOL are limited to the anterior segment of the eye.

Lens Material

The rigid non-foldable type of the IF-pIOL (Artisan and Verisyse) is manufactured from a single piece of Perspex CQ-UV polymethylmethacrylate. A foldable version (Artiflex and Veriflex) is made of hydrophobic polysiloxane with rigid haptics of Perspex CQ-UV

polymethylmethacrylate. Both have been tested for their safety and compatibility in extremely high-field magnetic resonance investigation (MRI). Both were found to be safe in 7 Tesla high field MRI. (Chapter 6) There are many kinds of IOLs available today, all made of slightly different materials and with slightly different properties. MRI is an important and powerful diagnostic tool widely used all over the world in all fields of medicine. Since intraocular lenses are among the most extensively used implants, future work should include testing of implants used in the field of ophthalmology to ensure patient safety.

Studies of the Artiflex and Artisan IF-pIOLs in myopic eyes have shown comparably favorable and stable visual and refractive results.[35] Although the Artiflex has the advantage of requiring a smaller incision site, in our clinic the Artisan is preferred to the Artiflex. The main reason for this preference is based on our experience of a higher incidence of deposits on the Artiflex IF-pIOL. This is in line with literature where incidence of precipitates is reported to be higher in the foldable IF-pIOL version compared to the rigid IF-pIOL version.[35-37] In myopic eyes, (non)pigmented deposits are rarely reported.(Chapter 4) The most likely reason for the higher incidence of cell deposits on the Artiflex compared to the Artisan is the difference in material. In hyperopic eyes, in which correction can only be achieved with the rigid IF-pIOL, there seems to be a higher rate of pigment dispersion and formation of posterior synechiae compared to myopic eyes. (Chapters 2 and 3) The reason for the difference in the incidence of posterior synechiae is most likely to be sought in the anatomy of the eye, possibly in combination with a slightly smaller IF-pIOL vault due to the hyperopic correction. However, since this is still not entirely clear, great care should be taken when implanting IF-pIOLs in hyperopic eyes. We recommend adjusting the minimum ACD and adding the crystalline lens rise as safety criteria in eligible hyperopic eyes in an attempt to decrease the incidence rate of pigment dispersion. Future studies should closely evaluate the anterior dimensions of hyperopic eyes in particular.

Overall

The most important safety aspect in any kind of surgery is patient selection. Especially in the case of elective surgery, safety is of the greatest concern. To aid decision-making for refractive surgeons, eligibility criteria are available. These criteria should be updated according to the latest long-term results, but it is also necessary for refractive surgeons to stay up-to-date on scientific developments. Peer experience is equally important in deciding what technique to use to correct the refractive error in a patient's eye. Modern imaging modalities to evaluate delicate internal structures and the anatomical relationship and dimensions within an eye are also rapidly developing and becoming increasingly more accurate. Despite technological advances, it is important

to keep in mind that the various imaging modalities available may produce different measurements. Such imaging modalities should therefore not be used interchangeably without prior comparison. When different measurements are found, the devices should be compared and eligibility criteria adjusted accordingly. (Chapters 7 and 8) Moreover, calibration differences are a proven source of measurement error and should be avoided at all times. (Chapter 8) Future work could focus on comparing the latest imaging techniques to investigate which imaging technique displays the most realistic, undistorted image of the eye.

The complication rate after IF-pIOL implantation is seemingly higher in eyes implanted in the early years of the IF-pIOL. For myopic eyes, this is reflected in the fact that the vast majority of eyes having an EC density <1500 cells/mm^2 at their last follow-up visit were implanted in or before the year 2001. Also, in the hyperopic eyes experiencing pigment dispersion, a considerable portion of these eyes were implanted in the very early years when iris configuration was not yet considered a safety criterion. During follow-up, safety criteria have been altered or added by the manufacturer, or surgeon, based on clinical experience and results. Future studies could focus on applying uniform safety criteria and on evaluating clinical results in a prospective manner.

In order to evaluate long-term safety on a large scale, and to enable proper comparison of different techniques for optical correction of refractive errors, a standardized reporting method is necessary, and protocols for prospective studies should be described in detail. Initiatives proposed by journal authors and editors to achieve uniformity should be supported and followed.[38,39]

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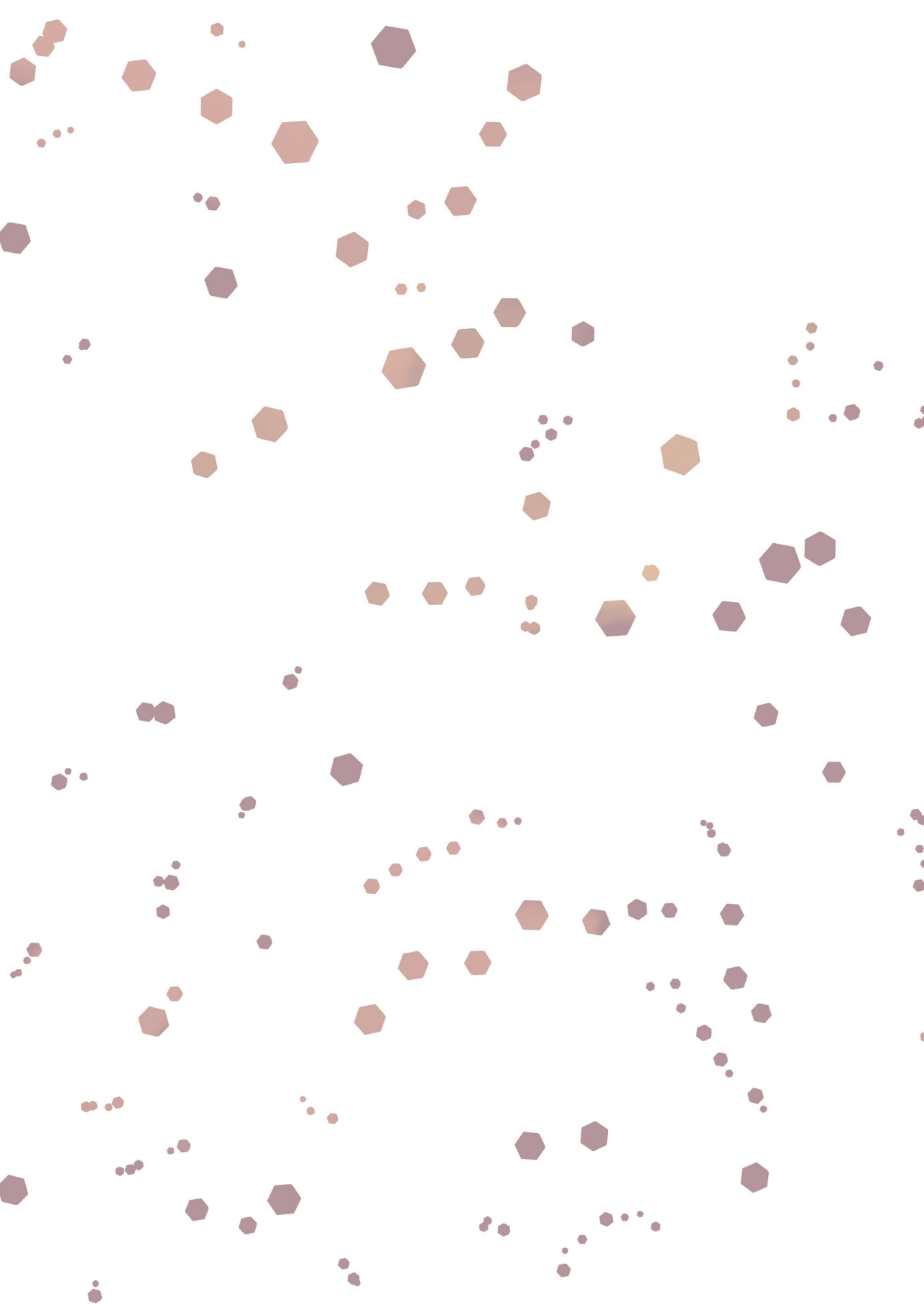


Chapter 10

English Summary

ENGLISH SUMMARY

In this thesis, we have attempted to provide an overview of the expected clinical benefits and risks after Artisan iris-fixated phakic intraocular lens (IF-pIOL) implantation. Additionally, we have attempted to investigate the reliability of measurements performed for patient selection.

Chapter 1 gives a brief overview of the Artisan IF-pIOL; including a brief history of the lens, a description of its design, the power calculation and implantation technique, the indications for its use and the minimum safety criteria currently applied.

Chapter 2 describes a pooled analysis and gives an overview of data from peer-reviewed papers on the IF-pIOL. There is a lack of data on long-term studies. Research on the correction of hyperopia with an IF-pIOL is limited. Care should be taken when implanting an IF-pIOL in hyperopic eyes since pigment dispersion might present a problem seldom seen in myopic eyes.

In chapter 3, we present the results of 61 hyperopic eyes implanted with an IF-pIOL with a follow-up of up to 15 years. The visual and refractive results are favorable and stable throughout long-term follow-up. IF-pIOL explantation was performed after a mean of 8 years. Reasons for explantation were endothelial cell (EC) loss, pigment dispersion and clinically significant cataract formation. EC loss occurred at an annual rate of 58 cells/mm^2. Pigment dispersion was the most common complication, observed in almost 15% of the eyes studied. The mechanism behind this remains unclear. Until we have a better understanding of the mechanism behind the development of pigment dispersion with an IF-pIOL in place, we recommend an anterior chamber depth (ACD) of >3.0 mm, measured from the corneal endothelium, as well as close evaluation and monitoring of the anterior chamber dimensions with modern anterior chamber imaging techniques in addition to a proper and careful enclavation technique.

In chapter 4, we present the results of 276 myopic eyes implanted with an IF-pIOL with a follow-up of up to 22 years. Visual and refractive results were very good up to 22 years post-implantation with no clinically relevant changes. IF-pIOL explantation was performed after a mean of 12 years. The main reasons for explantation were clinically significant cataract formation and EC loss. EC loss occurred at an annual rate of 56 cells/mm^2, which is comparable to the EC loss observed in hyperopic eyes (Chapter 3). At the last follow-up visit, 11% of the eyes had reached the threshold of <1500 cells/mm^2. These eyes seemed to have a slightly shallower ACD and higher age at implantation, though statistical significance was only just reached. Moreover, the majority of the eyes were

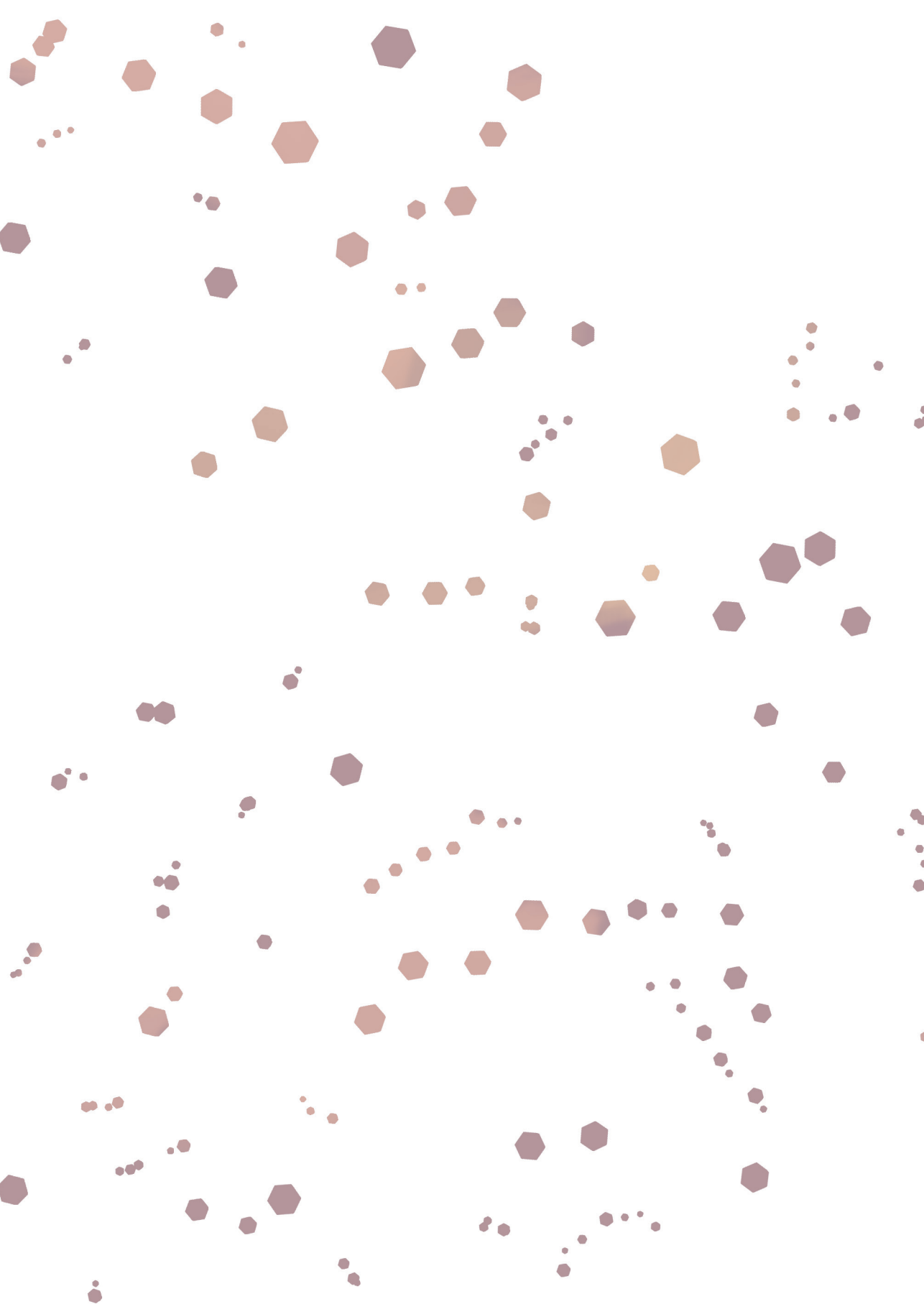
implanted in the early years, when safety-criteria were poorly defined. A minimum age-dependent EC density and application of up-to-date safety criteria might assure longer-term safety for the corneal endothelium with an IF-pIOL in place.

Chapter 5 reports on a case series of 3 patients with oculocutaneous albinism with successful implantation of an Artisan iris-fixated pIOL and a follow-up of 8 to 14 years. Visual acuity improved in all 3 cases with satisfied patients. No complications, particularly no dislocation or luxation, were observed. Although a translucent iris, as may be observed in oculocutaneous albinism, appears fragile, absence or lack of pigmentation does not appear to decrease the mechanical strength of the iris and proper enclavation of an IF-pIOL can be achieved. Additional monitoring of these eyes is necessary since EC monitoring may be more difficult due to ocular nystagmus, resulting in low-quality EC measurements.

Chapter 6 describes a set of 23 intraocular lenses (IOLs) that were selected based on the presence of dyes and metals and different geometric shapes. Magnetic resonance (MR) compatibility was evaluated in a high-field 7-Tesla MRI scanner according to the American Stand Test Method. No significant displacement was detected with any of the IOLs. A significant magnetic susceptibility artifact was caused by the small platinum component of the Worst Platinum Clip lens, the precursor of the modern IF-pIOL. Measurements of radiofrequency-induced heating showed no significant temperature changes of the tested IOLs. We conclude that all tested IOLs are considered safe for MRI up to and including 7-Tesla. One should keep in mind that the platinum component of the IOL iris clip causes an imaging artifact. Further testing of other surgical materials and implants used in the field of ophthalmology should be performed in order to ensure patient safety.

In chapter 7, we propose a method for improving interchangeability when different corneal specular microscopes (CSMs) are used and for obtaining precise endothelial cell counts when a CSM needs to be replaced. It involves checking magnification settings, re-checking magnification calibration with an external calibration device, and then calculating correction factors. The method we describe is not restricted to the Topcon specular microscopes (Topcon, Tokyo) and can be directly applied to other specular or confocal microscopes and their associated analysis software packages. Also, retrospective correction of EC counts when interchangeability issues are at play, is possible. This method has been used for the long-term studies described in chapters 3 and 4.

In chapter 8, we conclude that anterior segment optical coherence tomography (AS-OCT) and Scheimpflug imaging are both accurate techniques for measuring the distance from the anterior edge of an IF-pIOL to the corneal endothelium, with good reproducibility. Sixty-two eyes were measured with both imaging modalities and 2 researchers independently measured the distances between IF-pIOL and endothelium. AS-OCT (Visante, Carl Zeiss Meditec Inc.) provided significant larger measurements compared to Scheimpflug imaging (Pentacam HR, Oculus Optikgerate). This difference is of great clinical importance for the selection and follow-up of patients with an IF-pIOL. We recommend not using these imaging modalities interchangeably.



Chapter 11

Nederlandse Samenvatting

NEDERLANDSE SAMENVATTING

In dit proefschrift is gestreefd naar een zo volledig mogelijk overzicht te geven van de verwachte voordelen en risico's na implantatie van een Artisan iris-gefixeerde fake intra-oculaire lens (IF-fIOL). Tevens wordt de betrouwbaarheid van metingen die nodig zijn voor patiënt-selectie onder de loep genomen.

In hoofdstuk 1 wordt een introductie gegeven van de Artisan IF-fIOL; van een beknopte geschiedenis tot een beschrijving van het ontwerp, de implantatietechnieken, indicaties en patiënt-selectie met minimale veiligheidseisen.

Hoofdstuk 2 betreft een gepoolde analyse van de klinische resultaten van de hedendaags beschikbare literatuur omtrent de IF-fIOL. Hierin wordt duidelijk dat er weinig bekend is over de lange termijn resultaten van de IF-fIOL. Studies met betrekking tot IF-fIOL implantatie voor hypermetrope ogen zijn zeer beperkt beschikbaar. In korte- en middellange termijn studies wordt geconcludeerd dat er voorzichtigheid is geboden bij het implanteren van IF-fIOLs in hypermetrope ogen, omdat pigmentdispersie vaker lijkt voor te komen.

In hoofdstuk 3 worden de klinische resultaten gepresenteerd van een cohort van 61 hypermetrope ogen die een IF-fIOL implantatie hebben ondergaan met een follow-up van 15 jaar. In deze studie worden goede en stabiele visuele- en refractieve resultaten geobserveerd. Het gemiddelde jaarlijks endotheelcelverlies was 58 cellen/mm^2. De IF-fIOL werd na gemiddeld 8 jaar geëxplanteerd. De aanleidingen voor explantatie van de IF-fIOL waren endotheelcelverlies, pigmentdispersie en cataract. Pigmentdispersie was de meest voorkomende complicatie. Verschillende hypothesen voor het ontstaan van pigmentdispersie passeren de revue, maar het exacte mechanisme van het ontstaan van pigmentdispersie in ogen met een IF-fIOL blijft vooralsnog onbekend. In dit hoofdstuk worden aanbevelingen gedaan om de veiligheid van een IF-fIOL in hypermetrope ogen te verbeteren.

In hoofdstuk 4 worden de klinische resultaten gepresenteerd van 276 myope ogen die een IF-fIOL hebben ondergaan met een follow-up tot 22 jaar. Ook hier zijn de visuele- en refractieve resultaten goed en werden er geen klinisch relevante veranderingen gedurende de follow-up geobserveerd. De IF-fIOL werd gemiddeld na 12 jaar geëxplanteerd. De meest voorkomende redenen voor explantatie waren cataract en endotheelcelverlies. Er werd een jaarlijks endotheelcelverlies van 56 cellen/mm^2 gevonden, vergelijkbaar met dat van de hypermetrope ogen (hoofdstuk 3). Bij de laatste individuele follow-up bleek 11% van de ogen een endotheelcel aantal van minder

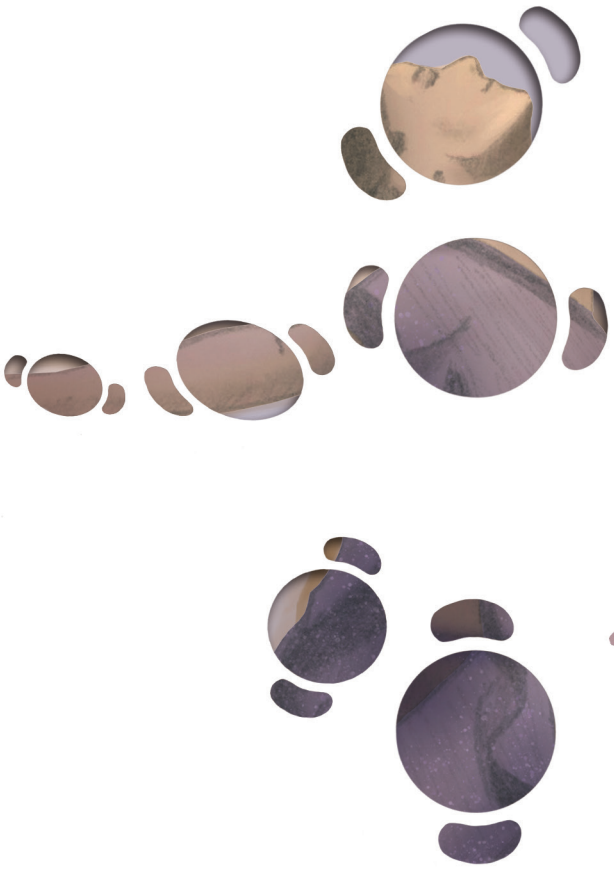
dan 1500 cellen/mm^2 te hebben. Opvallend is dat de meerderheid van deze ogen in de beginjaren van het bestaan van de Artisan IF-fIOL was geïmplanteerd. Er waren indertijd nog geen duidelijke veiligheidscriteria gedefinieerd. Een minimaal leeftijdsgerelateerd endotheelcel aantal en het gebruik van up-to-date veiligheidscriteria zouden de lange termijn veiligheid kunnen verbeteren.

In hoofdstuk 5 wordt een case-serie gepresenteerd van 3 patiënten met oculocutaan albinisme die een succesvolle IF-fIOL implantatie hebben ondergaan met een follow-up van 8 tot 14 jaar. In alle patiënten verbeterde de visus. Er werden geen complicaties gerapporteerd, met name geen luxatie of dislocatie van de IF-fIOL. Alhoewel een doorschijnende iris, zoals die in patiënten met oculocutaan albinisme kan worden geobserveerd, fragiel oogt, lijkt de afwezigheid van iris-pigment geen gevolgen te hebben voor de stevigheid van de iris en enclavatie van een IF-fIOL. Er wordt frequentere controle van deze ogen aangeraden gezien een oculaire nystagmus het monitoren van het corneale endotheel bemoeilijkt.

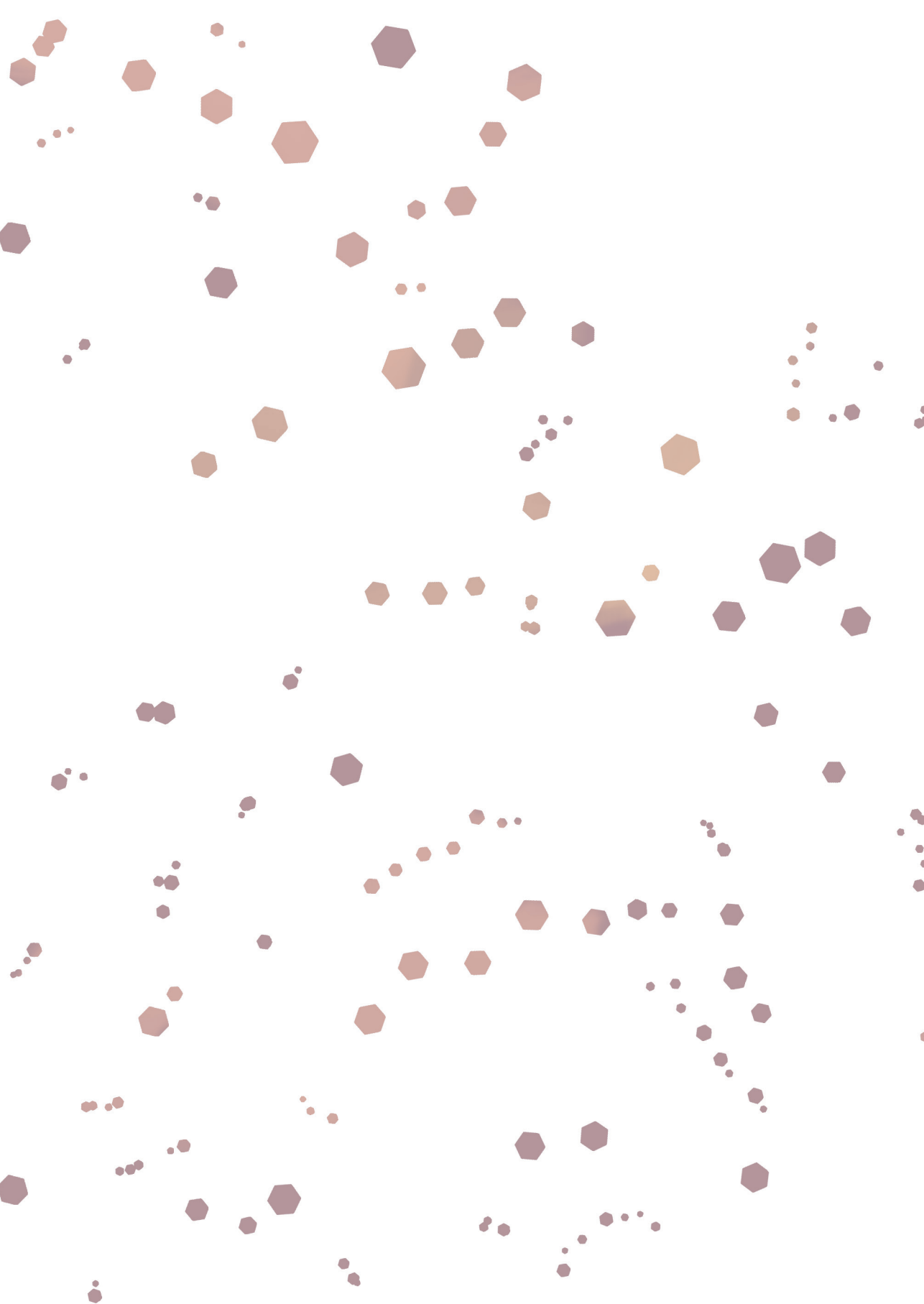
In hoofdstuk 6 wordt beschreven hoe de veiligheid van 23 verschillende soorten intra-oculaire lenzen is getest in een hoge veldsterkte 7-Tesla MRI volgens de Amerikaanse standaard test methode (ANSI). De geteste intra-oculaire lenzen werden geselecteerd op de aanwezigheid van kleurstoffen, metalen en verschillende geometrische vormen. Behoudens een beeldartefact rondom het platina onderdeel van de Worst Platinum Clip lens, de voorloper van de moderne Artisan IF-fIOL, werden er geen veiligheidsrisico's gevonden: er werd geen significante verplaatsing gezien als gevolg van het magnetisch veld, en er werd geen significante radiofrequentie-geïnduceerde opwarming gemeten. We concluderen dat alle geteste intra-oculaire lenzen veilig zijn in een MRI bij een veldsterkte tot en met 7-Tesla. Ook andere materialen en implantaten gebruikt in de oogheelkunde zouden getest moeten worden om de veiligheid in een MRI te kunnen garanderen.

In hoofdstuk 7 beschrijven we een methode waarmee de onderlinge uitwisselbaarheid van endotheelcelteltellingen die met verschillende corneale endotheelcelcamera's zijn gemaakt verbeterd wordt. De methode wordt beschreven voor een specifiek type endotheelcelcamera (Topcon, Tokyo), maar kan ook gebruikt worden voor andere endotheelcelcamera's. Betrouwbare retrospectieve correctie van endotheelcelteltellingen wordt op deze manier mogelijk gemaakt. Dit is met name waardevol voor (retrospectieve) lange termijn studies waarbij endotheelcel-aantal een belangrijke veiligheidsparameter is en tussentijds de endotheelcelcamera vervangen is. Deze methode is gebruikt voor de klinische lange termijn studies die worden beschreven in hoofdstukken 3 en 4.

In hoofdstuk 8 wordt beschreven dat optische coherentie tomografie van het voorsegment (AS-OCT) en Scheimpflug imaging beiden reproduceerbare technieken zijn om de afstanden van een IF-fIOL tot het endotheel van de cornea te meten, maar dat de metingen met deze methoden niet uitwisselbaar zijn. In deze studie werd in 62 ogen met een IF-fIOL met zowel de Visante AS-OCT (Carl Zeiss Meditec Inc.) als met de Pentacam HR (Oculus, Optikgerate) de afstand tussen de IF-fIOL en het corneale endotheel gemeten. De afstanden werden door 2 onderzoekers onafhankelijk van elkaar gemeten en met elkaar vergeleken. Met de Visante AS-OCT werden significant grotere afstanden gemeten vergeleken met de metingen van de Pentacam. Dit verschil is van belang in de overweging of een oog aan de gestelde veiligheidscriteria voldoet voor een IF-fIOL implantatie. Daarnaast is het van belang voor de interpretatie van de gegevens tijdens de follow-up van deze ogen. Wij raden aan de metingen die gemaakt zijn met deze 2 apparaten niet met elkaar uit te wisselen.



Addendum



Addendum

Appendices

APPENDIX 1

SEARCH

PubMed on August 3, 2018

("Phakic Intraocular Lenses"[Mesh] OR "Lens Implantation, Intraocular"[Mesh] OR Intraocular Lens*[tw] OR "Lenses, Intraocular"[Mesh]) AND ("Artisan"[tw] OR "artiflex"[tw] OR "verisyse"[tw] OR "veriflex"[tw] OR "iris claw"[tw] OR "iris fixated"[tw]).

Web of Science™ (Thomson Reuters) on August 28, 2018

TS = (Artisan OR artiflex OR verisyse OR veriflex OR iris claw OR iris-claw) AND TS = (Phakic OR Intraocular OR Lens OR implant*).

EMBASE on August 28, 2018

("exp phakic intraocular lens"/ OR exp lens implantation/ OR Intraocular Lens*.ti,ab. OR exp lens implant/) AND ("Artisan".ti,ab. OR "artiflex".ti,ab. OR "verisyse".ti,ab. OR "veriflex".ti,ab. OR "iris claw".ti,ab. OR "iris-claw".ti,ab. OR "iris fixated".ti,ab. OR "iris-fixated".ti,ab.).

Cochrane Library on August 28, 2018

(Phakic OR Intraocular Lens* OR Lens implant*) AND ("Artisan" OR "artiflex" OR "verisyse" OR "veriflex" OR "iris claw" OR "iris-claw" OR "iris fixated" OR "iris-fixated").

APPENDIX 2

Change in manifest spherical equivalent in myopic eyes

Study	Country	Publication
Asano-Kato et al.	Japan, Tokyo	2005
Benedetti et al.	Italy, Ancona	2007
Benedetti et al.	Italy, Ancona	2005
Bohac et al.	Croatia, Zagreb	2016
Bouheraoua et al.	France, Paris	2015
Chebli et al.	France, Lyon	2018
Guell et al.	Spain, Barcelona	2007
Guell et al.	Spain, Barcelona	2007
Landesz et al.	Netherlands, Rotterdam	2000 2000
Menezo et al.	Spain, Valencia	2004
Moshirfar et al.	USA, Utah	2007
Shajari et al.	Germany, Frankfurt am Main	2016
Silva et al.	USA, California Stanford	2008
Tahzib et al.	Netherlands, Maastricht	2007
Titiyal, et al.	India, New Delhi	2012
Yasa et al.	Turkey, Istanbul	2014

*group 1=Artisan Myopia 204; *group 2= Artisan myopia 206; no= number of eyes; D=diopters; pre-op=preoperative; post-op=postoperative; SE=spherical equivalent; FU-time=follow-up time; n.s=not specified

[a]not specified, mean follow-up 5,4 years (range1-10 years)

Eyes (count)	Mean pre-op SE (D)	Mean post-op SE (D)	Reported FU-time (year)
21	-12.8±2.94	-0.71±0.81	2
49	-13.60± 4.26	-1.32±1.20	n.s.
68 (group 1)*	-11.8±2.4	-0.91±0.77	2
25 (group 2)*	-18.9±2.0	-1.20±1.19	2
190	-13.27 ±5.1	-0.34 ±0.17	3
68	-13±4.10	−0.75 ± 0.74	5
113	-14.67±5.15	-0.53±0.80	final visit[a]
95 (group 1)*	-19.8±3.23	-0.78±0.88	3
150 (group 2)*	-11.27±3.11	-0.95±1.06	3
89 (group 1)*	-19.8±3.23	-0.5±0.89	5
165 (group 2)*	-11.27±3.11	-0.64±0.8	5
67	-14.70 ±4.90	-1.12±2.10	2
67	-14.70 ±4.90	-1.05±2.20	3
137	-16.17±2.75	-0.78± 1.21	2
85	-12.20±2.79	-0.50	2
78	-11.06±4.77	-0.37±0.48	2
67	-11.06±4.77	-0.42±0.57	3
95	-11.06±4.77	-0.42±0.47	4
20	-12.30±2.69	-0.38±0.78	3
19	-12.30±2.69	-0.37±0.69	5
89	-10.36±4.69	-0.71±0.99	6
89	-10.36±4.69	-0.70±1.00	10
51	-14.98	-0.87	4
62	-11.64±3.61	-0.82±0.55	2

Deviation of manifest refractive spherical equivalent from targeted refraction in myopic eyes

Study	Publication	Eyes (count)	≤0,5D (%)	≤1.0D (%)	FU-period (year)
Asano-Kato et al.	2005	21	55	55	2
Bouheraoua et al.	2015	68	38.2	69.1	3
		68	36.8	70.5	5
Budo et al.	2000	249	57.1	78.8	3
Guell et al.	2008	101 (group 1)	9.9	22.8	n.s.
		173 (group 2)	37.6	57.2	n.s.
Landesz et al.	2000	67	47.8	67.2	n.s.
Moshirfar et al.	2007	38	55	84	2
Qasem et al.	2010	68	31	65	2
		30	24	53	3
		16	12	28	4
		11	20	63	5
Shajari et al.	2016	95	72	94	4
Stulting et al.		434	85.4	97.7	3
Silva et al.	2008	20	75	85	3
		19	73.7	94.7	5
Tahzib et al.	2007	89	50.5	65.1	6
		89	43.8	68.8	10
Titiyal, et al.	2012	51	33.3	82.4	2
		51	31.4	74.5	3
		51	35.3	72.5	4
Yasa et al.	2014	62	68	90	2
Yuan et al.	2011	84	n.r.	93.2	n.s.

D=diopters; FU-period=follow-up period; n.s.=not specified; n.r.= not reported; ACRS=additional corneal refractive surgery; %=percentage; ≤equals or smaller than

Deviation of manifest refractive spherical equivalent from targeted refraction in hyperopic eyes

Study	Publication	Eyes (count)	≤ 0,5D (%)	≤ 1.0D (%)	FU-period (year)
Guell et al.	2008	41	34.8$^{\delta}$	64.2$^{\delta}$	n.s.
Qasem et al.	2010	6	50$^{\delta}$	100$^{\delta}$	2
		2	100$^{\delta}$	100$^{\delta}$	3

D=diopters; FU-period=follow-up period; n.s.=not specified; ACRS=additional corneal refractive surgery; %=percentage; ≤equals or smaller than

	Target	Notes
	emmetropia	data from graph numbers are estimated
	intended	
	intended	
	emmetropia	60.39% of the eyes ACRS
		19.6% of the eyes ACRS
	emmetropia	
	emmetropia	
	emmetropia	data from graph numbers are estimated, 17.9% of the eyes ACRS
		data from graph numbers are estimated, 17.9% of the eyes ACRS
		data from graph numbers are estimated, 17.9% of the eyes ACRS
		data from graph numbers are estimated, 17.9% of the eyes ACRS
	emmetropia	
	emmetropia	
	emmetropia	
	intended	
	emmetropia	
	emmetropia	
	intended	

Target	Notes
emmetropia	[δ]41.4% of the eyes ACRS
emmetropia	[δ]28.6% of eyes ACRS, data from graph numbers are estimated
emmetropia	[δ]28.6% of eyes ACRS, data from graph numbers are estimated

APPENDIX 3

Mean pre- and postoperative corrected distance visual acuity in myopic eyes

Study	Publication	Eyes (count)
Benedetti et al.	2007	49
Bohac et al.	2017	166
Budo et al.	2000	249
		249
Chebli et al.	2018	113
Landesz et al.	2000	67
Landesz et al.	2001	10
Senthil et al.	2006	60
Tahzib et al.	2007	89
Titiyal, et al.	2012	85
Yuan et al.	2012	84
		84
		84
		84

CDVA=corrected distance visual acuity; FU-time=follow-up time; pre-op=preoperative; post-op=postoperative; logM=logaritic angle of minimum resolution; n.s.= not specified

Mean pre- and postoperative corrected distance visual acuity in hyperopic eyes

Study	Publication	Eyes (count)
Saxena et al.	2003	10

CDVA=corrected distance visual acuity; FU-time=follow-up time; pre-op=preoperative; post-op=postoperative

	Mean pre-op CDVA (decimal)	Mean post-op CDVA (decimal)	Fu-time (year)
	0.80±0.20	0.86±0.20	n.s.
	0.67 ±0.20	0.77 ±0.18	3
	0.67±0.26	0.88± 0,19	2
	0.67±0.26	0.87±0.20	3
	0.18±0.18 logM	0.064±0.096 logM	last visit (range 1-10 years)
	20/40	20/32	n.s.
	20/32	20/25	n.s.
	20/39	20/32	n.s.
	0.16±0.23 logM	0.12±0.21 logM	10
	6/10	6/7	last visit (range 1-5 years)
	0.68±0.12	0.96±0.10	2
	0.68±0.12	0.96±0.08	3
	0.68±0.12	0.96±0.04	4
	0.68±0.12	0.95±0.08	5

Mean pre-op CDVA (decimal)	Mean post-op CDVA (decimal)	Fu-time (year)
0.86±0.59	0.75±0.52	3

Uncorrected distance visual acuity of myopic eyes (cumulative percentage of eyes)

Study	Publication	Eyes (count)	FU-time (year)	≥20/40 (%)	≥ 20/30 (%)
Bouheraoua et al.	2015	68	3	79.4	-
		68	5	82.3	65.5
Budo et al.	2000	249	3	76.8	-
Landesz et al.	2000	67	-	40.9	33.3
Moshirfar et al.	2007	85	2	84	-
Qasem et al.	2010	68	2	85*	65*
		30	3	72*	60*
		16	4	57*	32*
		11	5	45*	37*
Shajari et al.	2016	95	4	92*	-
Silva et al.	2008	20	3	85	85*
		19	5	94.7	90*
Stulting et al.	2008	356	2	87.1	71.7
		231	3	83.9	70.9
Tahzib et al.	2007	89	6	78.7	-
		-	10	82	-
Titiyal, et al.	2012	51	2	68.6	
		51	3	66.7	
		51	4	68.6	-
		28	5	64.3	-
Yuan et al.	2011	84	3	100	100
		84	5	100	95.2

- = no data available ; FU-time=follow-up time; ≥=equals or exceeds; %=percentage

Uncorrected distance visual acuity of hyperopic eyes (cumulative percentage of eyes)

Study	Publication	Eyes (count)	FU-time (year)	≥20/40 (%)	≥ 20/30 (%)
Qasem et al.	2010	6	2	100*	100*
		2	3	100*	100*

- = no data available ; FU-time=follow-up time; ≥=equals or exceeds; %=percentage

≥ 20/25 (%)	≥20/20 (%)	20/15 (%)	Notes
-	4.4	-	
23.5	5.9	-	
-	33.7	-	
15.2	12.1		
34	-	-	
-	29*	-	*data from graph, numbers are estimated 17.9% ACRS
-	18*	-	*data from graph, numbers are estimated 17.9% ACRS
-	7*	-	*data from graph, numbers are estimated 17.9% ACRS
-	9*	-	*data from graph, numbers are estimated 17.9% ACRS
76	53*	-	*data from graph, numbers are estimated
77*	60	-	*data from graph, numbers are estimated
74*	73.7	-	*data from graph, numbers are estimated
54.8	34.6	4.8	
51.9	31.1	4.3	
-	-	-	
-	-	-	
	15.7		
	15.7		
-	13.7	-	
-	21.4	-	
85.7	60.7	-	
85.7	39.3	-	

≥ 20/25 (%)	≥20/20 (%)	20/15 (%)	Notes
-	50*	-	data from graph, numbers are estimated
-	50*	-	data from graph, numbers are estimated

Efficacy and safety indices of myopic eyes

Study	Publication	FU-time (year)	Efficacy Index	Safety Index
Benedetti et al. - group 1*	2004	2	0.84	1.39
Benedetti et al. - group 2*		2	0.90	1.39
Bouheraoua et al.	2015	3	0.98	1.02
		5	1.02	1.10
Budo et al.	2000	-	1.03	1.31
Landesz et al.	2001	n.s.	0.91	1.21
Senthil et al.	2006	2	0.93	1.19
Silva et al.	2008	3	0.43	-
		5	0.63	-
Tahzib et al.	2007	6	0.83	1.10
		10	0.80	1.10
Titiyal et al.	2012	4	0.96	1.46

*group 1=Artisan Myopia 204; *group 2=Artisan Myopia 206; -= no data available; FU-time=follow-up time; n.s.=not specified

Efficacy and safety indices of hyperopic eyes

Study	Publication	FU-time (year)	Efficacy index	Safety index
Guell et al.	2008	2	0.81	0.95
		3	0.71	0.92
		4	0.74	0.98
		5	0.90	1.25

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APPENDIX 4

Endothelial cell change in myopic eyes - Part 1

Study	Publication	FU-time (year)	EC change (%)	Adjusted EC change (%)
Aerts et al.	2015	2	2.1 ±0.9	-
Benedetti et al.	2005	2	5.4	-
Benedetti et al.	2007	2	4.7	-
		3	6.7	-
		4	8.3	-
		5	9.0	-
Bohac et al.	2016	3	0.97*	-
Bouheraoua et al.	2015	2	11.26	-
		3	11.96	-
		4	14.58	-
		5	15.15	-
Budo et al.	2000	2	1.7	-
		3	0.7	-
Chebli et al.	2018	2	0.87*	-
		5	0.87*	-
		7	0.87*	-
		10	0.87*	-
Choi et al.	2014	2	1.32	-
		3	2.14	-
		4	3.44	-
		5	3	-
		6	3.33	-
		7	5.43	-
		8	4.91	-
		9	7.38	-
		10	22.5	-
Guell et al. - group 1	2008	2	10.1	-
		3	7.4	-
		4	1.5	-
		5	11.3	-

Eyes (count)	EC change from	Notes
262	6 months	
93	baseline	
-	baseline	
-	baseline	
-	baseline	
-	baseline	
166 (out of 198)	baseline	* EC loss annually
68	baseline	
68	baseline	
68	baseline	
68	baseline	
129 subgroup (out of 518)	baseline	
129 subgroup (out of 518)	baseline	
101 (out of 113)	1 year	calculated with mixed model, * EC loss annually
63 (out of 113)	1 year	calculated with mixed model, * EC loss annually
44 (out of 113)	1 year	calculated with mixed model, * EC loss annually
16 (out of 113)	1 year	calculated with mixed model, * EC loss annually
63 (out of 66)	baseline	
53 (out of 66)	baseline	
53 (out of 66)	baseline	
52 (out of 66)	baseline	
42 (out of 66)	baseline	
45 (out of 66)	baseline	
43 (out of 66)	baseline	
20 (out of 66)	baseline	
6 (out of 66)	baseline	
80 (out of 97)	baseline	
68 (out of 95)	baseline	
93 (out of 93)	baseline	
88 (out of 89)	baseline	

Endothelial cell change in myopic eyes - Part 1 (Continued)

Study	Publication	FU-time (year)	EC change (%)	Adjusted EC change (%)
Guell et al. - group 2	2008	2	5.11	-
		3	8.57	-
		4	2.07	-
		5	10.9	-
Jonker et al.	2018	5	7.9	5.2*
		5	4.1	-
		10	16.6	10.9*
		10	11.5	-
Landesz et al.	2000	2	-	9.1±8.9*
		3	-	10.9±8.6*
Landesz et al.	2001	2	n.r.	n.r.
Menezo et al.	2004	2	7.63	-
		5	10.51	-
Moshirfar et al.	2014	-	-	-
Moshirfar et al.	2007	2	6±10.75	4.80±10.7*
Na et al.	2013	2	-0.26 ±14.69	-0.27±17.32*
Pop et al.	2004	2	-0.75 ±17.41*	0.42±17.41*
Qasem et al.	2010	2	1.33[δ]	-
		3	2.22[δ]	-
		5	0	-

Eyes (count)	EC change from	Notes
136 (out of 170)	baseline	
150 (out of 168)	baseline	
155 (out of 168)	baseline	
165 (out of 166)	baseline	
193 (out of 381)	6 months	calculated with linear mixed model, * ECC loss adjusted for 0,6% physiological cell loss per year
193 (out of 381)	baseline	direct subgroup analysis
127 (out of 381)	6 months	calculated with linear mixed model, * ECC loss adjusted for 0,6% physiological cell loss per year
127 (out of 381)	baseline	direct subgroup analysis, as normally done
67 (out of 67)	baseline	* ECC loss adjusted for 0,6% physiological cell loss per year
61 (out of 67)	baseline	* ECC loss adjusted for 0,6% physiological cell loss per year
10 (out of 91)	-	
61	baseline	also older Worst-Fechner IOL was used, but no significant difference in ECC loss between old and new pIOL group
61	baseline	also older Worst-Fechner IOL was used, but no significant difference in ECC loss between old and new pIOL group
-	-	
n.s. (out of 56)	baseline	* ECC loss adjusted for 0,5% physiological cell loss per year
40 (out of 52)	baseline	* ECC loss adjusted for 0,6% physiological cell loss per year, gain in ECC was found
293 (out of 765)	baseline	* ECC loss adjusted for 0,6% physiological cell loss per year
84[δ]	-	[δ]data including 6 hyperopic eyes and 10 toric pIOL eyes
38[δ]	-	[δ]data including 2 hyperopic eyes and 6 toric pIOL eyes
11 (out of 151)	-	

Endothelial cell change in myopic eyes - Part 1 (Continued)

Study	Publication	FU-time (year)	EC change (%)	Adjusted EC change (%)
Saxena et al.	2008	2	0.8	-0.4*
		3	2.2	0.4*
		4	6.5	4.1*
		5	8.3	5.3*
		6	9.1	5.5*
		7	12.6	8.5*
Senthil et al.	2006	2	6.38	-
Shajari et al.	2016	2	6.2	-
		3	8.8	-
		4	11	-
Silva et al.	2008	3	9.98 ±16.86	-
		5	14.05 ±21.39	-
Stulting et al.	2008	2	1.43±9.5	-
		3	4.8 ±7.8	-
		3	3.8 ±9.8	-
Tahzib et al.	2007	6	-	-3.26±18.96*
		10	-	-8.86±16.01*
Titiyal et al.	2012	2	9.26	-
		3	11.07	-
		4	12.48	-
		5	15.59	-

Eyes (count)	EC change from	Notes
168 (out of 318)	baseline	data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment, gain in adjusted ECC was found
122 (out of 318)	baseline	data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment
69 (out of 318)	baseline	data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment
51 (out of 318)	baseline	data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment
28 (out of 318)	baseline	data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment
13 (out of 318)	baseline	data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment
60 (out of 60)	-	
78 (out of 95)	-	
67 (out of 95)	-	
95 (out of 95)	-	
20 (out of 26)	baseline	
16 (out of 26)	baseline	
57 (consistent cohort)	baseline	
107	baseline	
57 (consistent cohort)	baseline	
89 (out of 89)	baseline	* ECC loss adjusted for 0,6% physiological cell loss per year, gain in ECC was found
89 (out of 89)	baseline	* ECC loss adjusted for 0,6% physiological cell loss per year, gain in ECC was found
51 (constant cohort)	-	
51 (constant cohort)	-	
51 (constant cohort)	-	
28 (out of 85)	-	

Endothelial cell change in myopic eyes - Part 1 (Continued)

Study	Publication	FU-time (year)	EC change (%)	Adjusted EC change (%)
Yasa et al.	2016	2	0.3	-
Yuan et al.	2011	2	7.8	-
		3	2.9	-
		4	1.5	-
		5	<1.5	-

- = no data available or not specified; FU-time=follow-up time; EC=endothelial cell; ECC=endothelial cell count; pIOL=phakic intraocular lens; n.r=not reported

Endothelial cell change in myopic eyes - Part 2

Study	Publication	FU time (year)	minimum ACD (mm)	mean ACD (mm)
Aerts et al.	2015	2	-	3.6±0.34
Asano-Kato et al.	2005	2	3.0 epi	-
Benedetti et al.	2005	2	3.0 (n.r. epi or endo)	-
Benedetti et al.	2007	2	3.0 (n.r. epi or endo)	-
		3	3.0 (n.r. epi or endo)	-
		4	3.0 (n.r. epi or endo)	-
		5	3.0 (n.r. epi or endo)	-
Bohac et al.	2016	3	2.8 endo	3.35±0.36
Bouheraoua et al.	2015	2	3.0 epi	3.44±0.41
		3	3.0 epi	3.44±0.41
		4	3.0 epi	3.44±0.41
		5	3.0 epi	3.44±0.41
Budo et al.	2000	2	3.0 (n.r. epi or endo)	3.38±0.71
		3	3.0 (n.r. epi or endo)	3.38±0.71
Chebli et al.	2018	2	3.0 endo	3.42±0.26
		5	3.0 endo	3.42±0.26
		7	3.0 endo	3.42±0.26
		10	3.0 endo	3.42±0.26

Eyes (count)	EC change from	Notes
62 (out of 62)	6 months	
84	baseline	
84	baseline	
84	baseline	
84	baseline	

pre-op ECC (cells/mm^2)	post-op ECC (cells/mm^2)	Notes
-	-	
2831±304	2750±284	
2658±360	2514±305	
2616±347	2493±277	
2616±347	2441±349	
2616±347	2398±347	
2616±347	2379±344	
2613 ±185	around 2400*	* data from graph, number is estimated
2629±366	2341±314	
2629±366	2324±366	
2629±366	2263±354	
2629±366	2250±454	
2876±410	2626±424	
2876±410	2607±442	
2770±265	-	
2770±265	-	
2770±265	-	
2770±265	-	

Endothelial cell change in myopic eyes - Part 2 (Continued)

Study	Publication	FU time (year)	minimum ACD (mm)	mean ACD (mm)
Choi et al.	2014	2	3.0 endo	3.76±0.22
		3	3.0 endo	3.76±0.22
		4	3.0 endo	3.76±0.22
		5	3.0 endo	3.76±0.22
		6	3.0 endo	3.76±0.22
		7	3.0 endo	3.76±0.22
		8	3.0 endo	3.76±0.22
		9	3.0 endo	3.76±0.22
		10	3.0 endo	3.76±0.22
Guell et al. - group 1	2008	2	3.2 epi	-
		3	3.2 epi	-
		4	3.2 epi	-
		5	3.2 epi	-
Guell et al. - group 2	2008	2	3.2 epi	-
		3	3.2 epi	-
		4	3.2 epi	-
		5	3.2 epi	-
Jonker et al.	2017	5	2.8 endo	3.86±0.34
		10	2.8 endo	3.86±0.34
		5	2.8 endo	3.86±0.34
		10	2.8 endo	3.86±0.34
Landesz et al.	2000	2	-	3.7
Landesz et al.	2001	2	3.2 (n.r. epi or endo)	2.9-4.5 range
Menezo et al.	2004	2	3.2 (n.r. epi or endo)	3.41±0.12
		5	3.2 (n.r. epi or endo)	3.41±0.12
Moshifar et al.	2014		-	-
Moshirfar et al.	2007	2	3.2 (n.r. epi or endo)	-
Na et al.	2013	2	3.0 (n.r. epi or endo)	-
Pop et al.	2004	2	-	-

	pre-op ECC (cells/mm^2)	post-op ECC (cells/mm^2)	Notes
	2853±249	2815±252	
	2853±249	2792±292	
	2853±249	2755±366	
	2853±249	2767±257	
	2853±249	2758±311	
	2853±249	2698±300	
	2853±249	2713±355	
	2853±249	2642±434	
	2853±249	2211±146	
	2836±398	2548±398	
	2836±398	2625±447	
	2836±398	2791±246	
	2836±398	2514±529	
	2755±362	2614±469	
	2755±362	2519±372	
	2755±362	2698±576	
	2755±362	2454±588	
	2670±359	2588±425	
	2670±359	2302±451	
	2670±359	2588±425	
	2670±359	2302±451	
	-	-	
	2857	3049	1 patient (2 eyes) with ACD of 2.9 & 3.1mm was implanted with IF-pIOL
	-	-	also older Worst-Fechner IOL was used, but no significant difference in ECC loss between old and new pIOL group
	-	-	also older Worst-Fechner IOL was used, but no significant difference in ECC loss between old and new pIOL group
	-	-	-
	2713±361	2534±394	* ECC loss adjusted for 0,5% physiological EC loss per year
	2984±357	2847±445	* ECC loss adjusted for 0,6% physiological EC loss per year
	2631±422	2577±495	

Endothelial cell change in myopic eyes - Part 2 (Continued)

Study	Publication	FU time (year)	minimum ACD (mm)	mean ACD (mm)
Qasem et al.	2010	2	3.2 (n.r. epi or endo)	-
		3	3.2 (n.r. epi or endo)	-
		4	3.2 (n.r. epi or endo)	-
		5	3.2 (n.r. epi or endo)	-
Saxena et al.	2008	2	2.6 epi	3.70±0.30 (min. 2.89)
		3	2.6 epi	3.70±0.30 (min. 2.89)
		4	2.6 epi	3.70±0.30 (min. 2.89)
		5	2.6 epi	3.70±0.30 (min. 2.89)
		6	2.6 epi	3.70±0.30 (min. 2.89)
		7	2.6 epi	3.70±0.30 (min. 2.89)
Senthil et al.	2006	2	2.9 (n.r. epi of endo)	3.24±0.24
Shajari et al.	2016	4	2.6 (n.r. epi or endo)	3.11±0.40
		2	2.6 (n.r. epi or endo)	3.11±0.40
		3	2.6 (n.r. epi or endo)	3.11±0.40
Silva et al.	2008	3	3.2 (n.r. epi or endo)	3.87±0.34
		5	3.2 (n.r. epi or endo)	3.87±0.34
Stulting et al.	2008	3	3.2 (n.r. epi or endo)	-
		2	3.2 (n.r. epi or endo)	-
		3	3.2 (n.r. epi or endo)	-
Tahzib et al.	2007	6	3.0 (n.r. epi or endo)	3.30±0.28
		10	3.0 (n.r. epi or endo)	3.30±0.28
Titiyal et al.	2012	2	2.8 (n.r. epi or endo)	3.39±0.25
		3	2.8 (n.r. epi or endo)	3.39±0.25
		4	2.8 (n.r. epi or endo)	3.39±0.25
		5	2.8 (n.r. epi or endo)	3.39±0.25
Yasa et al.	2016	2	3.0 endo	3.4±0.2
Yuan et al.	2011	2	3.2 (n.r. epi or endo)	3.4
		3	3.2 (n.r. epi or endo)	3.4
		4	3.2 (n.r. epi or endo)	3.4
		5	3.2 (n.r. epi or endo)	3.4

-= no data available or not specified; FU-time=follow-up time; EC=endothelial cell; ECC=endothelial cell count; pIOL=phakic intraocular lens; pre-op= preoperative; post-op=postoperative;

pre-op ECC (cells/mm^2)	post-op ECC (cells/mm^2)	Notes
3171±456	-	
3171±456	-	
3171±456	-	
3171±456	-	
2817±356	2777±376	data including 57 myopic toric and 17 myopic Artiflex lenses
2817±356	2729±342	data including 57 myopic toric and 17 myopic Artiflex lenses
2817±356	2616±307	data including 57 myopic toric and 17 myopic Artiflex lenses
2817±356	2581±293	data including 57 myopic toric and 17 myopic Artiflex lenses
2817±356	2560±270	data including 57 myopic toric and 17 myopic Artiflex lenses
2817±356	2451±256	data including 57 myopic toric and 17 myopic Artiflex lenses
2741±313	2566±315	
2805±95	2497±329	
2805±95	2632	
2805±95	2559	
2481±291	2256±370	
2481±291	2156±495	
-	-	
-	-	
-	-	
2817±359	2734±360	
2817±359	2800±292	
2858±313	2587±298	constant cohort of 51 eyes
2858±313	2536±281	constant cohort of 51 eyes
2858±313	2499±354	constant cohort of 51 eyes
2923±237	2462±258	cohort of 28 eyes
2723±311	2612±264	
-	-	
-	-	
-	-	
-	-	

n.r.= not reported; epi=from corneal epithelium; endo=from corneal endothelium; ACD=anterior chamber depth

Endothelial cell change in hyperopic eyes - Part 1

Study	Publication	FU time (year)	EC loss (%)	Adjusted EC loss (%)
Guell et al.	2008	2	5.4%	-
		3	8.4%	-
		4	6.4%	-
		5	-	-
Saxena et al.	2003	2	8.5%	-
		3	11.7%	10.1%

-= no data available; FU time=follow-up time; EC=endothelial cell; No.=number

Endothelial cell change in hyperopic eyes - Part 2

Study	Publication	FU time (year)	minimum ACD (mm)	mean ACD (mm)
Guell et al.	2008	2	3.2 endo	-
		3	3.2 endo	-
		4	3.2 endo	-
		5	3.2 endo	-
Saxena et al.	2003	2	2.6 (n.r. epi or endo)	3.25±0.25 (min 2.87)
		3	2.6 (n.r. epi or endo)	3.25±0.25 (min 2.87)

FU-time=follow-up time; ECC=endothelial cell count; pre-op= preoperative; post-op=postoperative; n.r.= not reported; epi=from corneal epithelium; endo=from corneal endothelium; ACD=anterior chamber depth

Eyes (count)	EC loss from	Notes
35 (out of 40)	baseline	
34 (out of 39)	baseline	
34 (out of 39)	baseline	
28 (out of 33)	baseline	
15 (out of 26)	baseline	
10 (out of 26)	baseline	EC loss adjusted for 0,6% physiological cell loss per year

pre-op ECC (cells/mm^2)	post-op ECC (cells/mm^2)	Notes
2735±355	2587±551	
2735±356	2505±508	
2735±357	2560±335	
2735±358	-	
2749±348	2611±472	minimum required ACD was later changed to 3,0mm
2749±348	2471±372	

APPENDIX 5

Secondary surgical interventions in myopic eyes implanted with an IF-pIOL

Study	Publication	Total eyes (count)	Eyes treated (count)	Treated (%)
Asano-Kato et al.	2005	44	0	0
Baikoff et al.	2005	137	1	0.7
Benedetti et al.	2007	49	0	0
Benedetti et al.	2005	93	0	0
Bohac et al.	2016	198	1	0.5
Bouheraoua et al.	2015	68	2	2.9
Budo et al.	2000	249	22	8.8
Chebli et al.	2018	113	1	0.9
Guell et al.	2008	274	9	4.5
Landesz et al.	2000	67	1	0.9
Landesz et al.	2001	78	6	0.9
Menezo et al.	2004	137	2	1.5
Moshifar et al.	2014	213	7	3.3
Moshirfar et al.	2007	85	5	5.9
Qasem et al.	2010	151	10	6.6
Senthil et al.	2006	60	3	5
Shajari et al.	2016	95	1	1.1
Silva et al.	2008	26	2	7.7

	Reasons
	-
	1 eye (0.7%) pIOL exchange due to pigment dispersion, note study only reporting on pigment dispersion
	-
	-
	4 eyes (2%) re-enclavation due to inadequate enclavation; 1 eye (0.5%) repositioning due to decentration after trauma (after 27 months)
	1 eye (1.4%) pIOL repositioning after 3 years; 1 eye (=1.4%) pIOL exchange due to refractive error
	6 eyes (2.4%) repositioning of pIOL; 7 eyes (2.8%) explantation pIOL (1 wide pupil diameter, 1 EC-loss, 2 trauma, 3 cataract); 8 eyes (=3.2%) IOL exchanges for different power; 1 eye (0.4%) ACRS
	1 eye (0.81%) pIOL explantation due to EC loss (after 7 years)
	3 eyes (0.75%) pIOL explanted due to ECC loss; 2 eyes (0.5%) explanation pIOL due to nuclear cataract; 1 eye (0.25%) macular hemorrhage (after 4 months), 1 eye (0.25%) retinal detachment (after 3 years), 3 eyes (0.75%) pIOL re-enclavation (2 trauma; 1 spontaneously) (not specified which group)
	1 eye repositioning due to decentration
	2 eyes (2.6%) pIOL exchange due to undercorrection, 2 eyes (2.6%) pIOL explantation due to cataract, 2 eyes (2.6%) pIOL exchange due to glare/halo
	2 eyes (1.46%) pIOL explantation due to nuclear cataract (54.83±22.12 months, at patient age 53 and 56 years)
	5 eyes (2.3%) pIOL explantation due to cataract (after mean of 9.3 years (R 4.0-12.6) at mean age of 55 years (R 46-62); 2 eyes (0.9%) corneal decompensation
	3 eyes (3.5%) re-enclavation (2 after trauma, 1 surgeon error); 1 eye (1.2%) pIOL removal after IOP spikes and cataract development; 1 eye (1.2%) pIOL exchange due to undercorrection
	8 eyes (5.3%) pIOL re-enclavation (4 eyes (2.6%) after trauma in, 4 eyes (2.6%) inadequate enclavation); 2 eyes (1,3%) retinal detachment (after 2 years); 27 eyes (17.9%) ACRS
	1 eye (1.6%) pIOL explantation and trabeculectomy due to medically uncontrolled glaucoma; 1 eye (1.6%) pIOL repositioning after trauma ; 1 eye (1.6%) pIOL explantation after trauma; note 0% retinal detachment but 100% prophylactic panretinal laser photocoagulation
	1 eye (1.1%) pIOL re-enclavation
	1 eye (3.88%) pIOL explantation due to cataract; 1 eye (3.8%) pIOL was explanted due to glare/halo's

Secondary surgical interventions in myopic eyes implanted with an IF-pIOL (Continued)

Study	Publication	Total eyes (count)	Eyes treated (count)	Treated (%)
Stulting et al.	2008	1179	41	3.5
Tahzib et al.	2007	89	3	3.4
Titiyal, et al.	2012	85	23	27.1
Yasa et al.	2014	62	0	0
Yuan et al.	2011	84	0	0

-= no data available; (IF)-pIOL=(iris-fixated) phakic intraocular lens; EC=endothelial cell; ACRS=additional corneal refractive surgery; FU=follow-up; No.=number

Secondary surgical interventions in hyperopic eyes implanted with an IF-pIOL

Study	Publication	Total eyes (count)	Eyes treated (count)	Treated (%)
Baikoff et al.	2005	136	3	2.2
Qasem et al.	2010	14	4	28.6
Guell et al.	2008	41	19	46
Saxena et al.	2003	26	2	7.7

(IF)-pIOL=(iris-fixated) phakic intraocular lens; ACRS=additional corneal refractive surgery;

	Reasons
	13 eyes (1.1%) pIOL explantation (3 eyes (0.25%) nuclear cataract; 4 eyes (0.3%) trauma; 1 eye (0.08%) pupil>optic; 3 eyes (0.25%) inflammatory response; 2 eyes (0.17%) patient request); 12 eyes (1.0%) pIOL exchange (8 eyes (0.7%) power calculation error, 2 eyes (0.2%) pupil>optic; 2 eyes (0.2%) inadequate surgical fixation); 10 eyes (0.8%) pIOL re-enclavation (5 eyes (0.4%) trauma, 5 eyes (0.4%) inadequate surgical fixation); 6 eyes retinal repairs (0.51%) (4 eyes (0.3%) retinal detachment, 2 eyes (0.2%) macular hole)
	1 eye (1.1%) ACRS; 2 eyes (2.2%) pIOL explantation cataract (at 6 years FU)
	20 eyes (23.5%) pIOL repositioning (12 eyes (14%) (risk of) disenclavation; 8 eyes (9.4%) after trauma); 1 eye (1.2%) EC-loss; 2 eyes (2.4%) retinal pathology (1 eye (1.2%) retinal detachment (after 3 months); 1 eye (1.2%) retinal tear (at 3 years FU))
	-
	-

	Reasons
	3 eyes (2.2%) explanted due to severe pigment dispersion
	4 eyes (28.6%) ACRS
	2 eyes (4.9%) pIOL exchange due to residual refractive error; 17 (41.4%) eyes ACRS
	2 eyes (7.7%) pIOL explantation due to posterior synechiae and pigment cell deposits; 2 eyes posteroir synnechiae and pigment cell without consequences (convex iris configuration)

APPENDIX 6

Details of eyes which developed posterior synechiae

Patient	Eye	ACD pre-op	Iris configuration	Details
1	OD	3.25 mm	Unknown	Synechiae formation and pigment deposition from 14th year after implantation, ACD 2.92 mm
2	OS	2.97 mm	Unknown	Slowly progressive synechiae formation from 2nd year after implantation. At 10th year after implantation ACD 2.69 mm
3	OS	2.70 mm	Unknown	After 1.5 months pIOL explantation due to continuing inflammation, pigment loss with synechiae formation
4	OD	3.06 mm	Unknown	At 9th year after implantations pigment depositions, in 12th year after implantation synechiae formation ACD 2.69 mm
4	OS	2.98 mm	Unknown	At 12th year after implantation synechiae formation ACD 2.69 mm
5	OD	3.00 mm	Convex	From 2 months synechiae posterior formation, IF-pIOL explantation after 2 years
5	OS	3.00 mm	Convex	Uncontrollable inflammation and pigment deposits, IF-pIOL cleaning after 2 months, IF-pIOL explantation after 6 months
6	OS	3.05 mm	Unknown	At 10th year after implantation synechiae formation posterior ACD 2.78 mm
7	OD	3.35 mm	Unknown	At 12th year after implantation synechiae formation, ACD 3.11 mm
8	OD	3.30 mm	Convex	At 13th year after implantation synechiae formation, ACD 3.27 mm
8	OS	3.30 mm	Convex	At 4th year of implantation pigment deposits. At 13th year after implantation formation of synechiae posterior, ACD 3.27 mm

ACD=anterior chamber depth including corneal pachymetry (measured from epithelium); pre-op=preoperative; mm=millimeters

APPENDIX 7

Crosstabs synechiae formation in an anterior chamber depth above or below 3.0mm measured from the epithelium (A.) and measured from the endothelium (B.)

A.

ACD from epithelium above or below 3.0mm * synnechiae formation yes / no Crosstabulation

			synnechiae formation		Total
			No	Yes	
ACD from epithelium	ACD epithelium <3.00mm	Count	7	5	12
		% within ACD from epithelium	58.3%	41.7%	100.0%
	ACD epithelium >3.00mm	Count	43	6	49
		% within ACD from epithelium	87.8%	12.2%	100.0%
Total		Count	50	11	61
		% within ACD from epithelium	82.0%	18.0%	100.0%

ACD= anterior chamber depth; mm=millimeters

B.

ACD from endothelium above or below 3.0mm * synnechiae formation yes / no Crosstabulation

			Synnechiae formation		Total
			No	Yes	
ACD from endothelium	ACD endothelium <3.00mm	Count	40	11	51
		% within ACD from endothelium	78.4%	21.6%	100.0%
	ACD endothelium >3.00mm	Count	10	0	10
		% within ACD from endothelium	100.0%	0,0%	100.0%
Total		Count	50	11	61
		% within from ACD endothelium	82.0%	18.0%	100.0%

ACD= anterior chamber depth; mm=millimeters

A. In the group with an ACD >3.0 mm measured from the epithelium there is 12.2% synechiae formation (Fisher exact p=0.031)
B. In the group with an ACD >3.0 mm measured from the endothelium there is 0% synechiae formation (Fisher exact p=0.184)

APPENDIX 8

Cross-tabulation: Endothelial cell density below 1500 cells/mm² at final follow-up visit * Implantation date up to 2001

			Implantation date up to 2001		Total
			no	yes	
ECD <1500 cells/mm² at last follow-up	no	Count	89	154	243
		% within ECD <1500 cells/mm²	36.6%	63.4%	100.0%
		% within implantation up to 2001	94.7%	86.0%	89.0%
		% of total	32.6%	56.4%	89.0%
	yes	Count	5	25	30
		% within ECD <1500 cells/mm²	16.7%	83.3%	100.0%
		% within implantation up to 2001	5.3%	14.0%	11.0%
		% of total	1.8%	9.2%	11.0%
Total		Count	94	179	273
		% within ECD <1500 cells/mm²	34.4%	65.6%	100.0%
		% within implantation up to 2001	100.0%	100.0%	100.0%
		% of total	34.4%	65.6%	100.0%

In the group with an EC density <1500 cells/mm², 83.3% of the eyes were implanted up to the year 2001 (Continuity Correction p=0.049)

APPENDIX 9

Protocol for iris-fixated phakic IOL implantation:
Before surgery, the desired axis location is marked on the cornea with a corneal marker if a toric IOL is to be placed. Miotic drops (pilocarpine 2%) are administered preoperatively to prepare the iris for IOL fixation. A limbal beveled incision of 5.5 mm is made at 12 o'clock, and 2 paracenteses are made at 10 o'clock and 2 o'clock. The anterior chamber is opened and sodium hyaluronate 1.0% (Healon) introduced to maintain depth and to protect the endothelium. After implantation and correct positioning at the desired axis, the IOL is fixated to the midperipheral iris stroma with an enclavation needle. At the end of the procedure, a slit iridotomy is performed at 12 o'clock to prevent angle-closure glaucoma and the sodium hyaluronate 1.0% is manually removed by irrigation. The incision is closed with a 10-0 nylon running suture.

APPENDIX 10

The noncontact specular microscope SP- 2000P and SP-3000P (Topcon Corp.) was used to obtain multiple images of the endothelial cell layer of the central region of the cornea using automatic focusing and digital image capture. The raw endothelial cell images were imported into Konan KSS-300 software (Version 2.20) (Konan Medical) for recalibration and manual recount purposes. Prior to the procedure, the distance of the embedded tick marks on the image and the image magnification were checked. These were identical in both devices according to the manufacturer. The quality of the imported endothelial cell images was classified as good, fair, poor, or impossible. Two independent researchers manually counted all visible and countable endothelial cells in the image using the center-to-center method; the mean endothelial cell density was reported.

APPENDIX 11

To manually change the magnification (also referred to as “pixel size”) it is important to first verify IMAGEnet is closed.

After this has been verified, one has to create an additional entry into the Windows Registry (which can be started from the command prompt by typing “regedit”):

HKEY_CURRENT_USER/SOFTWARE/TOPCON/IMAGEnet ibase/System
ChangePixelSize REG_BINARY **01**
Here-after open IMAGEnet software, and enable the option to edit the properties of the loaded images. Then close the program.

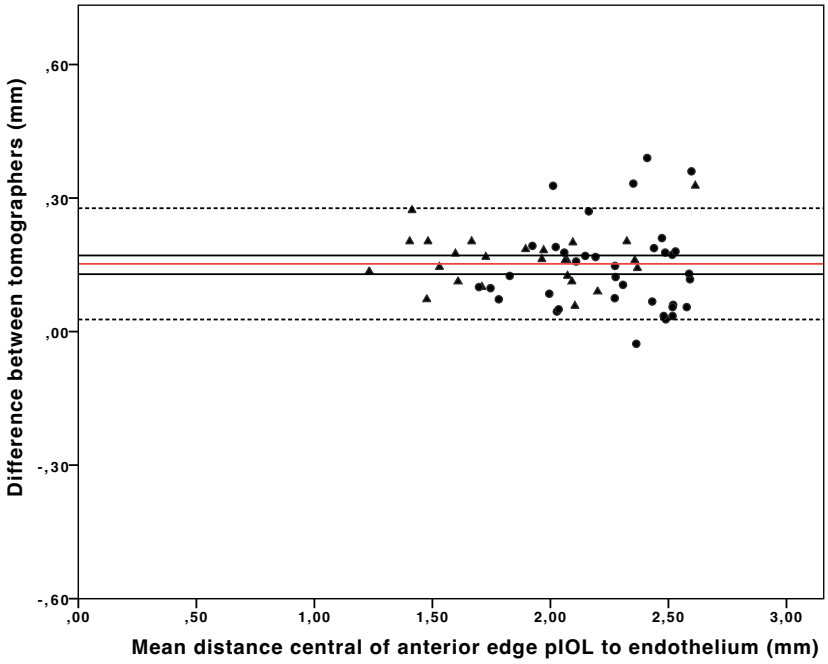
When an image is subsequently loaded in the IMAGEnet software, the pixel size can be altered by right-clicking on the image and selecting “show properties” (as is shown in Figure 1 of the manuscript).

Caution should be taken when manually changing pixel size; It is recommended to back-up your database before adjusting the magnification, since altered images are saved within the same database and erroneous modifications of registry entries might corrupt the database. We strongly advise to consult Topcon prior to changing magnification values, especially since this procedure might change depending on software version (the described method has been tested in version 3.10.5).

APPENDIX 12

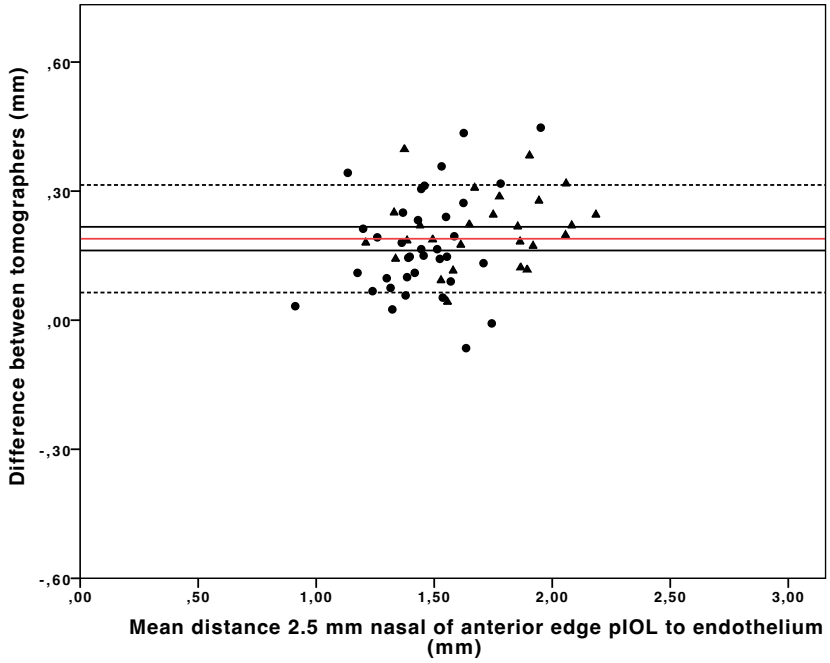
Supplementary Figure 1. Bland-Altman plots showing the difference in distance measurements between the anterior segment optical coherence tomography and Scheimpflug imaging modalities for (A.) central, (B.) 2.0 mm nasal, (C.) 2.0 mm temporal, (D.) 4.0 mm nasal, and (E.) 4.0 mm temporal of the anterior edge of the pIOL to the endothelium. The red line represents the mean, the black lines the upper and lower 95% confidence interval, the dashed lines the upper and lower 95% limits of agreement (LoA). *Triangles*: hyperopic eyes; *dots*: myopic eyes.

A.

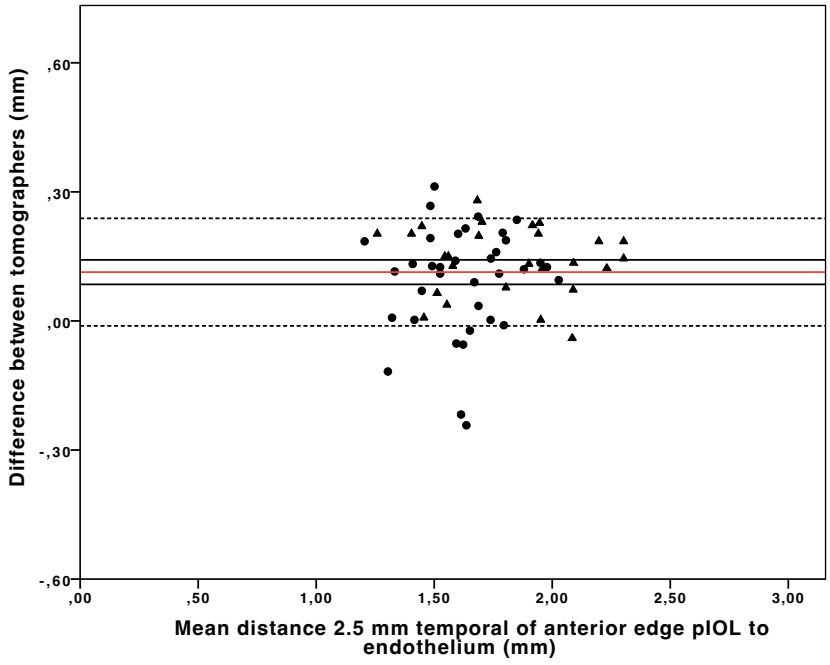


Supplementary Figure 1. Continued.

B.



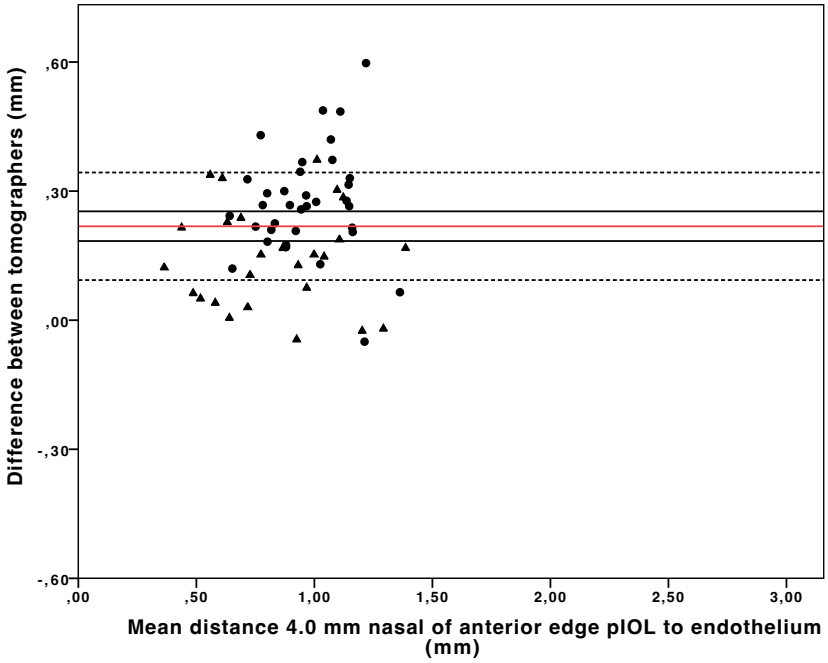
C.



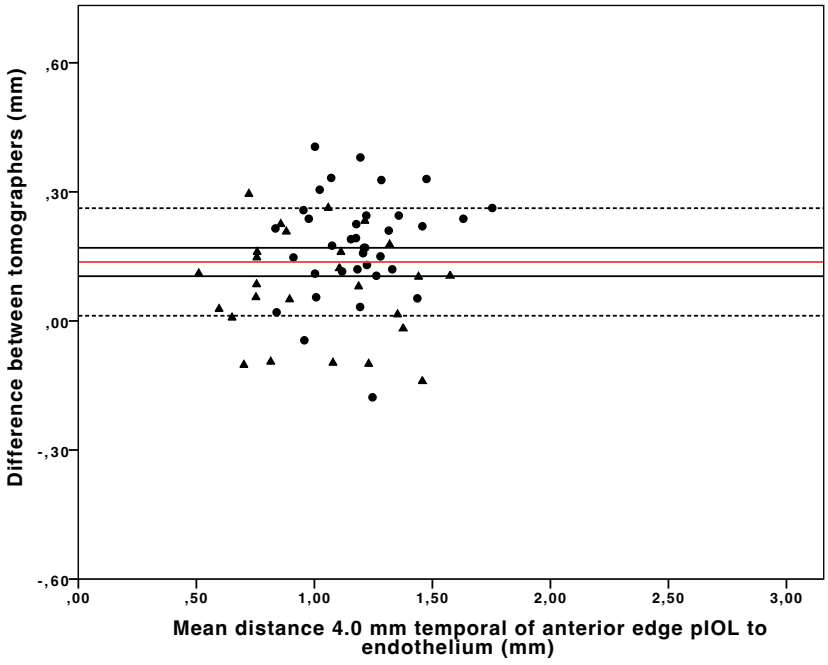
A

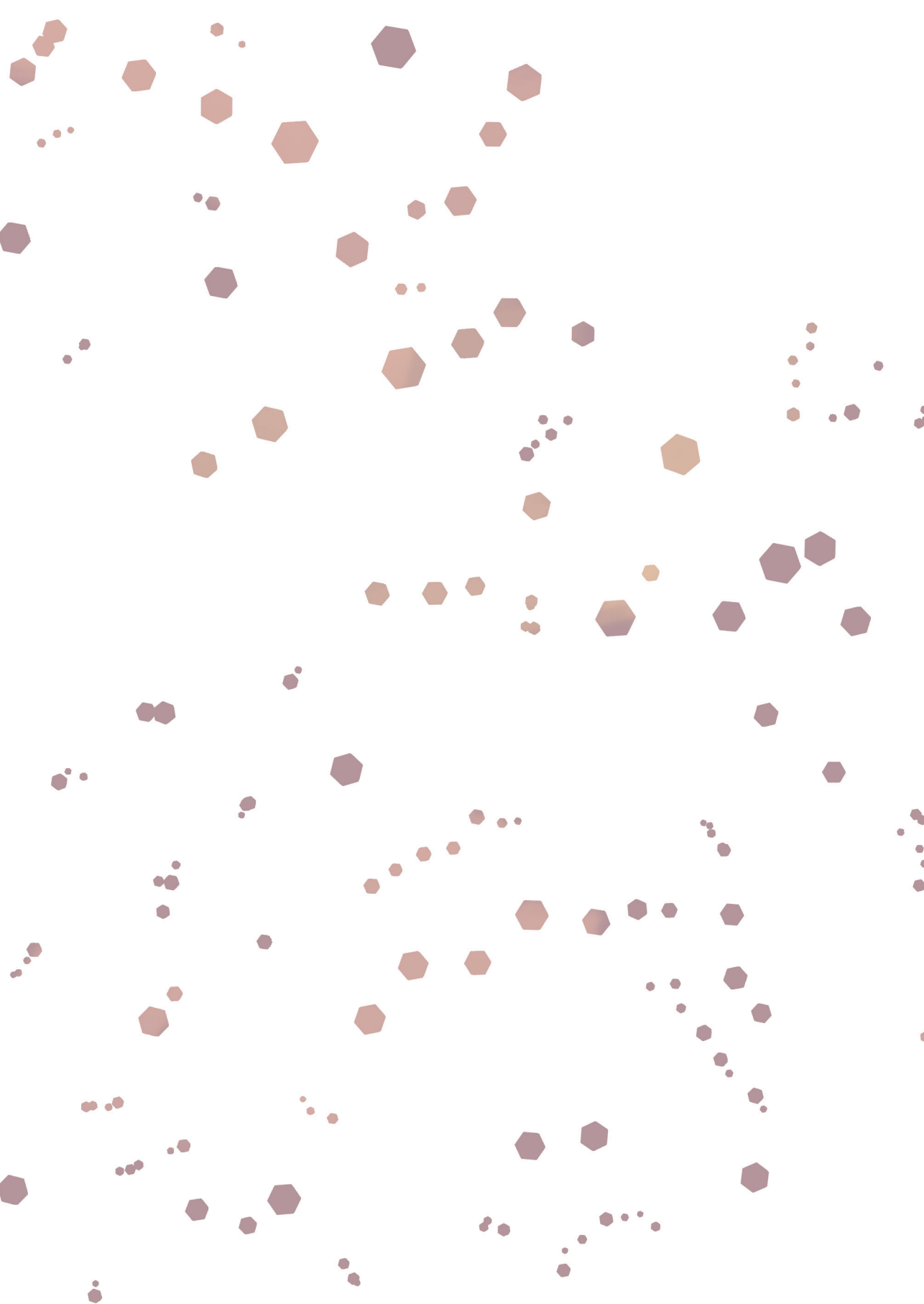
Supplementary Figure 1. Continued.

D.



E.





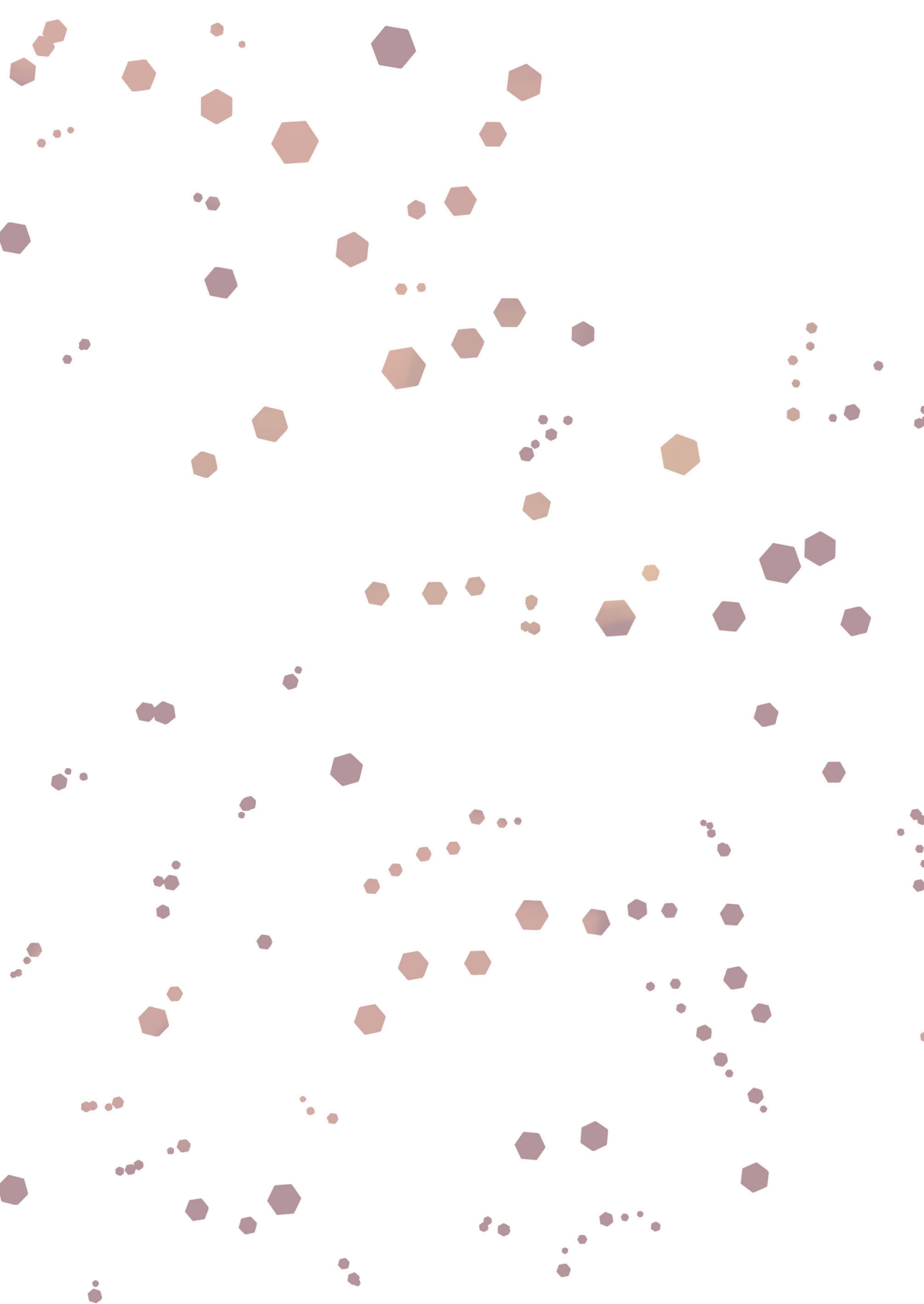
Addendum

Curriculum Vitae

CURRICULUM VITAE

Gwyneth Annemarie van Rijn is geboren op 17 oktober 1983 in Harlow, Engeland. In 2001 behaalde zij op het Northgo college te Noordwijk haar middelbareschooldiploma. Ze werd tot tweemaal uitgeloot voor de studie geneeskunde. In deze 'tussenjaren' behaalde ze haar propedeuse gezondheidswetenschappen aan de Universiteit van Maastricht en is ze voor een jaar afgereisd naar de Filippijnen om de taal en cultuur van haar moeder te leren kennen. In 2003 werd ze decentraal toegelaten voor de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Begin 2011 nam ze cum laude haar artsendiploma in ontvangst. Hierna is Gwyneth in het Leids Universitair Medisch Centrum een promotietraject gestart naar de lange termijn resultaten na implantatie van een fake intra-oculaire lens bij hoge refractieafwijkingen onder begeleiding van prof. dr. G.P.M. Luyten als promotor en dr. J.W.M. Beenakker als copromotor. De resultaten van het onderzoek zijn onder andere in dit proefschrift opgeschreven. Tijdens haar opleiding tot oogarts in het Leids Universitair Medisch Centrum, welke Gwyneth in 2020 afrondde, heeft ze het wetenschappelijk onderzoek naar de lange termijn resultaten van een iris-gefixeerde intra-oculaire lens voortgezet en is ze moeder geworden van twee prachtige kinderen, zoon Jukai en dochter Zehli.

Na haar opleiding tot oogarts heeft ze een fellowship medische en chirurgische cornea in het Oogziekenhuis Rotterdam gedaan. Zij is sinds 2021 werkzaam als oogarts met als subspecialisatie cornea in het Amsterdam Universitair Medisch Centrum te Amsterdam en in het Noordwest Ziekenhuis te Alkmaar.



Addendum

List of Publications

LIST OF PUBLICATIONS

van Rijn GA, Mourik JE, Teeuwisse WM, Luyten GP, Webb AG. Magnetic resonance compatibility of intraocular lenses measured at 7 Tesla. Invest Ophthalmol Vis Sci. 2012 Jun 8;53(7):3449-53. doi: 10.1167/iovs.12-9610. PMID: 22538424.

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Gaurisankar ZS, **van Rijn GA**, Lima JEE, Ilgenfritz AP, Cheng Y, Haasnoot GW, Luyten GPM, Beenakker JM. Correlations between ocular biometrics and refractive error: A systematic review and meta-analysis. Acta Ophthalmol. 2019 Dec;97(8):735-743. doi: 10.1111/aos.14208. Epub 2019 Aug 6. PMID: 31386806.

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van Rijn GA, Gaurisankar ZS, Ilgenfritz AP, Lima JEE, Haasnoot GW, Beenakker JM, Cheng YYY, Luyten GPM. Middle- and long-term results after iris-fixated phakic intraocular lens implantation in myopic and hyperopic patients: a meta-analysis. J Cataract Refract Surg. 2020 Jan;46(1):125-137. doi: 10.1097/j.jcrs.0000000000000002. PMID: 32050242.

van Rijn GA, Gaurisankar ZS, Luyten GPM, Beenakker JM. Differences between Scheimpflug and optical coherence tomography in determining safety distances in eyes with an iris-fixating phakic intraocular lens. Graefes Arch Clin Exp Ophthalmol. 2021 Jan;259(1):231-238. doi: 10.1007/s00417-020-04874-7. Epub 2020 Aug 6. PMID: 32766949; PMCID: PMC7790774. Shared first authorship with Gaurisankar ZS.

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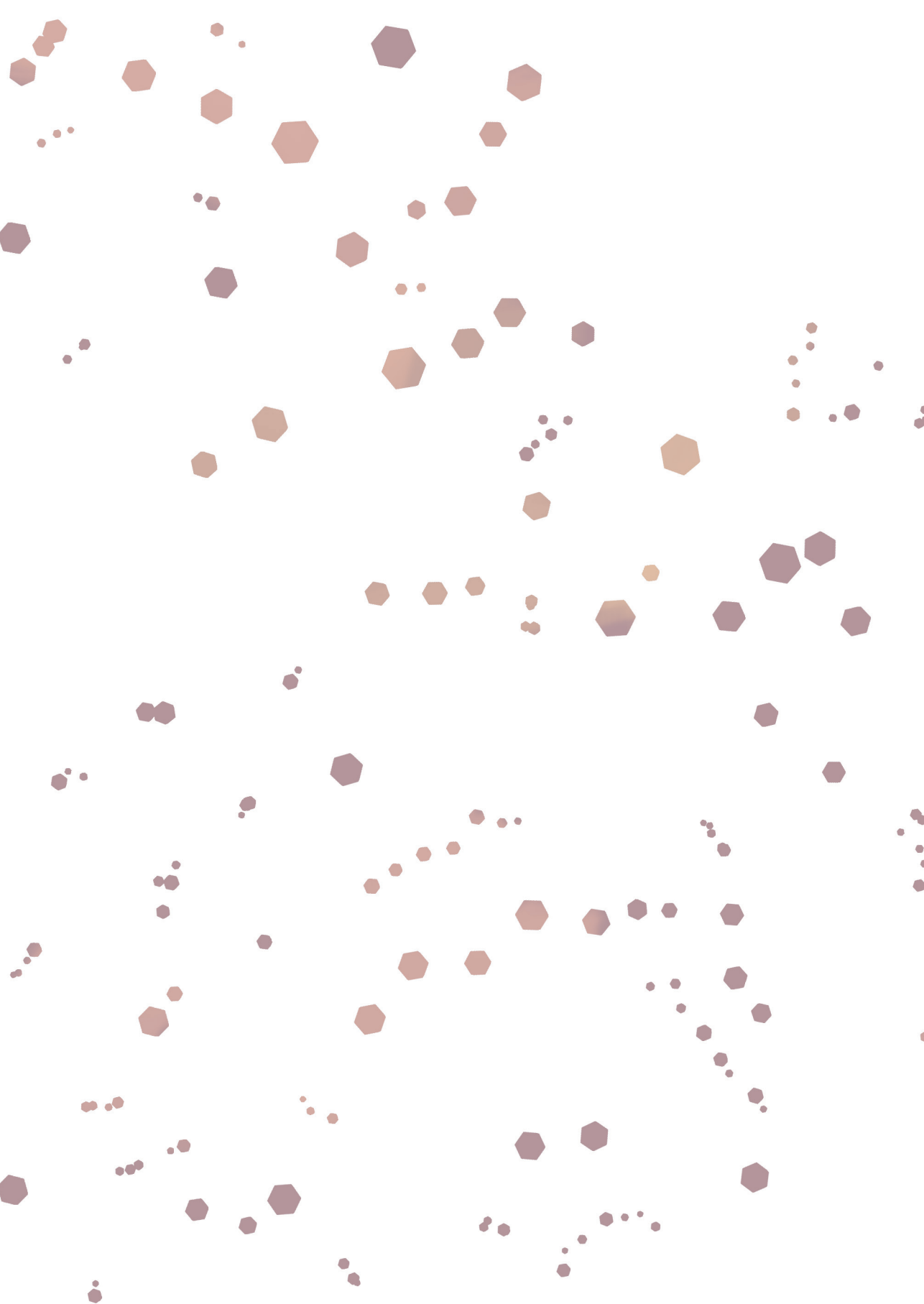

Addendum

Dankwoord

DANKWOORD

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