# **Phakic intraocular lens implantation:** A life-long patient journey

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**‘The real voyage of discovery consists not in seeking new landscapes, but in having new eyes’**

*Marcel Proust, French novelist, La Prisonnière (1923)*

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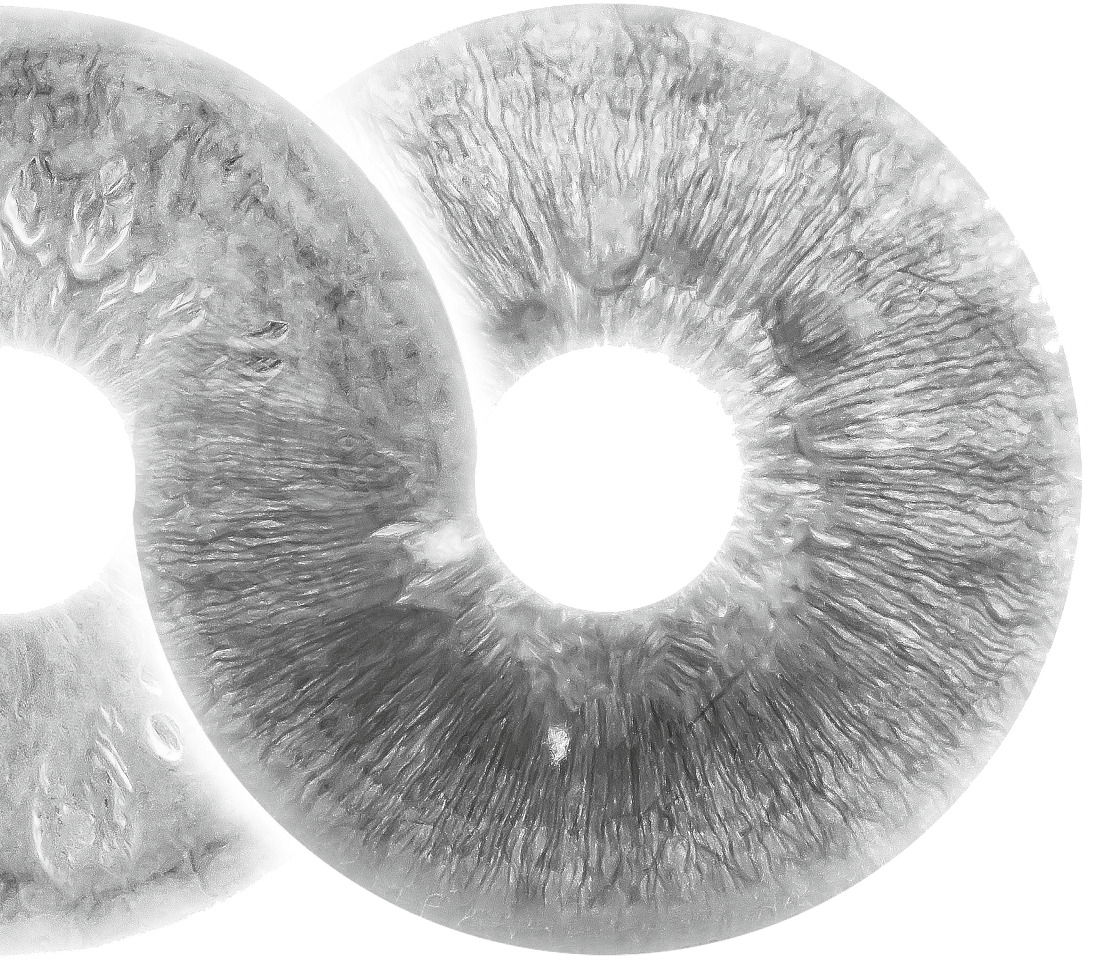


# CHAPTER 1.

## General introduction

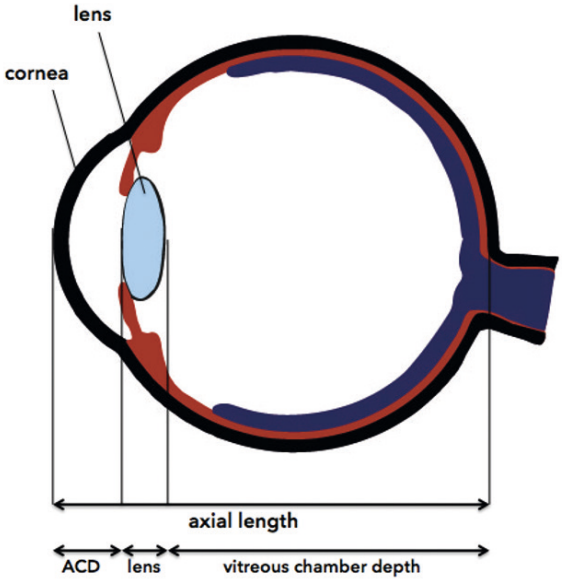
## 1.1 Refractive error

Emmetropia refers to an eye without any refractive error or optical defocus. In contrast, refractive errors result when images formed by the eye's optical system are not accurately projected on the retina, creating a blurred image that is transmitted to the brain. Refractive errors can broadly be classified in three categories: 1. Myopia, also known as near-sightedness, in which parallel rays of light entering the eye from an optically infinite distance meet at a focal point in front of the retina; 2. Hyperopia, also known as farsightedness, in which this focal point lies behind the retina; 3. Corneal astigmatism, in which a regular oval-shaped cornea distorts the image projected on the retina. Uncorrected refractive errors are the first cause of visual impairment and the second cause of visual loss worldwide, with 43% of visual impairments being attributed to refractive errors[1] with variations in prevalence due to ethnical differences[2,3] and among age groups[4,5]. Increasing prevalence world-wide resulted in the global initiative to eliminate avoidable blindness due to uncorrected refractive errors as one of its five priority eye diseases[6]. In Europe, it is estimated that over half of all young adults are affected by a refractive error, the largest contribution being myopia[4].

## 1.2 Biometry and the aetiology of refractive errors

Optical biometry is the measurement of the various dimensions of the eye and of its components and their interrelationships. The many subtleties of these optical properties of the eye, determining the refractive status, are highly complex. To understand the basic principle of the existence of refractive errors, optical biometrics can be broken down into several components, including the anterior corneal curvature, lens power, and the ocular axial length (**Figure 1**). The latter is a combination of anterior chamber depth (ACD), lens thickness and vitreous chamber depth. Most of the eye's optical power is provided by the air-tear film interface at the corneal plane. Overall corneal power accounts for approximately two thirds of the eye's refractive power: +40.00 to +45.00 diopters in the average eye. In the non-accommodative state, the lens contributes about 15.00 to 20.00 diopters. Refractive errors result when there is a mismatch between the optical power and the ocular axial length. **Chapter 2** provides a systematic review, explaining if and how the different optical system components that determine refractive error are correlated according to current literature. We investigated correlations between the parameters refractive error, the axial length, the anterior chamber depth, keratometry and corneal thickness.

**Figure 1.**
The major biometric determinants of refractive error (ACD: anterior chamber depth)




During early childhood, eye growth is regulated toward emmetropia, a process called emmetropization[7-9], resulting in changes in all the major determinants of refractive power, including corneal curvature[10], axial length[11], and lens power[12]. Emmetropization is generally complete by the age of 6. Therefore, the presence of a significant refractive error at this age, most commonly hyperopia, can be attributed to a primary failure of emmetropization[13]. Myopia development after the age of 6 has been observed to be a phase of relatively stable refraction, followed by a declining refraction during late childhood and early adulthood[14,15]. The primary growth response in such myopia progression is increasing axial length[16,17], and its pathophysiology is a complex and a still not completely understood mixture of genetic and environmental factors[18,19]. Although astigmatism can also occur alone, hyperopia and myopia are often found in combination with astigmatism.

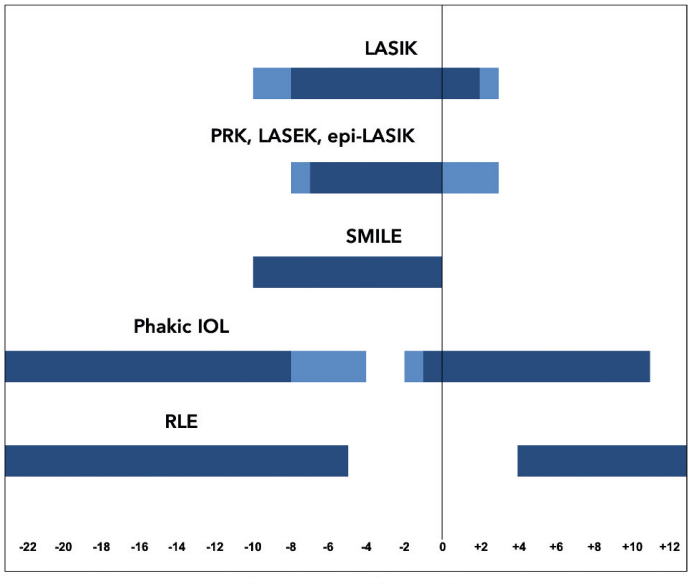
## 1.3 Treatment options

The traditional approach to correct refractive errors is by using glasses or contact lenses to move the rays of light to the correct position on the retina and restore clear vision. For many patients with a high refractive state, glasses are inconvenient to use in day-to-day activities, especially when the patient has an active lifestyle. Some patients have concerns about their aesthetic appearance. These lenses are often thick or the refractive index is high, hence

causing aesthetic disfigurement, image distortion and magnification effects. In addition, prismatic aberration can produce a roving ring scotoma, also called the jack-in-the-box phenomenon. In contrast, contact lenses provide a wider field of vision and less image magnification, which improves the quality of vision. However, contact lens intolerance and complications like giant papillary conjunctivitis, corneal abrasions and keratitis can prevent patients from benefitting from this treatment option. **Chapter 3** covers the effect of optical correction on straylight, another element contributing to the quality of vision. Straylight values were measured with the C-Quant (Oculus Optikgeräte, GmbH, Wetzlar, Germany) in near-emmetropic eyes with various negatively powered refractive lenses and in myopic eyes corrected with eye glasses and contact lenses. The effect of the different methods of refractive correction on straylight was studied.

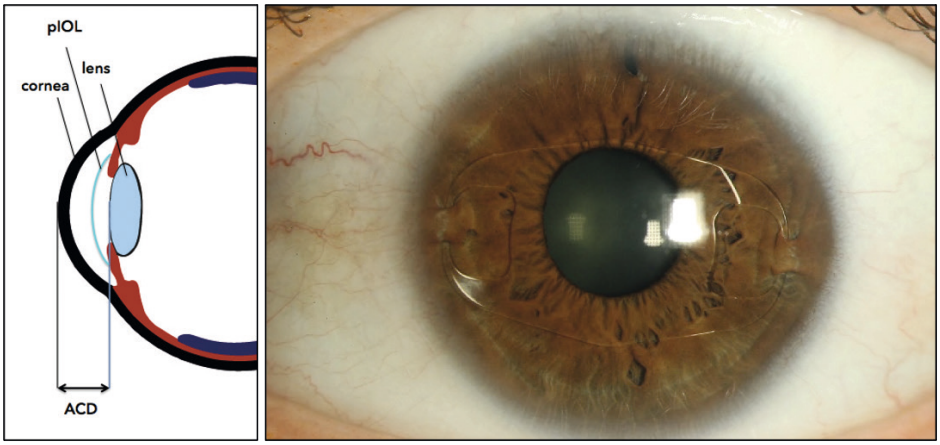
The more recent surgical treatment of refractive errors has developed into a separate field. Different surgical treatment methods cover the whole range of refractive errors (**Figure 2**). Radial keratotomy was the first refractive operation that was developed, but due to the numerous disadvantages this procedure is no longer performed in the Western world. A huge advance in the refractive surgery field was made in the 1980s with the arrival of concepts like keratomileusis, the microkeratome, and the excimer laser[20].

**Figure 2.**
Therapeutic (extended) ranges of refractive surgery



At present, there is a wide range of surgical procedures, from corneal reshaping with lasers to the insertion of artificial lenses. The various surgical procedures available are based on 1. reshaping the cornea through laser surgery, thereby correcting the eye's focusing ability; or 2. implanting a lens inside the eye. In the superficial techniques, including photorefractive keratectomy (PRK), laser-subepithelial keratomileusis (LASEK) and laser in situ keratomileusis (LASIK), corneal tissue is ablated with an excimer or femtosecond laser just below the corneal epithelium, which is the outermost of the five layers of the cornea. With more than 16 million procedures performed worldwide, LASIK is the golden standard for mild to moderate refractive errors with favourable outcomes[21]. Refractive lenticule extraction is the newest keratorefractive technique of which especially the small incision lenticule extraction (SMILE) has gained popularity over the last few years. The SMILE procedure corrects myopia up to –10.00 D with or without astigmatism of ≤ –5.00 D and involves using a femtosecond laser to delineate a refractive lenticule within the stroma by a small incision.[22,23] Although laser surgery is becoming more affordable and safer, it may not be recommendable for everybody. For candidates not suited for these methods, particularly patients with corneal pathology and high refractive errors, an intraocular lens can be implanted in the eye leaving the naturally existing crystalline lens untouched. These types of lenses are called phakic intraocular lenses. As an alternative, the crystalline lens can be replaced with an intraocular lens, which is known as refractive lens exchange. Both procedures leave the cornea untouched, but implantation with a phakic intraocular lens is particularly advantageous for retaining the ability to accommodate in (young) patients[24]. The three types of phakic intraocular lens (pIOL) are the angle-supported anterior chamber, iris-fixated anterior chamber, and posterior chamber lens. By the Dutch society of refractive surgeons, caution is advised in the use of angle-supported pIOLs due to the higher risks of increased endothelial cell loss and corneal decompensation[25]. In current practice, most commonly used are the iris-fixated anterior chamber lens and the posterior chamber lens and include the Artisan (Ophtec, Groningen, Netherlands), Artiflex (Ophtec, Groningen, Netherlands) and Visian implantable collamer lens (ICL) (Staar Surgical, Monrovia, CA, USA). The Artisan and Artiflex lens are iris-fixated because their optic is captured anterior to the iris (**Figure 3**) and the haptics fixate the lens by positioning it under the iris. The ICL is a posterior chamber phakic intraocular lens, meaning it is positioned behind the iris and in front of the natural lens. PIOL implantation is nowadays a safe alternative for treating a broad range of refractive errors. An extensive review of the 2-to-10-year results of the iris-fixated pIOL follows in **Chapter 4**.

**Figure 3.**
The iris-fixated phakic intraocular lens (pIOL)




## 1.4 Iris-fixated phakic intraocular lens implantation: from screening to follow-up

In this thesis, some clinical considerations for implanting an iris-fixated pIOL and postoperative follow-up were studied. The subsequent fictive *Case of Ms. Jansen* will introduce you to the topics of these following chapters.

**Case of Ms. Jansen**

*A 38-year-old woman (Ms. Jansen) presented to her ophthalmologist for options to correct her high myopia. She had been a satisfied contact lens wearer for 27 years, but for about 4 months, she has been experiencing contact lens intolerance, disabling her in her daily activities and discouraging her from doing any photography, which is her passion. She does not like wearing glasses and would like to be free of both contact lenses and glasses. Upon examination, her Snellen visual acuity was 0.8 in the right eye and 0.9 in the left eye, with a manifest refraction of S-10.50C-0.75x145 in the right eye and S-9.00C-0.50x164 in the left eye. Slit lamp examination showed clear corneas, normal pupil size and normal iris convexity. The intraocular pressure was 14 mm Hg in each eye. The crystalline lenses were clear. Careful examination of the retina showed no abnormalities. How would you counsel her?*

In such a case, a careful history and additional tests are crucial for the success of any type of refractive treatment. With her high ametropia and a central corneal thickness of 533 and 522 mm, laser refractive surgery is not suitable due to a high risk of keratectasia development. To

preserve her ability to accommodate, phakic intraocular lens implantation is the treatment of choice. The iris-fixated pIOL is the preferred implantable pIOL of her ophthalmologist. To determine if Ms. Jansen is an appropriate candidate for iris-fixated pIOL implantation, the following assessments should be performed in preoperative screening.

**Corneal topography**

Historically, the evolution of corneal tomography started with the introduction of Placido disk-based corneal topography in the 1980s.[26] By projecting a series of illuminated mires onto the anterior cornea, computerized analysis of the corneal surface was made possible, based on the size and distortion of the mires. The disadvantages of this Placido disk-based technique were the inadequate measurements in the case of an abnormal tear film, inaccurate measurement of the posterior surface of the cornea and lack of a pachymetry map.[27] Three-dimensional tomographic reconstruction of the cornea was the next technological advance that compensated for these drawbacks. Frequently used techniques for examining the front and back surfaces of the cornea and pachymetric mapping in refractive surgery planning include Scheimpflug imaging and optical coherence tomography, which are available in many commercial instruments. Scheimpflug imaging is based on the Scheimpflug principle by which an obliquely tilted object can be placed at maximum depth of focus with minimal image distortion. Anterior segment optical coherence tomography uses two scanning beams of light that are reflected off an ocular structure and then detected and compared to a reference beam to create a high-resolution cross-sectional image of the cornea, iris and anterior chamber.[28] The assessment of the cornea and corneal curvature is essential for screening for corneal diseases and irregularities. In refractive surgery in general, but especially in corneal refractive laser therapy, corneal topography is important to detect contraindications, such as ectasia, and to objectively measure the effect of treatment postoperatively.

**Endothelial cell density**

The main concern about anterior chamber phakic intraocular lenses is the loss of corneal endothelial cells and eventually the loss of endothelial integrity.[29] In the case of iris-fixated phakic intraocular lenses, damage to the corneal endothelium may be a result of direct contact between the lens and the endothelium layer on the surface of the cornea. Furthermore, subclinical inflammation may have a toxic effect on the endothelial cells.[29] Therefore, preoperative specular microscopy or confocal microscopy is mandatory. Patients with abnormal endothelial cell morphology or corneal endothelial cells below 2000 cells/mm$^2$ should be excluded from implantation of an iris-fixated pIOL.[24,30] Furthermore, an upper age limit of 50 years for pIOL implantation can be recommended. Aging namely

causes declining endothelial cell counts and reduction of the anterior chamber by increased crystalline lens thickness.

**Anterior chamber**

To assess whether or not sufficient anterior chamber space is available for a phakic intraocular lens implant to minimize the risk of increased endothelial cell loss, the anterior chamber dimensions are measured[24]. The ophthalmologist will respect three parameters: perfect adjustment to the internal diameter of the anterior chamber, minimum distance from the endothelium, and no contact with the iris and the crystalline lens.[31] In the past, anterior chamber depth was approximated during slit lamp examination. Nowadays, with the advent of anterior segment imaging techniques, such as anterior segment optical coherence tomography and Scheimpflug imaging, the internal dimensions of the anterior chamber can be determined more precisely. The internal depth of the anterior chamber is the measurement of the anterior chamber from the crystalline lens to the corneal endothelium. Different safe cut-off points of this preoperative anterior chamber depth have been proposed before, ranging from 2.8 to 3.35 mm (measured from the endothelium to the crystalline lens).[32-34]

Other selection criteria to reduce the number of complications when selecting patients for an iris-fixating pIOL are: a stable refraction of at least 1 year, a not too convex iris (subjective measure), and a mesopic pupil diameter smaller than 6 mm.

*Ms. Jansen appeared to be a good candidate for an anterior segment phakic intraocular lens. She was in good health. Corneal topography, obtained by Scheimpflug imaging, showed a bilateral pattern of mild symmetric astigmatism. The keratometry values were 42.61 × 26 / 43.20 × 116 in the right eye and 42.37 × 166 / 43.06 × 76 in the left eye. The anterior chamber depth was 3.41 and 3.43 mm (measured from the endothelium to the crystalline lens), respectively. Specular microscopy of the corneal endothelium revealed 2864 cells/mm$^2$ on the right eye and 2888 cells/mm$^2$ on the left eye. The ocular axial length was 29.30 mm in the right eye and 28.60 mm in the left, measured by the Lenstar LS900 optical biometer, a non-invasive automated method for measuring the anatomical characteristics of the eye. Her ophthalmologist then thoroughly explained to her why the preferred treatment was iris-fixated pIOL implantation and went on to describe the benefits of the procedure, such as excellent (uncorrected) visual outcomes, stable refraction over time, and safety. The risks were also discussed, including the possibility of over- and undercorrection, repositioning of the pIOL or explantation of the pIOL. The latter is most commonly due to age-related*

*cataract or increased endothelial cell loss over time. She was informed about the importance of regular check-ups. After giving her informed consent, pIOL implantation surgery of both eyes was performed. Ms. Jansen was extremely satisfied with the resulting Snellen visual acuity of 1.2 in both eyes without additional refractive correction. It was a new experience, waking up in the morning with a clear vision. She now feels more confident in both her private life and at work and is able to repursue her passion for photography.*



Regular postoperative follow-up visits to monitor endothelial cell density enable surgeons to detect patients with accelerated endothelial cell loss. With age, an approximately 20 µm forward thrust of the crystalline lens per year [35-37] causes a change in the anterior chamber depth as well as in the distance between the lens edge and the corneal endothelium. Periodically monitoring these dimensions may therefore help to detect early increased risk of complications. More recently, a new important criterion to warrant long-term safety is minimal distance from the edge of the phakic intraocular lens to the corneal endothelium.[38] In **Chapter 5,** we focus on the differences of this measurement when acquired with the two most commonly used imaging modalities: Scheimpflug imaging and anterior segment optical coherence tomography. The distance from the center of the pIOL to the corneal endothelium was compared between the devices, as well as the peripheral distances. This chapter also covers intra- and interobserver reliability and provides a conversion formula.

*Every year, Ms. Jansen had her routine check-up at the clinic. And so, decades passed. Seventeen years after her surgery, at the age of 55, she noticed that her vision had been slowly but progressively becoming blurrier, particularly in her left eye. By her next follow-up visit, she was unable to read the road signs at night. Visual acuity had deteriorated to 0.5 Snellen lines with a manifest refraction of S-1.50 D in the right eye. With her left eye, she had trouble reading up to the 0.4 Snellen line, with a manifest refraction of S-2.00 D. During slit lamp examination, the cornea and iris-fixated pIOLs were clear, but cataract was found to be the underlying cause of her deteriorating vision. In both eyes, a staphyloma in the macular area was determined by fundoscopy. The ophthalmologist decided together with Ms. Jansen to explant the Artisan lens and to perform cataract surgery with intraocular lens implantation. Axial length measurements were repeated to calculate the power of the posterior IOL to be implanted. These appeared to have increased over time by 1.53 mm in the right eye and 0.9 mm in the left, as measured by the Lenstar LS900 optical biometer. The anterior chamber depth was 2.83 and 2.81 mm (measured from the endothelium to the crystalline lens), respectively. Keratometry values had not changed over time. The endothelial cell density was 2040 and 2178 cells/mm$^2$, respectively.*

The main reason for pIOL explantation is visually significant cataract formation. At the time of cataract extraction with iris-fixated pIOL removal, patients were between 46 and 62 years at the time of cataract extraction.[39] Cataract formation might be associated with the pIOL but is generally described as being age-related as, up to now, there is no evidence for a direct causal relationship to the iris-fixated phakic intraocular lens.[40-42] In addition to cataract formation, her ophthalmologist noticed an increase in ocular axial length over time in Ms. Jansen's eyes. In this thesis, we studied this phenomenon of further myopic progression in (late) adulthood for the first time in a Caucasion population (**Chapter 6**). In myopic and hyperopic eyes, the change in axial length at two time points was determined at a mean time interval of 10 years. All eyes had undergone implantation with an iris-fixated pIOL. In addition, risk factors for axial elongation were analyzed.

In patients with an iris-fixated phakic intraocular lens, endothelial cell loss is the second cause for explantation.[43] After explanting the phakic intraocular lens, the common approach is to perform phacoemulsification, implanting a pseudophakic intraocular lens in the bag. In **Chapter 7**, an alternative surgical approach is described. We refer to this method as the Single Incision Technique wherein cataract surgery is performed underneath the iris-fixated pIOL. This chapter describes the advantages of this procedure over the conventional method and the 2-year results, including endothelial cell counts.

**In conclusion**

The aim of this thesis is to highlight different aspects that a clinician will encounter when considering a patient for iris-fixated phakic intraocular lens implantation. These include aspects related to the whole patient's journey: from screening to the results, follow-up, and explantation of the phakic intraocular lens.

Chapter 2 focuses on a better understanding of the factors establishing refractive error, and in Chapter 3 we study the effect of refractive correction on stray light. Chapter 4 provides a literature overview of the results after iris-fixated phakic intraocular lens implantation in myopic and hyperopic patients. In Chapter 5, we compare different devices to measure the distance from the iris-fixated phakic intraocular lens to the corneal endothelium. In Chapter 6, we evaluate axial length changes over time in myopic and hyperopic patients. In Chapter 7, we describe a surgical procedure and results for combined iris-fixated phakic lens removal and phacoemulsification.

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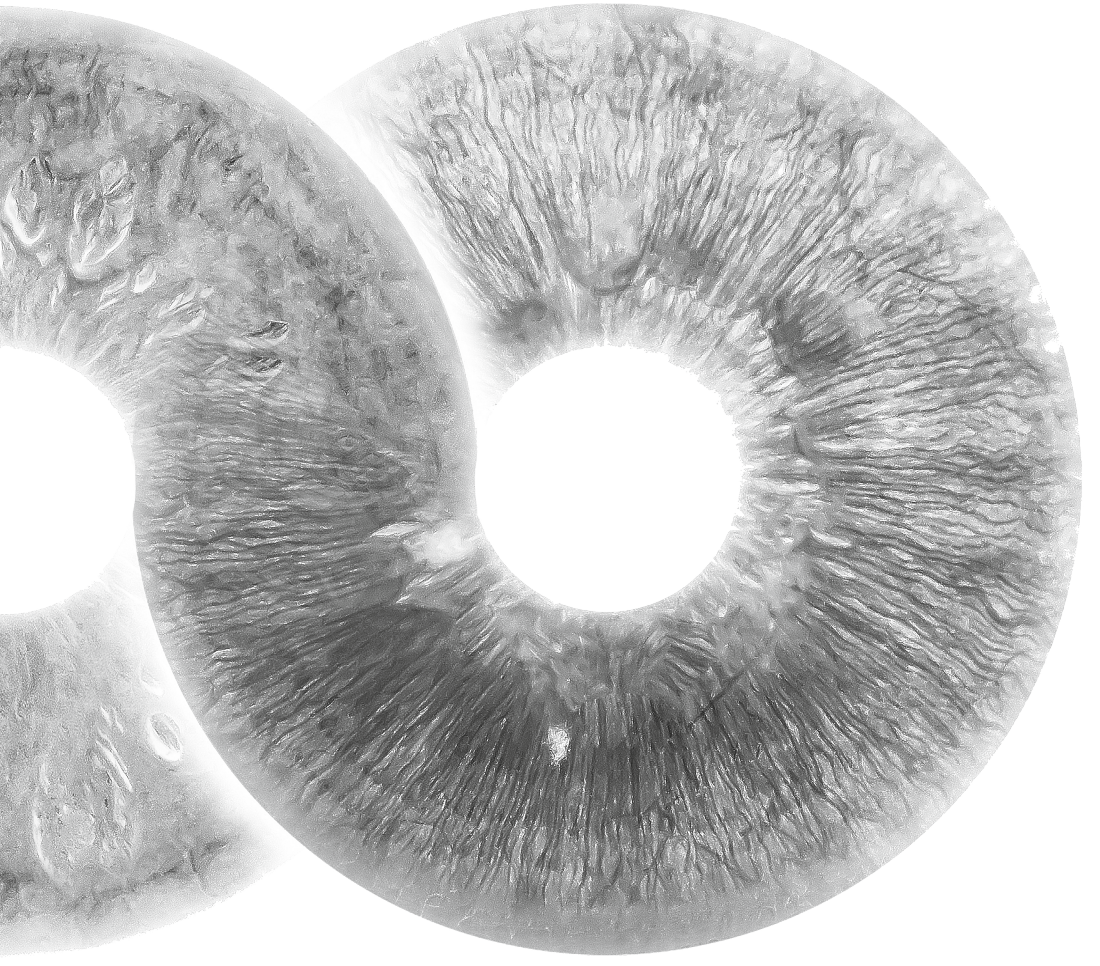

# CHAPTER 2.

## Correlations Between Ocular Biometrics And Refractive Error: A Systematic review and Meta-analysis

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Short running head: A meta-analysis of correlations in ocular biometry

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.

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## Abstract

The understanding of correlations between different biometric parameters is essential for personalized eye care in the field of cataract and refractive surgery. This systematic review offers a clear overview of the previous literature assessing these correlations including a meta-analysis. The review is focused on the following five correlations: 1) Axial Length and Refractive Error; 2) Anterior Chamber Depth and Refractive Error; 3) Axial Length and Anterior Chamber Depth; 4) Corneal Power and Refractive Error; 5) Corneal Power and Axial Length. An expected strong correlation between axial length and refractive error was found. Correlations including corneal power were weak and might be clinically insignificant.

## Introduction

With increasing prevalence of ageing and (high) refractive errors [1], patient-specific planning for cataract and refractive surgery is increasing in importance. To this end the methods of measuring the biometric characteristics have improved over the years. The comprehension of the relation between different biometric parameters can help offer better and more personalized eye care and therefore many studies have been performed to describe these relations. The correlation of axial length (AL) and refractive error [2-6] is nowadays inseparable in intraocular surgery planning. Other correlations have been investigated but varying outcomes have been published. For example the correlation of corneal power (K) and anterior chamber depth (ACD) are expected to change with AL as the former acts in a compensatory mechanism losing power during emmetropization [7], whereas the ACD, which is part of AL, might grow accordingly. However, the results for K and ACD correlated with refractive error vary among studies. Regarding ACD and refractive error, Chen et al [8] found a negative correlation, while Foster et al [9]state that this negative correlation is only significant in women. When it comes to K and refractive error, Olsen et al [10]reported a significant negative correlation between these measures. However, Iribarren et al, 2012 [11] did not consider corneal power as a determining factor for the refractive state.

In order to summarise what is known so far, this systematic review gathers existing evidence and infers conclusions based on the knowledge produced since 2000. We aimed to quantitatively assess the correlations of the different ocular biometrics and refractive error including ACD, AL and corneal power and provide a clear overview of the available literature.

## Methods

Our systematic review and meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

**Search strategy and selection criteria**

A broad literature search was performed on January 10th, 2018. We searched for all publications on correlations in ocular biometrics and refractive error using electronic databases including PubMed, Embase, Web of Science, Cochrane and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search strategy included the following MeSH search terms: "axial length", "eye", "anterior chamber", "refractive errors", "biometry" and "interferometry". Studies were included if they 1) mention information on at least one of the relevant correlations (refractive error and axial length; refractive error and anterior chamber depth; axial length and anterior chamber depth; corneal power and refractive error and corneal power and axial length); 2) investigated human adults; 3) published from 2000 and on; 4) published in English. By assessing the population selection methods, criteria for eye selection, examination protocols and participation rate (when applicable), the risk of study bias was assessed. Studies were excluded if they were conducted on the same population, or if there was no adequate statistical analysis mentioned in the methods section.

**Data collection**

The following information was extracted and recorded from studies (if available) via a standardized data extraction sheet: authors; year of publication; country of origin; study design; total sample size of patients and number of eyes; patient age; device(s) used for measurements. Correlation coefficients (CC) of the following correlations were extracted (or calculated out of the R-Squared):

A. Axial Length and Refractive Error
B. Anterior Chamber Depth and Refractive Error
C. Axial Length and Anterior Chamber Depth
D. Corneal Power and Refractive Error
E. Corneal Power and Axial Length

Strength of the positive and negative correlation was evaluated using the Evans (1996) guidelines: a) very weak: 0.00-0.19, b) weak: 0.20-0.39, c) moderate: 0.40-0.59, d) strong: 0.60-0.79,

e) very strong: 0.80-1.0 [13]. For studies with multiple groups, only the data from the relevant population were included and authors were contacted if further study details were needed.

**Statistical Analysis**

For each correlation, pooled CCs with 95% confidence intervals (CIs) were calculated using Hedges-Vevea random effects model and Z-test for overall effect. To control for unobserved heterogeneity (such as different populations, measurement devices) we used the random effects model in all analyses. We assessed publication bias using the Egger's regression model [14]. Statistical analysis was performed using Microsoft Excel 2010 for Windows (Microsoft, Redmond, WA, USA) and GraphPad Prism 6 (GraphPad, San Diego, CA, USA). $P < 0.05$ was considered statistically significant.



## Results

The search strategy identified 679 relevant abstracts. After removing the duplicates, 377 abstracts were evaluated. 329 studies were excluded based on title and abstract and 22 were excluded based on full text screening. In total, 26 articles remained for the meta-analysis as is schematically illustrated in **Figure 1**. In Appendix A, a detailed overview is provided of the literature included in this review.

**A. Axial Length and Refractive Error**

In accordance to the correlation coefficients provided by the included articles (**Figure 2**), AL and refractive error (spherical equivalent, SE) have a negative correlation. This corresponds to a more negative (myopic) refraction as AL increases. The strength varied from a weak to a very strong correlation between the articles, with most studies presenting a strong correlation. The smallest coefficient was presented by Jorge et al, 2007 [15], obtained with ultrasonography. On the other hand, the largest correlation was measured by Rabsilber et al, 2003[16] with the IOLMaster (Carl Zeiss, Meditec). The overall correlation between AL and refractive error was strong ($r = -0.67$; 95% CI: -0.76, -0.56).

A number of authors mentioned the regression coefficient of simple linear regression analysis [3,10,16-18]. The regression coefficients were compared as the variation in refractive error (D, Diopters) per 1-mm increase in AL, see **Table 1**. The smallest relation was found by Olsen et al, 2013 [10] with the ultrasonography, representing a change of -1.24D for each 1mm-increase in AL. Mallen et al, 2005 [3] found with ultrasonography a variation of -3.333D for the same increase.

**Figure 1.**
Study Inclusion Decision Tree using the PRISMA Flow Diagram [12]

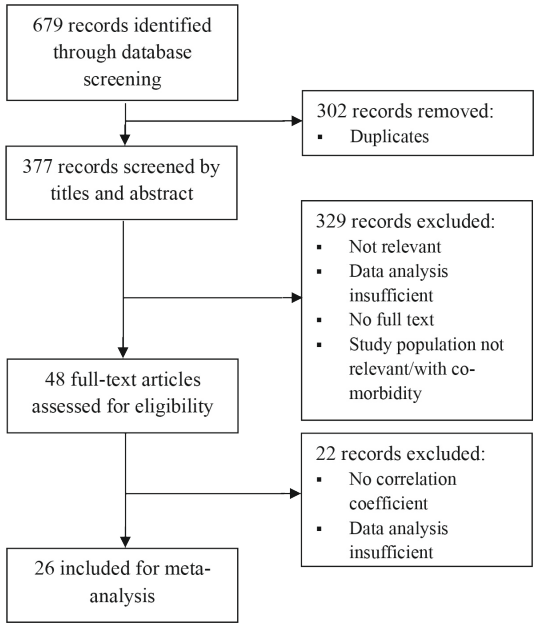



**Figure 2.**
Forest plot for Fisher's z-transformed correlation coefficient illustrating the correlation between AL and refractive error (SE). Symbol color presents the device used for AL measurement; red: optical low-coherence reflectometry (Lenstar LS900 or Allegro biograph); green: partial coherence interferometry (IOLMaster); blue: ultrasonography.

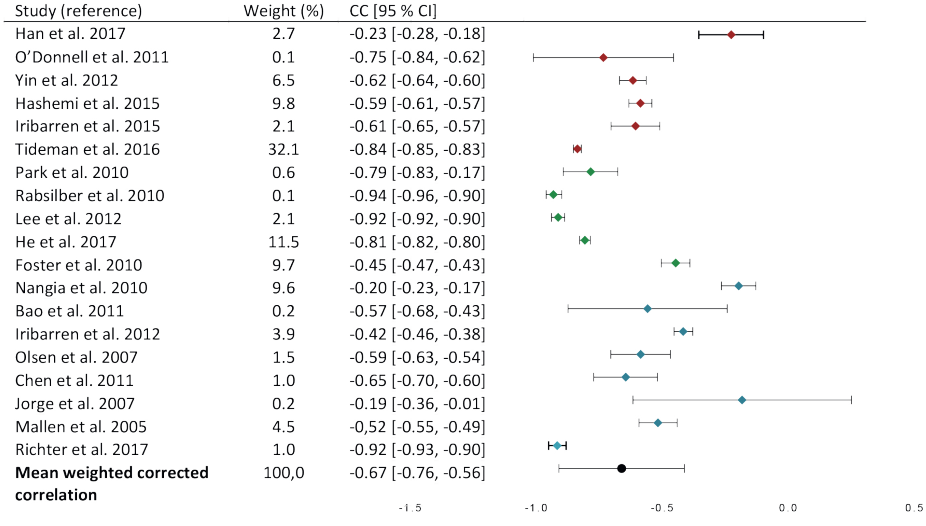


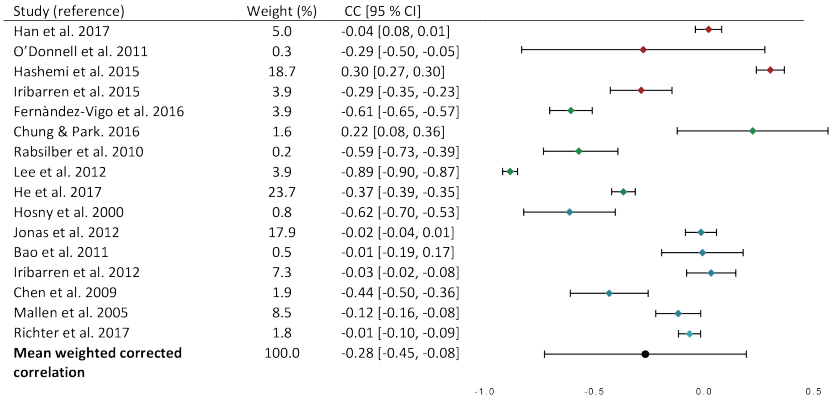
**Table 1.**
Overview of reported changes in spherical equivalent (SE) in diopters (D) for a 1 mm increase in AL (mm).

| Author | Device | SE in D/ 1-mm increase in AL |
|---|---|---|
| Rabsilber et al. 2010 | IOLMaster | -2.73D |
| Mallen et al. 2005 | US | -3.33D |
| Olsen et al. 2007 | US | -1.24D |
| Park et al. 2010 | IOLMaster | -1.68D |
| Richdale et al. 2016 | US | -2.70D |

### B. Anterior Chamber Depth and Refractive Error

The selected articles (**Figure 3**) agreed in showing a negative correlation between ACD and refractive error (SE). Therefore, as ACD is increased, the SE increased in the myopic direction. The corresponding correlation coefficients were mostly weak. The strongest correlation was found by Lee et al, 2012 [19], using the IOLMaster to measure ACD. A weaker correlation is found in the studies measuring the ACD with ultrasonography [3,11,20-22]. The overall correlation between ACD and refractive error was weak (r = -0.28; 95% CI: -0.45, -0.08).

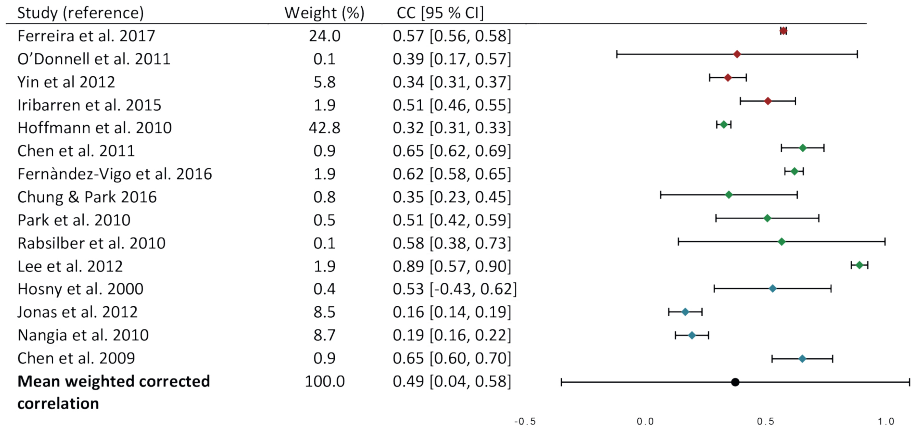
**Figure 3.**
Forest plot for Fisher's z-transformed correlation coefficient (CC) illustrating the correlation between ACD and refractive error (SE). Symbol color presents the device used for ACD measurement; red: optical low-coherence reflectometry (Lenstar LS900 or Allegro biograph); green: partial coherence interferometry (IOLMaster); blue: ultrasonography.




### C. Axial Length and Anterior Chamber Depth

AL and ACD have a positive correlation (**Figure 4**), which varied from weak to strong in strength. Thus, as AL increases, ACD increases as well. The highest correlation coefficient was measured with the IOLMaster [19], while the weakest correlation was measured with ultrasonography [21]. Overall, the correlation between ACD and AL was moderate but with a large variation (r = 0.49; 95% CI: -0.04, 0.58).

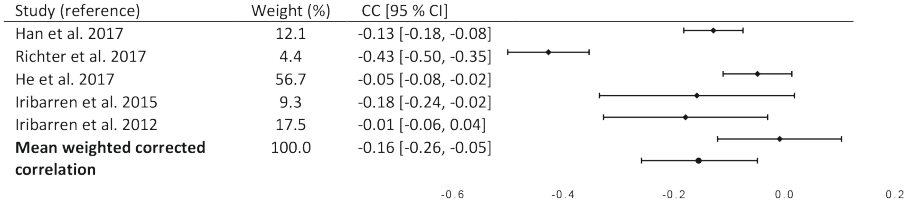
**Figure 4.**
Forest plot for Fisher's z-transformed correlation coefficient (CC) illustrating the correlation between ACD and AL. Symbol color presents the device used for all measurements; red: optical low-coherence reflectometry (Lenstar LS900 or Allegro biograph); green: partial coherence interferometry (IOLMaster); blue: ultrasonography.
* Fernàndez-Vigo et al. [23] used 2 devices for ACD measurements: Pentacam (Oculus Optikgerate, Germany) and IOLMaster and showed excellent agreement between devices.




## D. Corneal Power and Refractive Error

A negative correlation is suggested between corneal power (mean K) and refractive error (SE) (**Figure 5**). In other words, as corneal power increased, the SE achieved more negative (myopic) values. But the overall correlation is very weak (r = -0.16; 95% CI: -0.26, -0.05).

**Figure 5.**
Forest plot for Fisher's z-transformed correlation coefficient (CC) illustrating the correlation between corneal power and refractive error (SE). The studies use a wide variety of devices which are listed in Appendix A.

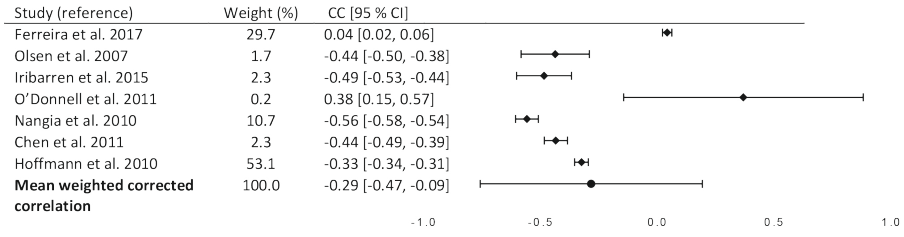



## E. Corneal Power and Axial Length

In the available data (**Figure 6**), corneal power and AL were negatively correlated, meaning that as AL increased, corneal power decreased. This correlation had some variations

between the studies. The largest correlation was demonstrated by Nangia [24], using ultrasonography to measure AL, but the device used to measure corneal power was not reported. O'Donnel et al [25] was the only one describing a weak positive correlation. The overall correlation between corneal power and AL was weak (r = -0.29; 95% CI: -0.47, -0.09).

**Figure 6.**
Forest plot for Fisher's z-transformed correlation coefficient (CC) illustrating the correlation between corneal power and AL. The studies use a wide variety of devices which are listed in Appendix A.




## Discussion

The findings of this systematic review and meta-analysis show that AL and ACD are the most important determinants of refractive error. This supports previously published research on biometric determinants for cataract and refractive surgery [26-28].

### Age, ethnicity, gender

Despite the large number of articles and eyes, it is important mentioning that the effect of age, ethnicity and sex on the correlations was not included in our analyses in order to provide a meta-analysis. To deal with the heterogeneity in the different study populations a random effects model was used. To still further describe the effect on these factors, an overview of the age, ethnicity and sex in the different study populations is provided in Appendix A and we searched each article on separate analysis of these parameters.

It is described that ACD tends to decrease as a consequence of age-related increase in lens thickness [4,29], lens vault and curvature of the iris [30]. In 12/27 studies included in our review the effect of age on ACD is described. 9 studies [3,9,18,22,23,31-34] also found a decrease of ACD as result of ageing. Foster et al.[9] however, additionally found a reversed effect of age on ACD in their age group of ≥ 80 years. Fernandez-Vigo et al. [23] described a decrease of 10.4 µm/year as Richdale et al. [18] found a decrease of 0.02 mm/year. In 3 studies, [10,19,35] ACD was not affected by age.

Furthermore, a decrease in average AL with increasing age has been reported [6,23,36]. In this review 2 studies [9,17] showed similar results, however 6 studies [19,31,32,35] did not found a significant effect of age on AL.

Considering sex, women have significantly shallower ACD [9,22,23,31-33,35] and shorter AL [3,8,9,22,31-33,35,37,38] compared to men in most studies describing this parameters.

For keratometry values the effect on age and sex varied between the studies assessing this [8,10,19,22,31-33,35] so no overall conclusion can be drawn.

The effect of ethnicity can also be appraised, as previous reports [21,39] revealed that Caucasians have deeper anterior chambers than South East Asians and East Asians. A similar difference has been described when comparing South East Asians with the latter group. Middle Eastern populations were found to have lower prevalence and lower mean degree of myopia compared to Far Eastern societies [3]. Possible explanations for these ethnic differences in biometry are environmental factors and hereditary components [29,40-42].

**Biometry devices**

Although we used the random effects model to deal with the heterogeneity of the different populations and devices used in the included articles, there are some clear differences between the biometrical measurements between different devices. The IOLMaster is described as more accurate than ultrasound for AL measurement, with higher resolution and lower variability [43]. The IOLMaster and Lenstar (Haag Streit, Switzerland) have a good correlation [31,34,44]. On the other hand, Lenstar and ultrasound report non-equivalent AL measurements [45], with the former providing patients' spherical equivalent values closer to their target refraction [46]. Concerning ACD measurements, the IOLMaster and Pentacam (Oculus Inc.) have excellent agreement [23] and the mean error between these devices is too small to create noticeable differences in refractive outcomes [47]. When measured by Lenstar, the ACD is considered to be significantly deeper compared to the IOLMaster, although the difference is clinically not significant [48]. The Lenstar and Pentacam can be used interchangeably for ACD measurements [49]. Moreover, there is a highly significant correlation for ACD measurements between the Lenstar and US [50], in contrast to the IOLMaster and US, measuring significantly shorter ACD with US. Yet this difference is clinically insignificant (on average -0.06 mm which is <2% of the ACD) [51]. Furthermore, the correlation between the US and Pentacam in ACD analysis is subject of current discussion, as for phakic eyes, they may be equivalent, while for pseudophakic eyes they appear not to be interchangeable [52].

For K readings, the Lenstar measurements of average K and IOL power (SRK/T formula) were considered to be similar to those from the IOLMaster [45]. A statistically significant difference was observed between mean keratometry measurements of IOLMaster, automated keratometry and Pentacam, as the Pentacam measures the posterior curvature of the cornea directly, while the IOLMaster approximate the posterior corneal radius as approximately 82.2% of the anterior surface radius [53]. However Sayed et al. described good agreement of the Pentacam and IOLMaster in K readings for biometry and phakic IOL power calculation [54].



## Conclusions

There is strong evidence on the correlation of axial length and refractive error; axial length increases when refractive error grows towards negative (myopic) values with on average 2.3 diopters decrease for each 1-mm elongation. Our meta-analysis shows that the ACD tends to grow concordantly but in a weaker fashion. Furthermore, deeper ACD is seen in longer eyes. Corneal power might have a clinically insignificant role in determining the refractive power.

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## Appendix A – Qualitative Analysis of Correlations

| Authors & reference | Country/ Ethnicity | Age (Mean ± SD) | Sex | No. of eyes | Equipment | AL-RE | ACD-RE | AL-ACD | CP-RE | CP-AL | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mallen et al. 2005** | Jordan/ Jordanian | 17-40 years (27.39 ± 6.45) | 643 female (58.8%) 450 male (41.2%) | 1093 right and 1093 left eyes | US, Grand Seiko GR-3100K autorefractor | Negative, moderate | Negative, very weak | N.R. | N.R. | N.R. | Low to medium |
| **Jorge et al. 2007** | Portugal/N.R. | N.R. (20.6 ± 2.3) | 84 female (71.2%) 34 male (28.8%) | 118 right eyes | US, Autokeratometer Nidek ARK-700A | Negative, strong | N.R. | N.R. | N.R. | N.R. | Low to medium |
| **Chen et al. 2009** | Taiwan/ Taiwanese Chinese | 40-80 years (60.9 ± 11.2) | 274 female (54.8%) 226 male (46.2%) | 500 eyes | US, Topcon KR-8800 autorefractor | Negative, strong | Negative, moderate | Positive, strong | N.R. | N.R. | Low to medium |
| **Foster et al. 2010** | UK/ Predominantly white older UK population | 48-88 years (N.R.) | 1429 female (56.7%) 1090 men (43.3%) | 4729 eyes | IOLMaster, Humphrey 500 autorefractor | Negative, moderate | N.R. | N.R. | N.R. | N.R. | Low to medium |

| Authors & reference | Country/ Ethnicity | Age (Mean ± SD) | Sex | No. of eyes | Equipment | AL-RE | ACD-RE | AL-ACD | CP-RE | CP-AL | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Olsen et al. 2007** | Iceland/ Caucasian | 55-100 years (68 ± 8.5) | 398 female (55%) 325 male (45%) | 723 right eyes | US, Auto-refracto-keratometer Nidek ARK 900 | Negative, moderate | N.R. | N.R. | N.R. | Negative, moderate | Low |
| **He et al. 2017** | Japan | 50-96 years (62.56 ± 8.0) | 3545 female (52.4%) 3224 male (47.6%) | 6099 eyes | Topcon KR 8900, IOL master | Negative, very strong | Negative, weak | N.R. | Negative, very weak | N.R. | Low |
| **Richdale et al. 2016** | United States/ Mostly White | 30-50 years (40.5 ± 6.1) | N.R. female (57%) N.R. male (43%) | 85 right eyes | US | Negative, moderate | No correlation | N.R. | N.R. | N.R. | Medium |
| **Tideman et al. 2016** | The Netherlands | N.R. (61.3 ± 11.4) | 8961 female (57.1%) 6732 male (42.9%) | 15693 eyes | Topcon RM-A2000 Auto-Refractor, Lenstar LS900, US (PacScan 300 AP) | Negative, very strong | N.R. | N.R. | N.R. | N.R. | Low |
| **Iribarren et al. 2015** | Iran/ Population from north of Iran | 55-64 years (N.R.) | 510 female (50,4%) 496 male (49,6%) | 1006 eyes | Allegro Biograph, Topcon KR8800 autorefractometer, Pentacam HR | Negative, strong | Negative, weak | Positive, moderate | Negative, very weak | Negative, moderate | Low to medium |

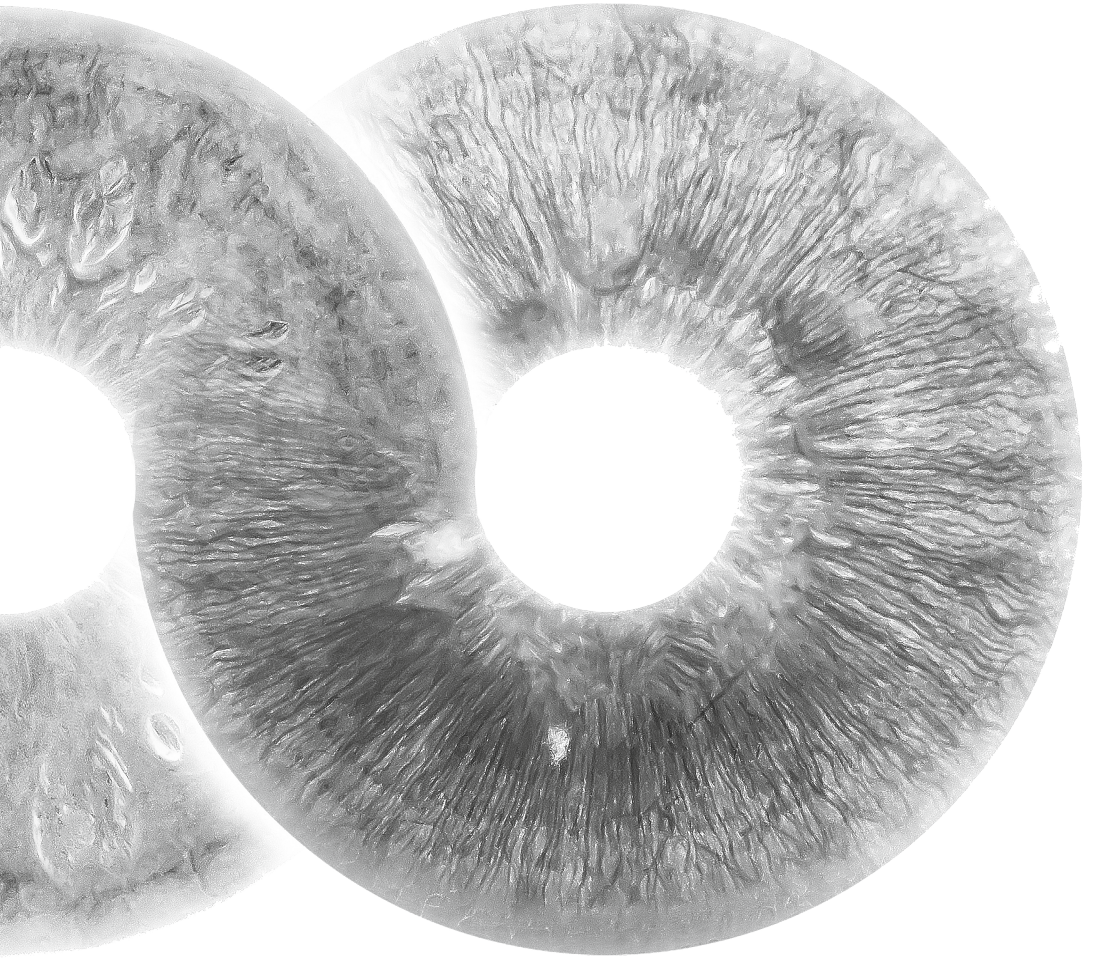
| Authors & reference | Country/ Ethnicity | Age (Mean ± SD) | Sex | No. of eyes | Equipment | AL-RE | ACD-RE | AL-ACD | CP-RE | CP-AL | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Hashemi et al. 2015** | Iran/ Population from north of Iran | 40-64 years (N.R.) | 2494 female (58.3%) 2696 male (41.7%) | 4820 eyes | Allegro Biograph, Topcon KR8800 autorefractometer | Negative, moderate | Negative, weak | N.R. | N.R. | N.R. | Low |
| **Yin et al. 2012** | China/Han Chinese | 50-93 years (64.1 ± 9.8) | 1787 female (56.6%) 1372 male (43.4%) | 3159 right eyes | LenStar 900 and Nidek AR-610 Autorefractometer | Negative, strong | N.R. | Positive, weak | N.R. | N.R. | Low |
| **Lee et al. 2012** | South Korea/ Korean | 22-46 years (30.05 ± N.R) | 544 female (53.8%) 467 male (46.2%) | 1011 right eyes | IOLMaster and Canon RK-F1 autorefractometer | Negative, very strong | Negative, very strong | Positive, very strong | N.R. | N.R. | Low to medium |
| **Iribarren et al. 2012** | India/ Central India Population | 50-100 years (N.R.) | 971 female (51.5%) 914 male (48.5%) | 1885 right eyes | US, non automatic keratometer | Negative, moderate | Negative, very weak | N.R. | Negative, very weak | N.R. | Low |
| **Rabsilber et al. 2010** | Germany | 22-82 years (43.83 ± 18.74) | 34 female (56.7%) 26 men (43.3%) | 30 right eyes, 30 left eye | Orbscan II, IOLMaster | Negative, very strong | Negative, moderate | Positive, moderate | N.R. | N.R. | Low |

| Authors & reference | Country/ Ethnicity | Age (Mean ± SD) | Sex | No. of eyes | Equipment | AL-RE | ACD-RE | AL-ACD | CP-RE | CP-AL | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **O'Donnell et al. 2011** | UK/N.R. | 19-60 years (28.53 ± 8.97) | 42 female (60%) 28 male (40%) | 70 right eyes | LenStar LS900 | Negative, strong | Negative, weak | Positive, weak | N.R. | Positive, weak | Medium |
| **Bao et al. 2011** | China/ Chinese population | 17-35 years (24.10 ± 3.66) | 32 female (52.4%) 29 male (47.6%) | 120 eyes | US, Orbscan IIz | Negative, moderate | Negative, very weak | N.R. | N.R. | N.R. | Low to medium |
| **Park et al. 2010** | South Korea/ Korean | 29-95 years (41.56 ± 15.70) | 144 female (49.5%) 147 male (50.5%) | 291 eyes | IOLMaster, Canon RK-F1 autorefractometer | Negative, strong | N.R. | Positive, moderate | N.R. | N.R. | Low to medium |
| **Nangia et al. 2010** | India/ Central India Population | 30-100 years (49.4 ± 13.4) | 2514 female (53.5%) 2184 male (46.5%) | 4698 eyes | US | Negative, weak | N.R. | Positive, very weak | N.R. | Negative, moderate | Low |
| **Chung & Park 2016** | Korea | 19-33 years (24.8 ± 4.7) | 289 female (70.1%) 123 male (29.9%) | 412 eyes | IOLMaster, autorefractometry | N.R. | Negative, weak | Positive, weak | N.R. | N.R. | Low to medium |

| Authors & reference | Country/ Ethnicity | Age (Mean ± SD) | Sex | No. of eyes | Equipment | AL-RE | ACD-RE | AL-ACD | CP-RE | CP-AL | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Fernandez-Vigo et al. 2016** | Spain/ Caucasian | 18-84 years (49.1 ± 15.2) | N.R. female (61%) N.R. male (39%) | 1006 right eyes | Pentacam, IOLMaster | N.R. | Negative, strong | Positive, strong | N.R. | N.R. | Low to medium |
| **Jonas et al. 2012** | India/ Central India Population | 30-100 years (49.1 ± 13.2) | 2469 female (53.5%) 2146 male (46.5%) | 4615 eyes | US, non automatic keratometer | N.R. | Negative, very weak | Positive, very weak | N.R. | N.R. | Low |
| **Hosny et al. 2000** | Spain | 18-78 years (40.35 ± 16.3) | N.R. | 211 eyes | US, Nidek Autorefractor/ Keratometer | N.R. | Negative, strong | Positive, moderate | N.R. | N.R. | Medium |
| **Chen et al. 2011** | China | 50-98 years (N.R.) | 548 female (54.0%) 467 male( 46.0%) | 1015 eyes | IOLMaster | N.R. | N.R. | Positive, strong | N.R. | Negative, moderate | Low |
| **Hoffmann & Hutz 2010** | Germany/N.R. | 74 (Median age) (N.R.) | N.R. | 23239 eyes | IOLMaster | N.R. | N.R. | Positive, weak | N.R. | Negative, weak | Low to medium |
| **Richter et al. 2017** | United States/ Chinese American | 50-N.R. years (60.5 ± 8.1) | 2575 female (63.3%) 1496 male (36.7%) | 4071 right eyes | US | Negative, very strong | Negative, very weak | N.R. | Negative, moderate | N.R. | Low to medium |

| Authors & reference | Country/ Ethnicity | Age (Mean ± SD) | Sex | No. of eyes | Equipment | AL-RE | ACD-RE | AL-ACD | CP-RE | CP-AL | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Han et al. 2017** | China/N.R. | 35-N.R. years (51.4 ± 10.6) | N.R. female (54,5%) N.R. male (45.5%) | 1300 right eyes | IOLMaster and Lenstar LS900 | Negative, weak | Negative, very weak | N.R. | Negative, very weak | N.R. | Low |
| **Ferreira et al. 2017** | Portugal/ Caucasian | 44-99 years (69 ± 10) | 3721 female (57.2%) 2785 male (42.8%) | 13012 eyes | Lenstar LS900 | N.R. | N.R. | Positive, moderate | N.R. | Positive, very weak | Low |

N.R., Not reported; US, Ultrasonography.



# CHAPTER 3.

## Straylight as the result of refractive correction

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## Abstract

Purpose: To investigate the effect of refractive correction on straylight.

Patients and methods: Straylight values were measured with the C-Quant (Oculus Optikgeräte, GmbH, Wetzlar, Germany) in (i) near-emmetropic eyes (n=30) with various negative powered refractive lenses and in (ii) myopic eyes (n=30) corrected with prescribed eyeglasses and contact lenses. The straylight measurements in each group were compared in the different conditions.

Results: In the near-emmetropic group a significant effect ($p<0.001$) of each added negative diopter was found to increase straylight values with 0.006 log-units. In the second group no significant correlation with type of correcting lens was found on straylight values.

Conclusions: Refractive correction with high minus power (contact) lenses result in subtle increase of straylight values. These changes are relatively small and do not lead to visual disability in clinical setting.

## Introduction

The prevalence of refractive errors, in particular myopia, is increasing worldwide [1-4]. Patients with (high) refractive errors, who have inadequate vision with spectacles and are contact lens intolerant, may choose for refractive correction by laser surgery or intraocular lens (IOL) implantation. But correction of refractive errors, even when leading to excellent visual acuity, may, however, not necessarily lead to complete patient satisfaction if vision is tinged by troublesome glare. Since the beginning of the 20th century, it is known that straylight has great effect on the quality of vision [5-7]. The International committee on illumination (CIE) has defined disability glare as "the effect of straylight in the eye whereby visibility and visual performance are reduced" [7].



Straylight is the result of forward intraocular light scatter on the retina. For each beam of light that reaches the eye, the light is scattered to some extent by imperfections of optical media, before it reaches the retina [5,8,9]. In every eye, this mechanism is responsible for an amount of straylight in the presence of a (bright) light source. Normal values of straylight will induce limited visual disability effects, but an increase in straylight can lead to symptoms that affect the quality of vision seriously. These symptoms include halos and loss of contrast, but also blurred vision, decreased color vision, and difficulty in face recognition [5].

Many clinical studies have evaluated the pre- and postoperative effect on straylight after refractive surgery. The results were consistent: post-operative straylight values in myopes after laser-assisted in situ keratomileusis (LASIK)/ laser-assisted epithelial keratomileusis (LASEK) [10-14] or after phakic intra-ocular lens (pIOL) implantation [15,16] were on average slightly lower than pre-operative straylight measurements. Assumptions were made that these improvements are the result of ill-tolerated contact lenses pre-operatively [13,15,16]. Another factor that might have played a role in these findings is the effect of change in retinal image size due to correction of the refractive error. For example, after pIOL implantation in high myopic eyes, visual acuity may increase 1 or more lines due to image magnification effects [15,17,18]. Labuz et al [19] demonstrated differences in elevated straylight as the result of multifocal contact lens wearers. Van der Meulen et al [20] showed increased straylight during rigid contact lens wear, possibly as a result of deposits on the contact lens, but the degree of refractive error was not taken into account.

The effect of different degrees of refractive correction on retinal straylight, with its concomitant effect on retinal image size, has not yet been investigated and remains unclear.

We therefore want to examine if different refractive corrections, resulting in different retinal image sizes, have an effect on straylight values.

## Material and Methods

**Subjects**

This study involves two study groups with an age range of 18 – 35 years: (i) a near-emmetropic group (n=30 eyes of 15 subjects), defined as having a spherical refractive error between -1.00 and +1.00 dioptres (D) and a cylindrical refractive error not exceeding -2.00 D. (ii) A myopic group (n=30 eyes of 15 subjects) with a spherical refractive error of at least -6.00 D and a cylindrical refractive error not exceeding -2.00 D. Subjects with a history of ocular pathology, cataract, corneal opacities, visual acuity of < 0.2 Snellen or epilepsy, were excluded. The participants were recruited and assessed at the Leiden University Medical Center (LUMC) in the Netherlands between May 2013 and October 2014. The study was conducted in accordance with the Declaration of Helsinki and approved by the medical ethical committee of the LUMC. All participants provided written informed consent.

**Straylight measurements**

Straylight values were measured using the compensation comparison-based Oculus C-Quant (Oculus Optikgeräte, GmbH, Wetzlar, Germany). This method for assessing straylight has been described in detail in the literature and has been thoroughly validated [6,17,18,21,22]. The amount of straylight is quantified by means of the straylight parameter *s*, given logarithmically as log(*s*). All measurements were performed in identical light conditions. The test was repeated to obtain 2 reliable measurements for each condition. The mean of the 2 measurements was used for analysis. The reliability outputs of the measurement were chosen as follows: an estimated standard deviation of ≤ 0.08 and a shape factor Q of ≥ 0.5 [17,21].

**Study Design**

For each study group, we used a different approach to change refractive correction;
In the first group, (i) the near-emmetropic group, straylight values were measured under 5 conditions: with a trial lens (provided by the manufacturer of the C-Quant) with a spherical power of (a) -14.00 D, (b) -10.00 D, (c) -6.00 D, (d) -4.00 D and (e) without any correction. Right and left eye were tested alternately. Between every measurement a pause of 30 seconds was given. Relative magnification of the different retinal image sizes was calculated with the standard spectacle magnification formula (1) for values for spectacle magnification [23].

$SM = 1/1-(t/n)D_1 * 1/1-hD$ (1)

SM = Spectacle magnification
t = thickness of the lens in meters
n = refractive index of the lens material
$D_1$ = the base curve or front surface power of the lens in diopters
h = the vertex distance + 3 mm, converted to meters
D = actual power of the lens in diopters

In the second group, (ii) the myopic group, straylight values were measured under 3 conditions: with correction by (a) trial lens, (b) spectacles and (c) contact lens. The same standard formula (1) was used to determine the image magnification resulting from different vertex distance *a* under the various test-conditions: (a) *a* = 0.026 m (trial lenses), (b) *a* = 0.016 m (spectacles) and (c) *a* = 0.003 m (contact lenses). In **Figure 1** the lens magnification factor is plotted as a function of different refractive lens powers. Prior to straylight measurements, autorefraction (Topcon KR 8900 Ref, Tokyo, Japan), corneal topography (Oculus Pentacam HR, Wetzlar, Germany), axial length (Lenstar LS 900 Haag-Streit, Koeniz, Switzerland) and slitlamp examination, was performed. Best-corrected visual acuity (BCVA), own-spectacle-corrected visual acuity and contact-lens-corrected visual acuity (if applicable) were determined by ETDRS assessment (logMAR units). Trial lenses and prescribed spectacles were thoroughly cleaned before examination and new contact lenses were used. Only non-tinted spectacles with no macroscopic scratches and refractive index of 1.67 was used. In case spectacles were worn, a vertex distance of 16 mm was maintained.

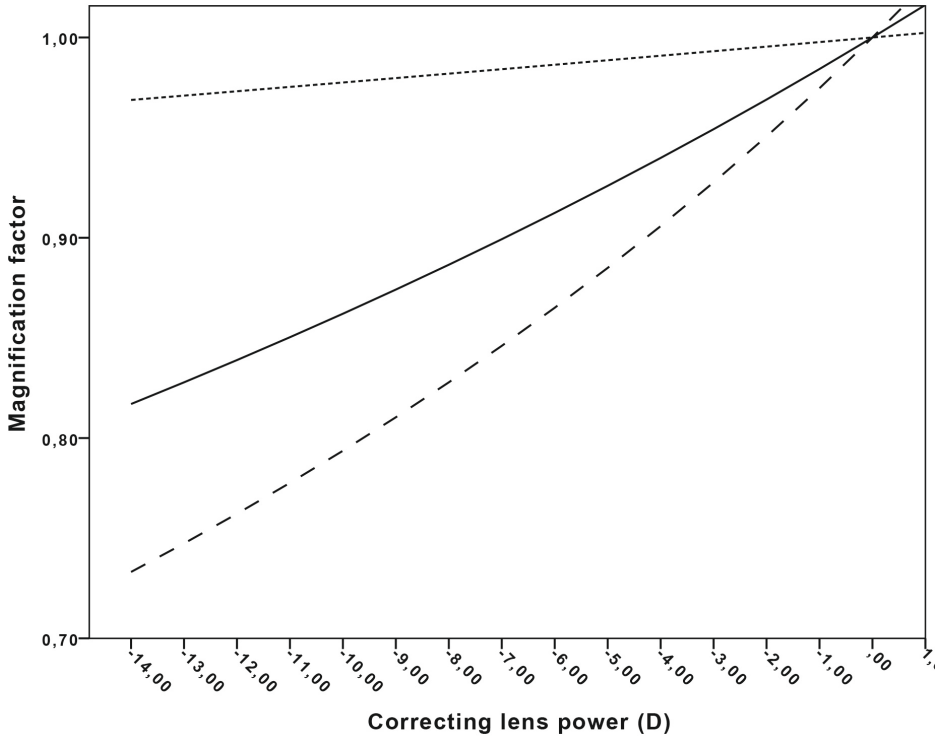
**Statistical analysis**

Statistical analysis was performed using SPSS statistics software version 23 (IBM). Descriptive statistics including means, standard deviations, proportions, and frequency distributions, were generated for subject characteristics. Bland–Altman analysis was performed and 95% limits of agreement (LoA) were estimated by mean difference ± 1.95 x standard deviation (SD) of the difference. Data are expressed as the mean ± SD. The normality of data was checked with the Kolmogorov-Smirnov test. Means, standard deviations and boxplots were used to visualize the data. A linear mixed model with random intercept was used to examine the relationship between straylight values and the different test-conditions. We chose this statistical model in order to deal with the potential correlation of repeated measures of right and left eye. The correlation between straylight and the various test-conditions was tested with a linear as well as a quadratic function. Our primary variable and all the possible

variables were implemented in a model. We compared all the possible combinations by removing the variables with the highest p-value > 0.05 once at a time to create the best fit model (backward selection). In addition, each variable was tested individually in separate models on having an effect on straylight measurements. The model with the minimum value for Akaike's information criterion (AIC) was identified as the optimal model for the specific outcome measure. To evaluate the normal distribution of the final models, residual scatter plots and histograms were used. Statistical significance was defined as a p-value of less than 0.05.

Power calculations were made to determine the sample size. A significance level (adjusted for sidedness) of 0.025, a power of 90%, and a standard deviation of the difference of 0.1, provided a minimum sample size of 13 patients for each group to satisfy valid conclusions. We included 15 patients in each group to meet the required sample size, allowing for dropouts.

**Figure 1.**
Calculated magnification factor as a function of refractive correction power in diopters (D) for thin contact lenses (*dashed line*), spectacles (*solid line*) and trial lenses (*interrupted line*).



# Results

### Characteristics of the participants

The characteristics of the study-groups are shown in **Table 1**.

**Table 1.**
Characteristics of the near-emmetropic (A) and myopic study group (B).

A.

| **Near-emmetropic population** | Mean | SD | N | % |
|---|---|---|---|---|
| Male eyes | | | 16 | 53 |
| Female eyes | | | 14 | 47 |
| Age (years) | 23.3 | 4.3 | | |
| SE refraction (D) | 0.16 | 0.6 | | |
| Blue/Green iris colour | | | 18 | 60 |
| Brown iris colour | | | 12 | 40 |

B.

| **Myopic population** | Mean | SD | N | % |
|---|---|---|---|---|
| Male eyes | | | 4 | 13 |
| Female eyes | | | 26 | 87 |
| Age (years) | 23.2 | 2.8 | | |
| SE refraction (D) | -8.78 | 1.69 | | |
| BCVA (logMAR) | -0.07 | 0.11 | | |
| VA with own spectacles (logMAR) | -0.06 | 0.12 | | |
| VA with contact lens (logMAR) | -0.10 | 0.11 | | |
| Keratometry mean (D) | 43.7 | 1.17 | | |
| Axial length (mm) | 26.8 | 0.77 | | |
| Pupil size (mm) | 3.45 | 0.59 | | |
| Blue/Green iris colour | | | 18 | 60 |
| Brown iris colour | | | 12 | 40 |
| Rigid contact lens | | | 2 | 7 |
| Soft contact lens | | | 28 | 93 |

SD: standard deviation; SE: spherical equivalent; D: diopters; BCVA: best-corrected visual acuity; VA: visual acuity

### Straylight results

The repeatability of the straylight measurements was very good in both groups and comparable with previous reports [17,18,22,24], with repeated measures standard deviations of 0.068 and 0.056 log-units for the near-emmetropic and myopic groups respectively, also shown in Bland Altman plots (**Figure 2**).

The measured straylight values are shown in **Table 2** and with boxplot analysis (**Figure 3**). The mean baseline straylight value of the near-emmetropic group (measurements without trial lens, therefore no altering of retinal image size) is 0.91 log-units. In the myopic group the mean baseline straylight value (measurements with contact lens, therefore minimal altering of retinal image size) is 0.97 log-units. Comparison of baseline straylight values between the near-emmetropic and myopic group shows no significant difference (Mann-Whitney significance 0.133 / Independent sample T-test p = 0.062).

i. In the near-emmetropic group the refractive correction, with its concomitant image size altering effect, had a significant effect ($p<0.001$) on the log(*s*) straylight value. None of the other parameters tested (eye, age, SE, and iris pigmentation) had significant effect on straylight. For more details see **Table 3A.**
ii. In the myopic group the different refractive corrections had no significant effect on retinal straylight values ($p = 0.150$). There was no significant difference between the different test conditions, ie trial lenses, soft contact lenses and spectacles. None of the other parameters (eye, age, SE, keratometry, iris pigmentation, AL, pupil size) had significant effect on straylight. For more details see **Table 3B.**

**Table 2.**
Measured straylight values at different conditions of retinal image size for the near-emmetropic (A) and myopic (B) eyes

A.

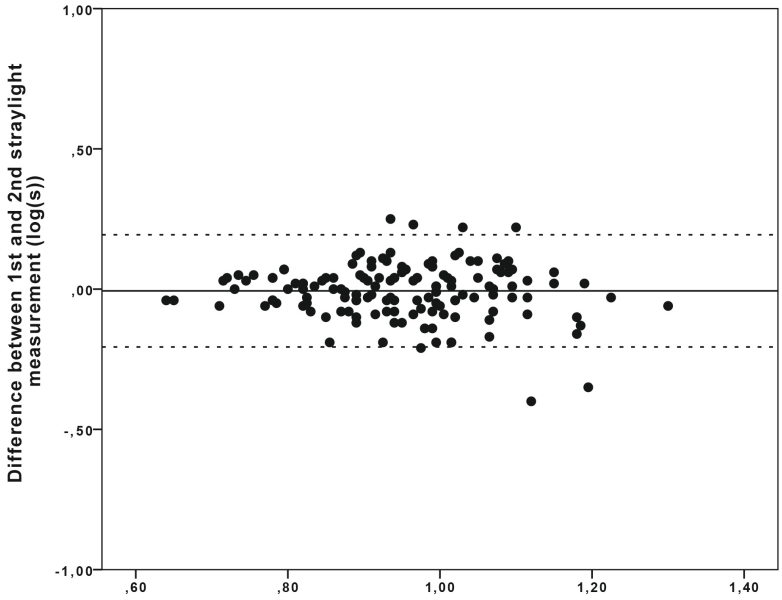
| Trial lens (D) | Mean log(*s*) | SD | N |
|---|---|---|---|
| 0 | 0.91 | 0.14 | 30 |
| -4 | 0.96 | 0.12 | 30 |
| -6 | 0.92 | 0.11 | 30 |
| -10 | 0.99 | 0.10 | 30 |
| -14 | 0.99 | 0.11 | 29 |

B.

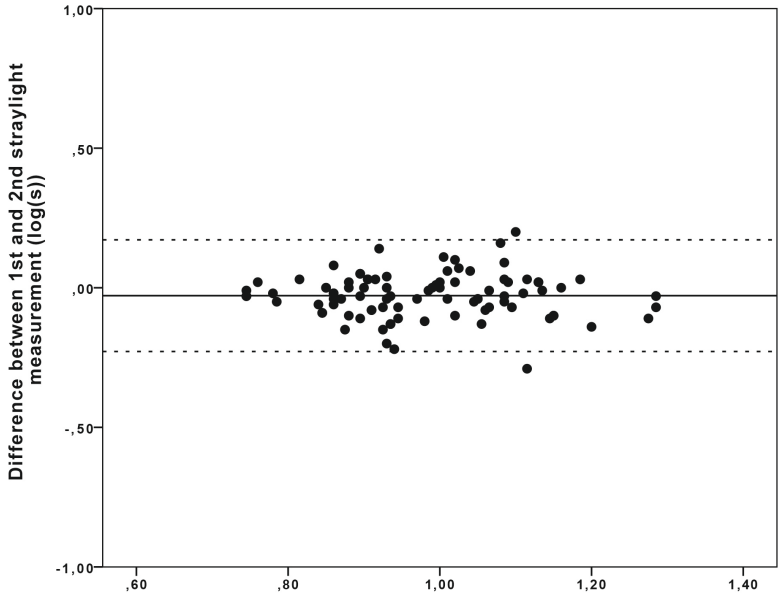
| Condition | Mean log(*s*) | SD | N |
|---|---|---|---|
| Own glasses | 0.98 | 0.15 | 30 |
| Triallens | 0.99 | 0.11 | 30 |
| Contactlens | 0.97 | 0.11 | 30 |

D: diopters; SD: standard deviation

**Figure 2.**
Bland-Altman plots for the first and second straylight measurement differences with 95% limits of agreement (LoA) in the (a) near-emmetropic group and the (b) myopic group. *Solid line:* mean, *dashed line:* upper and lower LoA.




a.




b.

**Figure 3.**
Boxplot of the straylight values measured by C-Quant in log-units (Log(*s*)) for the 30 near-emmetropic eyes (*white*) and the 30 myopic eyes (*gray*) under the different test conditions.

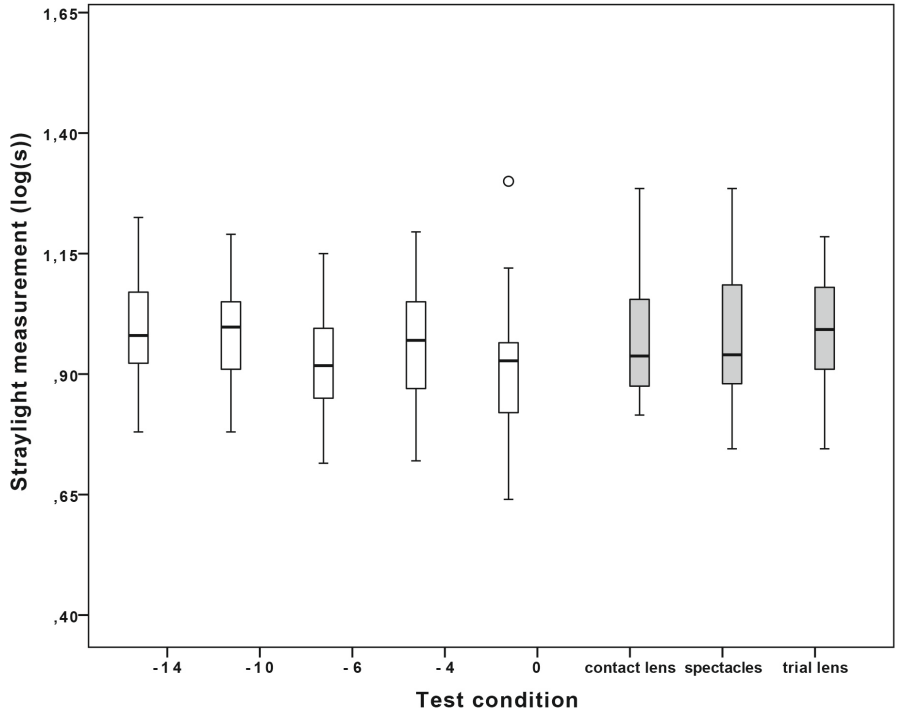



**Table 3.**
Associations of mean straylight values and possible predictor variables generated by linear mixed models in the near-emmetropic study group (A) and the myopic study group (B).

A

| **Variable** | **Estimate** | **95% CI** | ***P* value** |
|---|---|---|---|
| Intercept | 0.911 | +0.853 to +0.969 | <0.001 |
| Lens power | 0.006 | +0.004 to +0.008 | <0.001 |
| Eye | -0.017 | -0.039 to +0.004 | 0.118 |
| Age | -0.006 | -0.022 to +0.010 | 0.445 |
| SE | 0.008 | -0.078 to +0.093 | 0.861 |
| Iris pigmentation | 0.062 | -0.051 to +0.175 | 0.259 |

B

| **Parameter** | **Estimate** | **95% CI** | ***P* value** |
|---|---|---|---|
| Intercept | 2.556 | +0.821 to +4.292 | 0.005 |
| Lens Type spect/ctl | -0.129 | -0.298 to +0.040 | 0.130 |
| trial/ctl | -0.233 | -0.514 to +0.048 | 0.102 |

| | | | |
|---|---|---|---|
| Magnification | -1.617 | -3.404 to +0.170 | 0.075 |
| Eye | -0.035 | -0.071 to +0.005 | 0.053 |
| SE | -0.028 | -0.058 to +0.003 | 0.073 |
| Iris pigmentation | -0.016 | -0.115 to +0.082 | 0.721 |
| K mean | 0.026 | -0.015 to +0.067 | 0.204 |
| Age | -0.011 | -0.032 to +0.011 | 0.297 |
| Axial length | -0.003 | -0.062 to +0.057 | 0.924 |
| Pupil size | 0.017 | -0.074 to +0.109 | 0.699 |

## Discussion



The main conclusion is that the effects of glasses and soft contact lenses, including the degree of refractive error it corrects, on straylight are modest and all the measurements were below 1.47 log(s) which is the threshold for serious hindrance. In the first (near-emmetropic) group, a significant effect was found of the different powers of lenses, which must partly be attributed to the known effects of scatter angle (image size), but our hypothesis is that accommodation might also play a role in this finding. During accommodation the crystalline lens takes on a more spherical shape, and lens thickness increases with 0.045 mm for every diopter of added accommodation stimulus [24].

To our knowledge, we are the first to describe the effects of glasses on straylight. The effect of contact lenses on straylight, however, has been described by van der Meulen et al [20]. They demonstrated straylight values of 0.934 log(s) during soft contact lens wear in a study population with normal eyes, comparable to 0.938 log(s) after removal of the lens. The straylight values of our myopic study population are slightly higher, probably due to the refractive power of the lens. Rigid contact lenses [20] and multifocal contact lenses [19] have also shown some slightly elevated straylight values, possibly as the result of other underlying mechanisms, such as deposits on the contact lens or diffractive effects, respectively. Therefore, these results cannot be compared with our findings, as we only used soft contact lenses in our study.

Although some studies have shown that age and iris pigmentation [9,17,18,25-28] can have significant effect on straylight values, in the present study, age, iris pigmentation, and all the other tested parameters were not significant. Probably, the fact that age is not significant in our study population is caused by a selection effect because we only selected subjects between 18-35 years of age. Maybe the pigmentation spread was not sufficient either in our small cohort.

What might explain the differences between the near-emmetropic and myopic study group? The first thing we should consider is the accommodation effect as described earlier. Second, a possible effect of the contact lenses used in the study as myopic participants' own contact lenses were used for visual correction and contact lenses have previously been shown to influence straylight values [20,29,30].

Another factor that may be considered is that data of the near-emmetropic eyes group may have resulted in better statistical power due to more straylight measurements and greater range of magnification factor. However, if we exclude the data generated by test conditions with trial lenses of powers -14 D and -4D, resulting in a similar number of observations as in the myopic group, a clearly statistic significant effect remained ($p < 0.001$).

## Conclusions

The effect of the degree and the method of correction, including eyeglasses and soft contact lenses, of refractive correction on straylight are modest and clinically irrelevant. The small effects found, might partly be attributed to known effects of scatter angle (image size), but accommodation might also play a role in this finding. Further in depth studies in this issue need to be pursued.

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## Financial and proprietary interests

Dr. van den Berg developed the method to assess straylight. This is licensed by the Royal Academy to Oculus for the C-Quant instrument.

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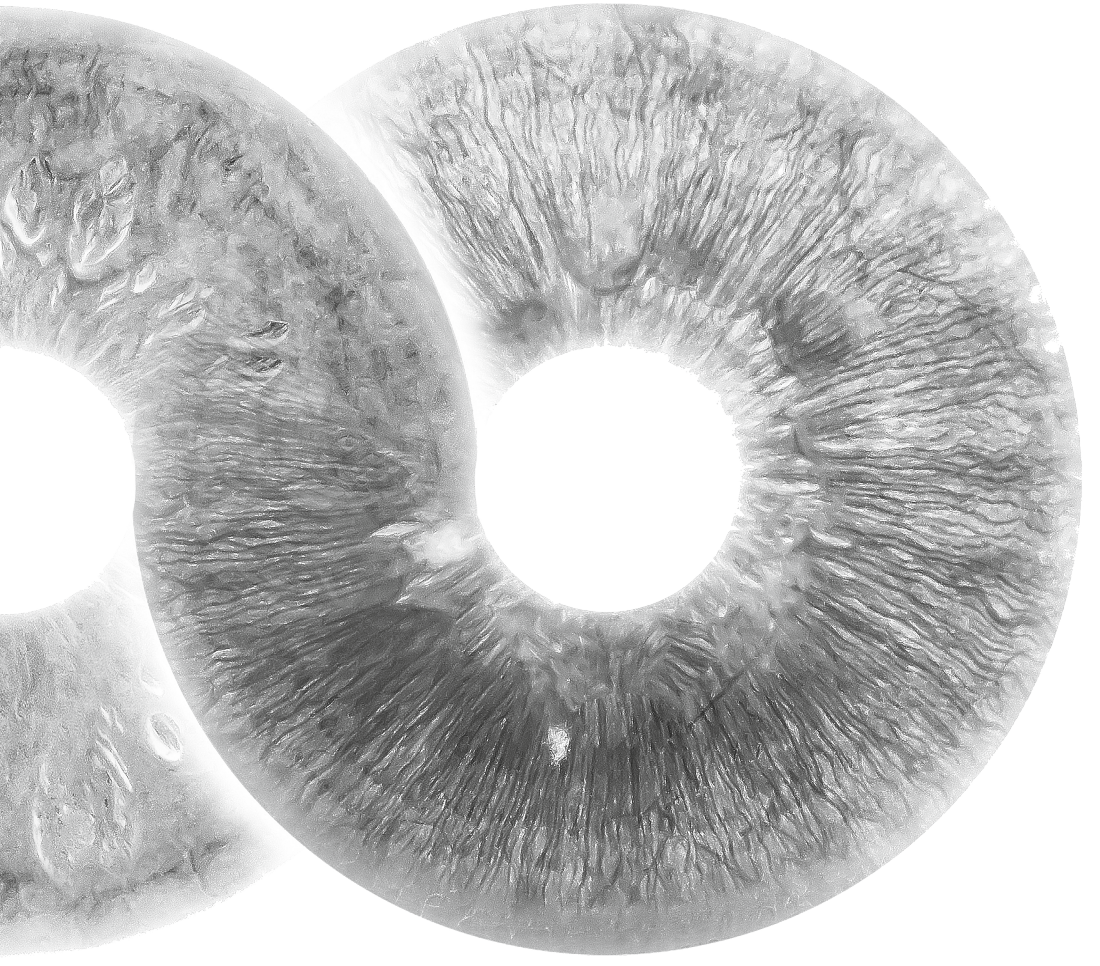

# CHAPTER 4.

## Middle- and long-term results after iris-fixated phakic intraocular lens implantation in myopic and hyperopic patients: a meta-analysis

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van Rijn GA, Gaurisankar ZS, Ilgenfritz AP, Lima JEE, Haasnoot GW, Beenakker JM, Cheng YYY, Luyten GPM.

*J Cataract Refract Surg. 2020 Jan;46(1):125-137. Doi: 10.1097/j.jcrs.0000000000000002.*

## 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 per-

formed 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.

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

**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

## Results

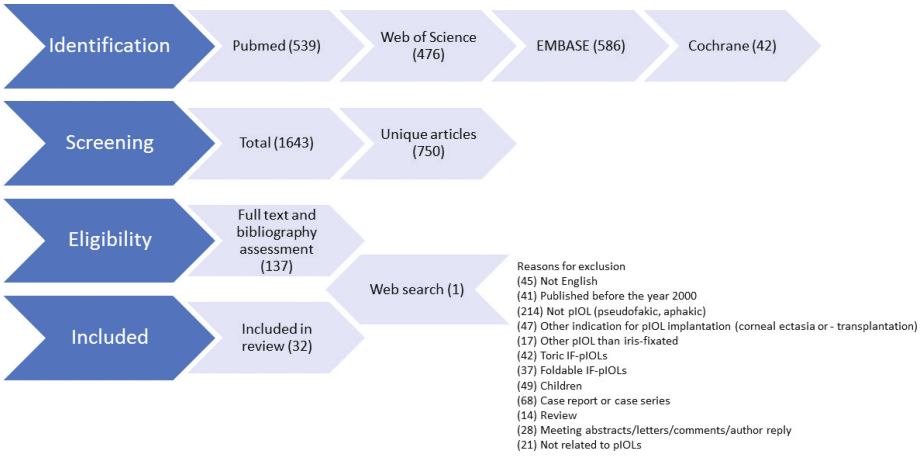
The selected studies comprised 5523 myopic eyes and 217 hyperopic eyes. The sample sizes in the articles range from 26 to 1140 myopic eyes and from 14 to 136 hyperopic eyes. Twenty-nine articles describe the results after iris-fixated pIOL implantation in myopic eyes.[3–18,20–32] Four articles describe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

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




### 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

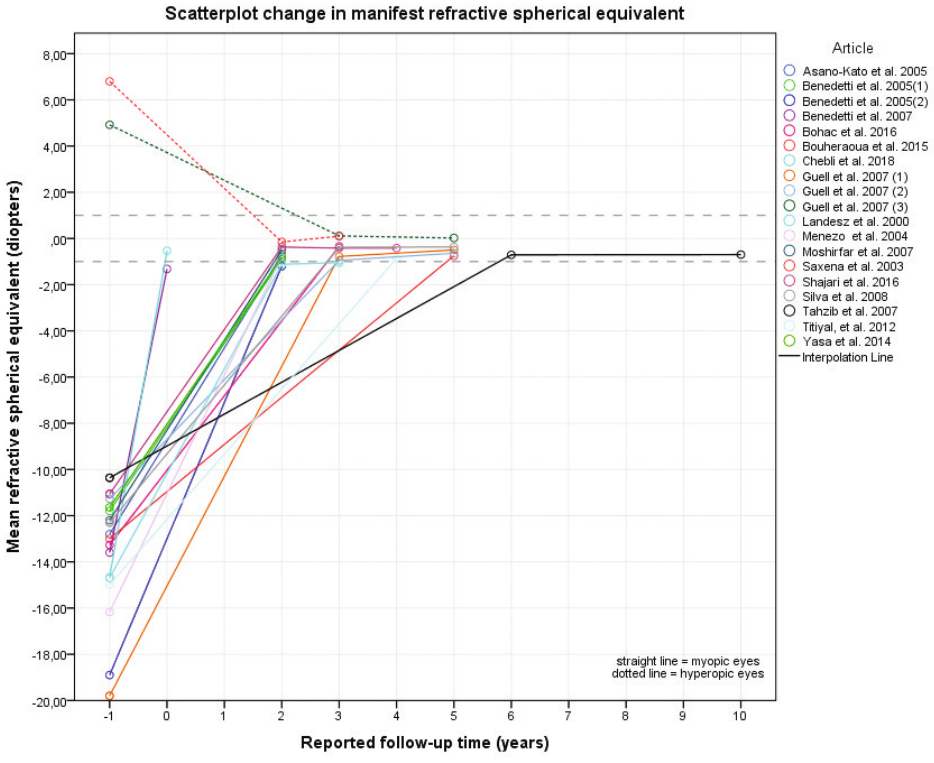


**Table 1.**

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 | 4 years | 5 years | 6 years | 10 years |
|---|---|---|---|---|---|---|
| Number of eyes | 534 | 589 | 146 | 341 | 89 | 89 |
| Mean SE pre-op (D) (range) (SD) | -13.6 (-18.9;-11.6) (2.3) | -13.7 (-19.8;-11.06) (2.9) | -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) |
| Median SE pre-op (D) (range) (SD) | -12.2 (-18.9;-11.6) (2.3) | -13.3 (-19.8;-11.06) (2.9) | -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) |
| Mean SE post-op (D) (range) (SD) | -0.8 (-1.2;-0.4) (0.25) | -0.7 (-1.1;-0.3) (0.29) | -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) |
| Median SE post-op (D) (range) (SD) | -0.8 (-1.2;-0.4) (0.25) | -0.8 (-1.1;-0.3) (0.29) | -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) |
| Number of studies | 7 | 5 | 2 | 3 | 1 | 1 |

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) | Mean pre-op SE (D) | Mean post-op SE (D) | Reported FU time (Year) |
|---|---|---|---|---|---|
| Guell et al.* | 2008 | 34 | 4.92±1.7 | -0.11±0.74* | 3 |
| | | 28 | 4.92±1.7 | 0.02±0.51* | 5 |
| Saxena et al. | 2003 | 15 | 6.80±1.97 | -0.15±0.89 | 2 |
| | | 10 | 6.80±1.97 | +0.10±0.85 | 3 |

D=diopters; pre-op=preoperative; post-op=postoperative; MRSE=manifest refractive spherical equivalent; FU time=follow-up time; *41.4% additional corneal refractive surgery; IOL=intraocular lens

*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**.



*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.

**Table 3.**

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

| Follow-up | 2 years | | 3 years | | 4 years | | 5 years | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Deviation from emmetropia** | **within0.5D** | **within1.0D** | **within0.5D** | **within1.0D** | **within0.5D** | **within1.0D** | **within0.5D** | **within1.0D** | **within0.5D** | **within1.0D** |
| Number of eyes | 172 | 172 | 505 | 505 | 146 | 146 | 19 | 19 | 909 | 909 |
| Median | 55.0 | 84.0 | 85.4 | 97.7 | 72.0 | 94.0 | 73.7 | 94.7 | 73.7 | 94.0 |
| Mean | 53.3 | 82.1 | 79.5 | 94.9 | 59.2 | 86.5 | 73.7 | 94.7 | 68.8 | 89.1 |
| Minimum | 33.3 | 55.0 | 31.4 | 74.5 | 35.3 | 72.5 | 73.7 | 94.7 | 31.4 | 55.0 |
| Maximum | 68.0 | 90.0 | 85.4 | 97.7 | 72.0 | 94.0 | 73.7 | 94.7 | 85.4 | 97.7 |
| Standard deviation | 14.1 | 10.7 | 16.3 | 7.3 | 17.6 | 10.3 | 0 | 0 | 19.6 | 10.1 |
| Number of studies | 5 | 5 | 4 | 4 | 3 | 3 | 2 | 2 | 10 | 10 |

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 | | 6 years | | 10 years | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Deviation intended** | **within0.5D** | **within1.0D** | **within0.5D** | **within1.0D** | **within0.5D** | **within1.0D** | **within0.5D** | **within1.0D** | **within0.5D** | **within1.0D** |
| Number of eyes | 317 | 317 | 68 | 68 | 89 | 89 | 89 | 89 | 563 | 647 |
| Median | 57.1 | 78.8 | 36.8 | 70.5 | 50.5 | 65.1 | 43.8 | 68.8 | 50.5 | 78.8 |
| Mean | 53.0 | 76.7 | 36.8 | 70.5 | 50.5 | 65.1 | 43.8 | 68.8 | 49.2 | 75.5 |
| Minimum | 38.2 | 69.1 | 36.8 | 70.5 | 50.5 | 65.1 | 43.8 | 68.8 | 36.8 | 65.1 |
| Maximum | 57.1 | 78.8 | 36.8 | 70.5 | 50.5 | 65.1 | 43.8 | 68.8 | 57.1 | 93.2 |
| Standard deviation | 7.8 | 4.0 | 0 | 0 | 0 | 0 | 0 | 0 | 8.1 | 5.5 |
| Number of studies | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 4 | 4 |

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

**Table 5.**
Pooled estimates of UDVA in myopic eyes

| Follow-up time | 2 years | 3 years | 4 years | 5 years | 6 years |
|---|---|---|---|---|---|
| Number of eyes | 560 | 733 | 162 | 210 | 89 |
| Mean % UDVA ≥ 20/40 (range) | 85 (67;87) | 81 (67;100) | 81 (57;92) | 86 (45;100) | 79 (79) |
| Median % UDVA ≥ 20/40 (range) | 87 (67;87) | 79 (67;100) | 92 (57;92) | 82 (45;100) | 79 (79) |
| Standard deviation | 5.2 | 8.3 | 13.3 | 15.5 | 0 |
| Number of studies | 4 | 7 | 3 | 5 | 1 |
| Number of eyes | 475 | 733 | 162 | 210 | - |
| Mean % UDVA ≥ 20/20 (range) | 32 (16;35) | 32 (4;60) | 36 (7;53) | 28 (6;74) | - |
| Median % UDVA ≥ 20/20 (range) | 35 (16;35) | 31 (4;60) | 53 (7;53) | 21 (6;74) | - |
| Standard deviation | 5.9 | 14.7 | 20.3 | 20.6 | |
| Number of studies | 3 | 7 | 3 | 5 | - |

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 | 4 years | 5 years | 6 years | 10 years |
|---|---|---|---|---|---|---|
| Number of eyes | 153 | 88 | 51 | 87 | 89 | 89 |
| Median efficacy index (range) | 0.90 (0.83;0.93) | 0.98 (0.43;0.98) | 0.96 (0.96) | 1.02 (0.63;1.02) | 0.83 (0.83) | 0.8 (0.8) |
| Mean efficacy index (range) | 0.89 (0.83;0.93) | 0.86 (0.43;0.98) | 0.96 (0.96) | 0.93 (0.63;1.02) | 0.83 (0.83) | 0.8 (0.8) |
| Standard deviation | 0.04 | 0.23 | 0 | 0.16 | 0 | 0 |
| Number of studies | 2 | 2 | 1 | 2 | 1 | 1 |
| Number of eyes | 153 | 68 | 51 | 68 | 89 | 89 |
| Median safety index (range) | 1.19 (1.12;1.39) | 1.02 (1.02) | 1.46 (1.46) | 1.10 (1.10) | 1.10 (1.10) | 1.10 (1.10) |
| Mean safety index (range) | 1.19 (1.12;1.39) | 1.02 (1.02) | 1.46 (1.46) | 1.10 (1.10) | 1.10 (1.10) | 1.10 (1.10) |
| Standard deviation | 0.09 | 0 | 0 | 0 | 0 | 0 |
| Number of studies | 2 | 1 | 1 | 1 | 1 | 1 |

EI=efficacy index; SI=safety index

*CDVA and Safety*

Data on CDVA are often reported as the change in visual acuity pre-implantation 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.

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

| Study | Publication | Eyes | FU time | ≥Lines (%) | ≤ 2 Lines (%) | Notes |
|---|---|---|---|---|---|---|
| Asano-Kato et al. | 2005 | 44 | 2 | 95.5 | 4.5 | 2 eyes; age-related cataract |
| Bohac et al. | 2017 | 166 | 3 | 99.5 | 0.5 | 1 eye; choroidal neovascularization at 18-month follow-up |
| Bouheraoua et al. | 2015 | 68 | 5 | 98.5 | 0 | |
| Budo et al. | 2000 | 249 | 3 | 95.8 | 1.2 | 3 eyes; 1 eye nuclear cataract, 2 eyes macular myopic degeneration |
| Landesz et al. | 2000 | 67 | 3 | 92.5 | 3 | 2 eyes cataract, 1 eye unclear reason |
| Landesz et al. | 2001 | 78 | 2 | 91 | 2.6 | 2 eyes nuclear cataract |
| Qasem et al. | 2010 | 151 | 5 | 100 | 0 | |
| Shajari et al. | 2016 | 95 | 4 | 93 | 0 | |
| Silva et al. | 2008 | 26 | 5 | - | 0 | 1 eye; progressive cataract at 3–year follow-up |
| Stulting et al. | 2008 | 355 | 2 | 96 | 0.3 | |
| Stulting et al. | 2008 | 228 | 3 | 92,5 | 0.9 | 2 eyes; 1 eye retinal detachment & macular hole, 1 eye posterior capsular opacification |
| Tahzib et al. | 2007 | 89 | 10 | - | 3.6 | 3 eyes; 1 eye myopic maculopathy, 1 eye guttate dystrophy, 1 eye cataract |
| Titiyal, et al. | 2012 | 51 | 4 | 96.1 | 1.9 | 1 eye, reason not specified |
| 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 | 3 years | 4 years | 5 years | 10 years |
|---|---|---|---|---|---|
| Number of eyes | 333 | 499 | 84 | 84 | 89 |
| Mean CDVA pre-op in logM (range) (SD) | 0.17 (0.17) (0) | 0.17 (0.17) (0) | 0.17 (0.17) | 0.17 (0.17) (0) | 0.16 (0.16) (0) |
| Median CDVA pre-op in logM (range) (SD) | 0.17 (0.17) (0) | 0.17 (0.17) (0) | 0.17 (0.17) | 0.17 (0.17) (0) | 0.16 (0.16) (0) |
| Mean CDVA post-op in logM (range) (SD) | 0.05 (0.02;0.06) (0.02) | 0.07 (0.02; 0.11) (0.03) | 0.02 (0.02) | 0.02 (0.02) (0) | 0.12 (0.16) (0) |
| Median CDVA post-op in logM (range) (SD) | 0.05 (0.02;0.06) (0.02) | 0.06 (0.02; 0.11) (0.03) | 0.02 (0.02) | 0.02 (0.02) (0) | 0.12 (0.16) (0) |
| Number of studies | 2 | 3 | 1 | 1 | 1 |

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



*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)

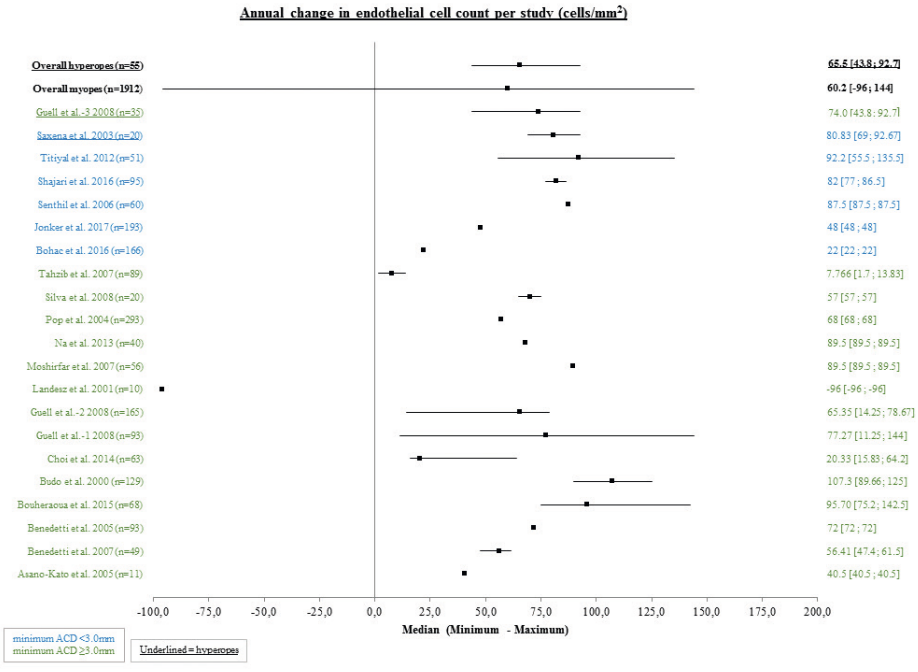


**Figure 5.**
Scatterplot of reported absolute endothelial cell changes

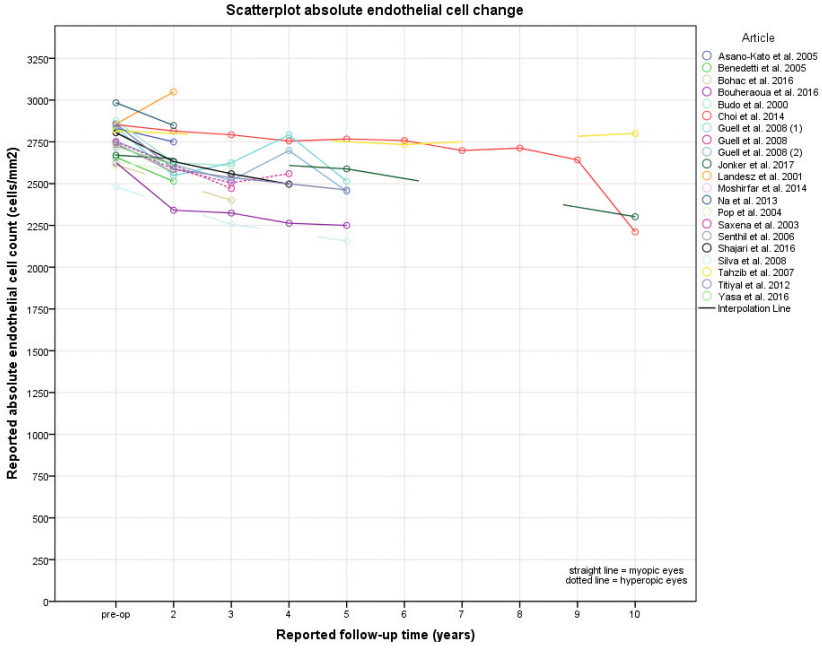



**Table 9.**
Pooled estimates of annual absolute EC change in myopic eyes

| 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 |

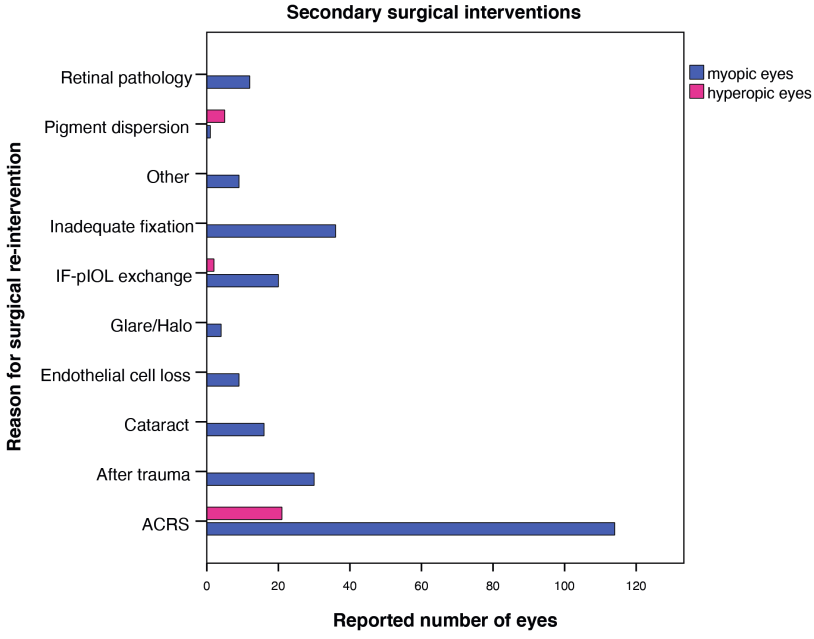
EC=endothelial cell

### 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.

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




*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]

**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

*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]

*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 powers 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]

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 3 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 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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# 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 | Eyes (count) | Mean pre-op SE (D) | Mean post-op SE (D) | Reported FU-time (year) |
|---|---|---|---|---|---|---|
| Asano-Kato et al. | Japan, Tokyo | 2005 | 21 | -12.8±2.94 | -0.71±0.81 | 2 |
| Benedetti et al. | Italy, Ancona | 2007 | 49 | -13.60± 4.26 | -1.32±1.20 | n.s. |
| Benedetti et al. | Italy, Ancona | 2005 | 68 (group 1)* | -11.8±2.4 | -0.91±0.77 | 2 |
| | | | 25 (group 2)* | -18.9±2.0 | -1.20±1.19 | 2 |
| Bohac et al. | Croatia, Zagreb | 2016 | 190 | -13.27 ±5.1 | -0.34 ±0.17 | 3 |
| Bouheraoua et al. | France, Paris | 2015 | 68 | -13±4.10 | −0.75 ± 0.74 | 5 |
| Chebli et al. | France, Lyon | 2018 | 113 | -14.67±5.15 | -0.53±0.80 | final visit[a] |
| Guell et al. | Spain, Barcelona | 2007 | 95 (group 1)* | -19.8±3.23 | -0.78±0.88 | 3 |
| | | | 150 (group 2)* | -11.27±3.11 | -0.95±1.06 | 3 |
| Guell et al. | Spain, Barcelona | 2007 | 89 (group 1)* | -19.8±3.23 | -0.5±0.89 | 5 |
| | | | 165 (group 2)* | -11.27±3.11 | -0.64±0.8 | 5 |
| Landesz et al. | Netherlands, Rotterdam | 2000 | 67 | -14.70 ±4.90 | -1.12±2.10 | 2 |
| | | 2000 | 67 | -14.70 ±4.90 | -1.05±2.20 | 3 |
| Menezo et al. | Spain, Valencia | 2004 | 137 | -16.17±2.75 | -0.78± 1.21 | 2 |
| Moshirfar et al. | USA, Utah | 2007 | 85 | -12.20±2.79 | -0.50 | 2 |
| Shajari et al. | Germany, Frankfurt am Main | 2016 | 78 | -11.06±4.77 | -0.37±0.48 | 2 |
| Shajari et al. | Germany, Frankfurt am Main | 2016 | 67 | -11.06±4.77 | -0.42±0.57 | 3 |
| Shajari et al. | Germany, Frankfurt am Main | 2016 | 95 | -11.06±4.77 | -0.42±0.47 | 4 |
| Silva et al. | USA, California Stanford | 2008 | 20 | -12.30±2.69 | -0.38±0.78 | 3 |
| Silva et al. | USA, California Stanford | 2008 | 19 | -12.30±2.69 | -0.37±0.69 | 5 |
| Tahzib et al. | Netherlands, Maastricht | 2007 | 89 | -10.36±4.69 | -0.71±0.99 | 6 |
| Tahzib et al. | Netherlands, Maastricht | 2007 | 89 | -10.36±4.69 | -0.70±1.00 | 10 |
| Titiyal, et al. | India, New Delhi | 2012 | 51 | -14.98 | -0.87 | 4 |
| Yasa et al. | Turkey, Istanbul | 2014 | 62 | -11.64±3.61 | -0.82±0.55 | 2 |

*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 ( range 1-10 years)

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

| Study | Publication | Eyes (count) | ≤0,5D (%) | ≤1.0D (%) | FU-period (year) | Target | Notes |
|---|---|---|---|---|---|---|---|
| Asano-Kato et al. | 2005 | 21 | 55 | 55 | 2 | emmetropia | data from graph numbers are estimated |
| Bouheraoua et al. | 2015 | 68 | 38.2 | 69.1 | 3 | intended | |
| | | 68 | 36.8 | 70.5 | 5 | | |
| Budo et al. | 2000 | 249 | 57.1 | 78.8 | 3 | intended | |
| Guell et al. | 2008 | 101 (group 1) | 9.9 | 22.8 | n.s. | emmetropia | 60.39% of the eyes ACRS |
| | | 173 (group 2) | 37.6 | 57.2 | n.s. | | 19.6% of the eyes ACRS |
| Landesz et al. | 2000 | 67 | 47.8 | 67.2 | n.s. | emmetropia | |
| Moshirfar et al. | 2007 | 38 | 55 | 84 | 2 | emmetropia | |
| Qasem et al. | 2010 | 68 | 31 | 65 | 2 | emmetropia | data from graph numbers are estimated, 17.9% of the eyes ACRS |
| | | 30 | 24 | 53 | 3 | | data from graph numbers are estimated, 17.9% of the eyes ACRS |
| | | 16 | 12 | 28 | 4 | | data from graph numbers are estimated, 17.9% of the eyes ACRS |
| | | 11 | 20 | 63 | 5 | | data from graph numbers are estimated, 17.9% of the eyes ACRS |
| Shajari et al. | 2016 | 95 | 72 | 94 | 4 | emmetropia | |
| Stulting et al. | | 434 | 85.4 | 97.7 | 3 | emmetropia | |
| Silva et al. | 2008 | 20 | 75 | 85 | 3 | emmetropia | |
| | | 19 | 73.7 | 94.7 | 5 | | |
| Tahzib et al. | 2007 | 89 | 50.5 | 65.1 | 6 | intended | |
| | | 89 | 43.8 | 68.8 | 10 | | |
| Titiyal, et al. | 2012 | 51 | 33.3 | 82.4 | 2 | emmetropia | |
| | | 51 | 31.4 | 74.5 | 3 | | |
| | | 51 | 35.3 | 72.5 | 4 | | |
| Yasa et al. | 2014 | 62 | 68 | 90 | 2 | emmetropia | |
| Yuan et al. | 2011 | 84 | n.r. | 93.2 | n.s. | intended | |

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) | Target | Notes |
|---|---|---|---|---|---|---|---|
| Guell et al. | 2008 | 41 | 34.8[δ] | 64.2[δ] | n.s. | emmetropia | [δ]41.4% of the eyes ACRS |
| Qasem et al. | 2010 | 6 | 50[δ] | 100[δ] | 2 | emmetropia | [δ]28.6% of eyes ACRS, data from graph numbers are estimated |
| | | 2 | 100[δ] | 100[δ] | 3 | emmetropia | [δ]28.6% of eyes ACRS, data from graph numbers are estimated |

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

# Appendix 3.

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

| Study | Publication | Eyes (count) | Mean pre-op CDVA (decimal) | Mean post-op CDVA (decimal) | Fu-time (year) |
|---|---|---|---|---|---|
| Benedetti et al. | 2007 | 49 | 0.80±0.20 | 0.86±0.20 | n.s. |
| Bohac et al. | 2017 | 166 | 0.67 ±0.20 | 0.77 ±0.18 | 3 |
| Budo et al. | 2000 | 249 | 0.67±0.26 | 0.88± 0,19 | 2 |
| | | 249 | 0.67±0.26 | 0.87±0.20 | 3 |
| Chebli et al. | 2018 | 113 | 0.18±0.18 logM | 0.064±0.096 logM | last visit (range 1-10 years) |
| Landesz et al. | 2000 | 67 | 20/40 | 20/32 | n.s. |
| Landesz et al. | 2001 | 10 | 20/32 | 20/25 | n.s. |
| Senthil et al. | 2006 | 60 | 20/39 | 20/32 | n.s. |
| Tahzib et al. | 2007 | 89 | 0.16±0.23 logM | 0.12±0.21 logM | 10 |
| Titiyal, et al. | 2012 | 85 | 6/10 | 6/7 | last visit (range 1-5 years) |
| Yuan et al. | 2012 | 84 | 0.68±0.12 | 0.96±0.10 | 2 |
| | | 84 | 0.68±0.12 | 0.96±0.08 | 3 |
| | | 84 | 0.68±0.12 | 0.96±0.04 | 4 |
| | | 84 | 0.68±0.12 | 0.95±0.08 | 5 |

CDVA=corrected distance visual acuity; FU-time=follow-up time; pre-op=pre-operative; 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) | Mean pre-op CDVA (decimal) | Mean post-op CDVA (decimal) | Fu-time (year) |
|---|---|---|---|---|---|
| Saxena et al. | 2003 | 10 | 0.86±0.59 | 0.75±0.52 | 3 |

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

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

| Study | Publication | Eyes (count) | FU-time (year) | ≥20/40 (%) | ≥ 20/30 (%) | ≥ 20/25 (%) | ≥20/20 (%) | 20/15 (%) | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Bouheraoua et al. | 2015 | 68 | 3 | 79.4 | - | - | 4.4 | - | |
| | | 68 | 5 | 82.3 | 65.5 | 23.5 | 5.9 | - | |
| Budo et al. | 2000 | 249 | 3 | 76.8 | - | - | 33.7 | - | |
| Landesz et al. | 2000 | 67 | - | 40.9 | 33.3 | 15.2 | 12.1 | | |
| Moshirfar et al. | 2007 | 85 | 2 | 84 | - | 34 | - | - | |
| Qasem et al. | 2010 | 68 | 2 | 85* | 65* | - | 29* | - | *data from graph, numbers are estimated 17.9% ACRS |
| | | 30 | 3 | 72* | 60* | - | 18* | - | *data from graph, numbers are estimated 17.9% ACRS |
| | | 16 | 4 | 57* | 32* | - | 7* | - | *data from graph, numbers are estimated 17.9% ACRS |
| | | 11 | 5 | 45* | 37* | - | 9* | - | *data from graph, numbers are estimated 17.9% ACRS |
| Shajari et al. | 2016 | 95 | 4 | 92* | - | 76 | 53* | - | *data from graph, numbers are estimated |
| Silva et al. | 2008 | 20 | 3 | 85 | 85* | 77* | 60 | - | *data from graph, numbers are estimated |
| | | 19 | 5 | 94.7 | 90* | 74* | 73.7 | - | *data from graph, numbers are estimated |
| Stulting et al. | 2008 | 356 | 2 | 87.1 | 71.7 | 54.8 | 34.6 | 4.8 | |
| | | 231 | 3 | 83.9 | 70.9 | 51.9 | 31.1 | 4.3 | |
| Tahzib et al. | 2007 | 89 | 6 | 78.7 | - | - | - | - | |
| | | - | 10 | 82 | - | - | - | - | |

| Study | Publication | Eyes (count) | FU-time (year) | ≥20/40 (%) | ≥ 20/30 (%) | ≥ 20/25 (%) | ≥20/20 (%) | 20/15 (%) | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Titiyal, et al. | 2012 | 51 | 2 | 68.6 | | | 15.7 | | |
| | | 51 | 3 | 66.7 | | | 15.7 | | |
| | | 51 | 4 | 68.6 | - | - | 13.7 | - | |
| | | 28 | 5 | 64.3 | - | - | 21.4 | - | |
| Yuan et al. | 2011 | 84 | 3 | 100 | 100 | 85.7 | 60.7 | - | |
| | | 84 | 5 | 100 | 95.2 | 85.7 | 39.3 | - | |

- = 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 (%) | ≥ 20/25 (%) | ≥20/20 (%) | 20/15 (%) | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Qasem et al. | 2010 | 6 | 2 | 100* | 100* | - | 50* | - | data from graph, numbers are estimated |
| | | 2 | 3 | 100* | 100* | - | 50* | - | data from graph, numbers are estimated |

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

**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**

| 21.049 mm | 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 |

# Appendix 4.

**Endothelial Cell Change in Myopic Eyes - Part 1**

| Study | Publication | FU-time (year) | EC change (%) | Adjusted EC change (%) | Eyes (count) | EC change from | Notes |
|---|---|---|---|---|---|---|---|
| Aerts et al. | 2015 | 2 | 2.1 ±0.9 | - | 262 | 6 months | |
| Benedetti et al. | 2005 | 2 | 5.4 | - | 93 | baseline | |
| Benedetti et al. | 2007 | 2 | 4.7 | - | - | baseline | |
| | | 3 | 6.7 | - | - | baseline | |
| | | 4 | 8.3 | - | - | baseline | |
| | | 5 | 9.0 | - | - | baseline | |
| Bohac et al. | 2016 | 3 | 0.97* | - | 166 (out of 198) | baseline | * EC loss annually |
| Bouheraoua et al. | 2015 | 2 | 11.26 | - | 68 | baseline | |
| | | 3 | 11.96 | - | 68 | baseline | |
| | | 4 | 14.58 | - | 68 | baseline | |
| | | 5 | 15.15 | - | 68 | baseline | |
| Budo et al. | 2000 | 2 | 1.7 | - | 129 subgroup (out of 518) | baseline | |
| | | 3 | 0.7 | - | 129 subgroup (out of 518) | baseline | |
| Chebli et al. | 2018 | 2 | 0.87* | - | 101 (out of 113) | 1 year | calculated with mixed model, * EC loss annually |
| | | 5 | 0.87* | - | 63 (out of 113) | 1 year | calculated with mixed model, * EC loss annually |
| | | 7 | 0.87* | - | 44 (out of 113) | 1 year | calculated with mixed model, * EC loss annually |
| | | 10 | 0.87* | - | 16 (out of 113) | 1 year | calculated with mixed model, * EC loss annually |

| Study | Publication | FU-time (year) | EC change (%) | Adjusted EC change (%) | Eyes (count) | EC change from | Notes |
|---|---|---|---|---|---|---|---|
| Choi et al. | 2014 | 2 | 1.32 | - | 63 (out of 66) | baseline | |
| | | 3 | 2.14 | - | 53 (out of 66) | baseline | |
| | | 4 | 3.44 | - | 53 (out of 66) | baseline | |
| | | 5 | 3 | - | 52 (out of 66) | baseline | |
| | | 6 | 3.33 | - | 42 (out of 66) | baseline | |
| | | 7 | 5.43 | - | 45 (out of 66) | baseline | |
| | | 8 | 4.91 | - | 43 (out of 66) | baseline | |
| | | 9 | 7.38 | - | 20 (out of 66) | baseline | |
| | | 10 | 22.5 | - | 6 (out of 66) | baseline | |
| Guell et al. - group 1 | 2008 | 2 | 10.1 | - | 80 (out of 97) | baseline | |
| | | 3 | 7.4 | - | 68 (out of 95) | baseline | |
| | | 4 | 1.5 | - | 93 (out of 93) | baseline | |
| | | 5 | 11.3 | - | 88 (out of 89) | baseline | |
| Guell et al. - group 2 | 2008 | 2 | 5.11 | - | 136 (out of 170) | baseline | |
| | | 3 | 8.57 | - | 150 (out of 168) | baseline | |
| | | 4 | 2.07 | - | 155 (out of 168) | baseline | |
| | | 5 | 10.9 | - | 165 (out of 166) | baseline | |
| Jonker et al. | 2018 | 5 | 7.9 | 5.2* | 193 (out of 381) | 6 months | calculated with linear mixed model, * ECC loss adjusted for 0,6% physiological cell loss per year |
| | | 5 | 4.1 | - | 193 (out of 381) | baseline | direct subgroup analysis |
| | | 10 | 16.6 | 10.9* | 127 (out of 381) | 6 months | calculated with linear mixed model, * ECC loss adjusted for 0,6% physiological cell loss per year |
| | | 10 | 11.5 | - | 127 (out of 381) | baseline | direct subgroup analysis, as normally done |

| Study | Publication | FU-time (year) | EC change (%) | Adjusted EC change (%) | Eyes (count) | EC change from | Notes |
|---|---|---|---|---|---|---|---|
| Landesz et al. | 2000 | 2 | - | 9.1±8.9* | 67 (out of 67) | baseline | * ECC loss adjusted for 0,6% physiological cell loss per year |
| | | 3 | - | 10.9±8.6* | 61 (out of 67) | baseline | * ECC loss adjusted for 0,6% physiological cell loss per year |
| Landesz et al. | 2001 | 2 | n.r. | n.r. | 10 (out of 91) | - | |
| Menezo et al. | 2004 | 2 | 7.63 | - | 61 | baseline | also older Worst-Fechner IOL was used, but no significant difference in ECC loss between old and new pIOL group |
| | | 5 | 10.51 | - | 61 | baseline | also older Worst-Fechner IOL was used, but no significant difference in ECC loss between old and new pIOL group |
| Moshirfar et al. | 2014 | - | - | - | - | - | |
| Moshirfar et al. | 2007 | 2 | 6±10.75 | 4.80±10.7* | n.s. (out of 56) | baseline | * ECC loss adjusted for 0,5% physiological cell loss per year |
| Na et al. | 2013 | 2 | -0.26 ±14.69 | -0.27±17.32* | 40 (out of 52) | baseline | * ECC loss adjusted for 0,6% physiological cell loss per year, gain in ECC was found |
| Pop et al. | 2004 | 2 | -0.75 ±17.41* | 0.42±17.41* | 293 (out of 765) | baseline | * ECC loss adjusted for 0,6% physiological cell loss per year |
| Qasem et al. | 2010 | 2 | 1.33$^{\delta}$ | - | 84$^{\delta}$ | - | $^{\delta}$data including 6 hyperopic eyes and 10 toric pIOL eyes |
| | | 3 | 2.22$^{\delta}$ | - | 38$^{\delta}$ | - | $^{\delta}$data including 2 hyperopic eyes and 6 toric pIOL eyes |
| | | 5 | 0 | - | 11 (out of 151) | - | |

| Study | Publication | FU-time (year) | EC change (%) | Adjusted EC change (%) | Eyes (count) | EC change from | Notes |
|---|---|---|---|---|---|---|---|
| Saxena et al. | 2008 | 2 | 0.8 | -0.4* | 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 |
| | | 3 | 2.2 | 0.4* | 122 (out of 318) | baseline | data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment |
| | | 4 | 6.5 | 4.1* | 69 (out of 318) | baseline | data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment |
| | | 5 | 8.3 | 5.3* | 51 (out of 318) | baseline | data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment |
| | | 6 | 9.1 | 5.5* | 28 (out of 318) | baseline | data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment |
| | | 7 | 12.6 | 8.5* | 13 (out of 318) | baseline | data including 57 myopic toric and 17 myopic Artiflex lenses; *0,6% physiological loss adjustment |
| Senthil et al. | 2006 | 2 | 6.38 | - | 60 (out of 60) | - | |
| Shajari et al. | 2016 | 2 | 6.2 | - | 78 (out of 95) | - | |
| | | 3 | 8.8 | - | 67 (out of 95) | - | |
| | | 4 | 11 | - | 95 (out of 95) | - | |
| Silva et al. | 2008 | 3 | 9.98 ±16.86 | - | 20 (out of 26) | baseline | |
| | | 5 | 14.05 ±21.39 | - | 16 (out of 26) | baseline | |
| Stulting et al. | 2008 | 2 | 1.43±9.5 | - | 57 (consistent cohort) | baseline | |
| | | 3 | 4.8 ±7.8 | - | 107 | baseline | |
| | | 3 | 3.8 ±9.8 | - | 57 (consistent cohort) | baseline | |

| Study | Publication | FU-time (year) | EC change (%) | Adjusted EC change (%) | Eyes (count) | EC change from | Notes |
|---|---|---|---|---|---|---|---|
| Tahzib et al. | 2007 | 6 | - | -3.26±18.96* | 89 (out of 89) | baseline | * ECC loss adjusted for 0,6% physiological cell loss per year, gain in ECC was found |
| | | 10 | - | -8.86±16.01* | 89 (out of 89) | baseline | * ECC loss adjusted for 0,6% physiological cell loss per year, gain in ECC was found |
| Titiyal et al. | 2012 | 2 | 9.26 | - | 51 (constant cohort) | - | |
| | | 3 | 11.07 | - | 51 (constant cohort) | - | |
| | | 4 | 12.48 | - | 51 (constant cohort) | - | |
| | | 5 | 15.59 | - | 28 (out of 85) | - | |
| Yasa et al. | 2016 | 2 | 0.3 | - | 62 (out of 62) | 6 months | |
| Yuan et al. | 2011 | 2 | 7.8 | - | 84 | baseline | |
| | | 3 | 2.9 | - | 84 | baseline | |
| | | 4 | 1.5 | - | 84 | baseline | |
| | | 5 | <1.5 | - | 84 | baseline | |

- = 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) | pre-op ECC (cells/mm²) | post-op ECC (cells/mm²) | Notes |
|---|---|---|---|---|---|---|---|
| Aerts et al. | 2015 | 2 | - | 3.6±0.34 | - | - | |
| Asano-Kato et al. | 2005 | 2 | 3.0 epi | - | 2831±304 | 2750±284 | |
| Benedetti et al. | 2005 | 2 | 3.0 ( n.r. epi or endo) | - | 2658±360 | 2514±305 | |
| Benedetti et al. | 2007 | 2 | 3.0 ( n.r. epi or endo) | - | 2616±347 | 2493±277 | |
| | | 3 | 3.0 ( n.r. epi or endo) | - | 2616±347 | 2441±349 | |
| | | 4 | 3.0 ( n.r. epi or endo) | - | 2616±347 | 2398±347 | |
| | | 5 | 3.0 ( n.r. epi or endo) | - | 2616±347 | 2379±344 | |
| Bohac et al. | 2016 | 3 | 2.8 endo | 3.35±0.36 | 2613 ±185 | around 2400* | * data from graph, number is estimated |
| Bouheraoua et al. | 2015 | 2 | 3.0 epi | 3.44±0.41 | 2629±366 | 2341±314 | |
| | | 3 | 3.0 epi | 3.44±0.41 | 2629±366 | 2324±366 | |
| | | 4 | 3.0 epi | 3.44±0.41 | 2629±366 | 2263±354 | |
| | | 5 | 3.0 epi | 3.44±0.41 | 2629±366 | 2250±454 | |
| Budo et al. | 2000 | 2 | 3.0 (n.r. epi or endo) | 3.38±0.71 | 2876±410 | 2626±424 | |
| | | 3 | 3.0 ( n.r. epi or endo) | 3.38±0.71 | 2876±410 | 2607±442 | |
| Chebli et al. | 2018 | 2 | 3.0 endo | 3.42±0.26 | 2770±265 | - | |
| | | 5 | 3.0 endo | 3.42±0.26 | 2770±265 | - | |
| | | 7 | 3.0 endo | 3.42±0.26 | 2770±265 | - | |
| | | 10 | 3.0 endo | 3.42±0.26 | 2770±265 | - | |
| Choi et al. | 2014 | 2 | 3.0 endo | 3.76±0.22 | 2853±249 | 2815±252 | |
| | | 3 | 3.0 endo | 3.76±0.22 | 2853±249 | 2792±292 | |
| | | 4 | 3.0 endo | 3.76±0.22 | 2853±249 | 2755±366 | |
| | | 5 | 3.0 endo | 3.76±0.22 | 2853±249 | 2767±257 | |
| | | 6 | 3.0 endo | 3.76±0.22 | 2853±249 | 2758±311 | |
| | | 7 | 3.0 endo | 3.76±0.22 | 2853±249 | 2698±300 | |
| | | 8 | 3.0 endo | 3.76±0.22 | 2853±249 | 2713±355 | |
| | | 9 | 3.0 endo | 3.76±0.22 | 2853±249 | 2642±434 | |
| | | 10 | 3.0 endo | 3.76±0.22 | 2853±249 | 2211±146 | |

| Study | Publication | FU time (year) | minimum ACD (mm) | mean ACD (mm) | pre-op ECC (cells/mm²) | post-op ECC (cells/mm²) | Notes |
|---|---|---|---|---|---|---|---|
| Guell et al. - group 1 | 2008 | 2 | 3.2 epi | - | 2836±398 | 2548±398 | |
| | | 3 | 3.2 epi | - | 2836±398 | 2625±447 | |
| | | 4 | 3.2 epi | - | 2836±398 | 2791±246 | |
| | | 5 | 3.2 epi | - | 2836±398 | 2514±529 | |
| Guell et al. - group 2 | 2008 | 2 | 3.2 epi | - | 2755±362 | 2614±469 | |
| | | 3 | 3.2 epi | - | 2755±362 | 2519±372 | |
| | | 4 | 3.2 epi | - | 2755±362 | 2698±576 | |
| | | 5 | 3.2 epi | - | 2755±362 | 2454±588 | |
| Jonker et al. | 2017 | 5 | 2.8 endo | 3.86±0.34 | 2670±359 | 2588±425 | |
| | | 10 | 2.8 endo | 3.86±0.34 | 2670±359 | 2302±451 | |
| | | 5 | 2.8 endo | 3.86±0.34 | 2670±359 | 2588±425 | |
| | | 10 | 2.8 endo | 3.86±0.34 | 2670±359 | 2302±451 | |
| Landesz et al. | 2000 | 2 | - | 3.7 | - | - | |
| Landesz et al. | 2001 | 2 | 3.2 ( n.r. epi or endo) | 2 . 9 - 4 . 5 range | 2857 | 3049 | 1 patient (2 eyes) with ACD of 2.9 & 3.1mm was implanted with IF-pIOL |
| Menezo et al. | 2004 | 2 | 3.2 ( n.r. epi or endo) | 3.41±0.12 | - | - | also older Worst-Fechner IOL was used, but no significant difference in ECC loss between old and new pIOL group |
| | | 5 | 3.2 ( n.r. epi or endo) | 3.41±0.12 | - | - | also older Worst-Fechner IOL was used, but no significant difference in ECC loss between old and new pIOL group |
| Moshifar et al. | 2014 | | - | - | - | - | - |
| Moshirfar et al. | 2007 | 2 | 3.2 ( n.r. epi or endo) | - | 2713±361 | 2534±394 | * ECC loss adjusted for 0,5% physiological EC loss per year |
| Na et al. | 2013 | 2 | 3.0 ( n.r. epi or endo) | - | 2984±357 | 2847±445 | * ECC loss adjusted for 0,6% physiological EC loss per year |
| Pop et al. | 2004 | 2 | - | - | 2631±422 | 2577±495 | |

| Study | Publication | FU time (year) | minimum ACD (mm) | mean ACD (mm) | pre-op ECC (cells/mm²) | post-op ECC (cells/mm²) | Notes |
|---|---|---|---|---|---|---|---|
| Qasem et al. | 2010 | 2 | 3.2 ( n.r. epi or endo) | - | 3171±456 | - | |
| | | 3 | 3.2 ( n.r. epi or endo) | - | 3171±456 | - | |
| | | 4 | 3.2 ( n.r. epi or endo) | - | 3171±456 | - | |
| | | 5 | 3.2 ( n.r. epi or endo) | - | 3171±456 | - | |
| Saxena et al. | 2008 | 2 | 2.6 epi | 3.70±0.30 | 2817±356 | 2777±376 | data including 57 myopic toric and 17 myopic Artiflex lenses |
| | | 3 | 2.6 epi | 3.70±0.30 | 2817±356 | 2729±342 | data including 57 myopic toric and 17 myopic Artiflex lenses |
| | | 4 | 2.6 epi | 3.70±0.30 | 2817±356 | 2616±307 | data including 57 myopic toric and 17 myopic Artiflex lenses |
| | | 5 | 2.6 epi | 3.70±0.30 | 2817±356 | 2581±293 | data including 57 myopic toric and 17 myopic Artiflex lenses |
| | | 6 | 2.6 epi | 3.70±0.30 | 2817±356 | 2560±270 | data including 57 myopic toric and 17 myopic Artiflex lenses |
| | | 7 | 2.6 epi | 3.70±0.30 | 2817±356 | 2451±256 | data including 57 myopic toric and 17 myopic Artiflex lenses |
| Senthil et al. | 2006 | 2 | 2.9 ( n.r. epi of endo) | 3.24±0.24 | 2741±313 | 2566±315 | |
| Shajari et al. | 2016 | 4 | 2.6 ( n.r. epi or endo) | 3.11±0.40 | 2805±95 | 2497±329 | |
| | | 2 | 2.6 ( n.r. epi or endo) | 3.11±0.40 | 2805±95 | 2632 | |
| | | 3 | 2.6 ( n.r. epi or endo) | 3.11±0.40 | 2805±95 | 2559 | |
| Silva et al. | 2008 | 3 | 3.2 ( n.r. epi or endo) | 3.87±0.34 | 2481±291 | 2256±370 | |
| | | 5 | 3.2 ( n.r. epi or endo) | 3.87±0.34 | 2481±291 | 2156±495 | |
| 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 | 2817±359 | 2734±360 | |
| | | 10 | 3.0 ( n.r. epi or endo) | 3.30±0.28 | 2817±359 | 2800±292 | |

| Study | Publication | FU time (year) | minimum ACD (mm) | mean ACD (mm) | pre-op ECC (cells/mm²) | post-op ECC (cells/mm²) | Notes |
|---|---|---|---|---|---|---|---|
| Titiyal et al. | 2012 | 2 | 2.8 ( n.r. epi or endo) | 3.39±0.25 | 2858±313 | 2587±298 | constant cohort of 51 eyes |
| | | 3 | 2.8 ( n.r. epi or endo) | 3.39±0.25 | 2858±313 | 2536±281 | constant cohort of 51 eyes |
| | | 4 | 2.8 ( n.r. epi or endo) | 3.39±0.25 | 2858±313 | 2499±354 | constant cohort of 51 eyes |
| | | 5 | 2.8 ( n.r. epi or endo) | 3.39±0.25 | 2923±237 | 2462±258 | cohort of 28 eyes |
| Yasa et al. | 2016 | 2 | 3.0 endo | 3.4±0.2 | 2723±311 | 2612±264 | |
| 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; 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 (%) | Eyes (count) | EC loss from | Notes |
|---|---|---|---|---|---|---|---|
| Guell et al. | 2008 | 2 | 5.4% | - | 35 (out of 40) | baseline | |
| | | 3 | 8.4% | - | 34 (out of 39) | baseline | |
| | | 4 | 6.4% | - | 34 (out of 39) | baseline | |
| | | 5 | - | - | 28 (out of 33) | baseline | |
| Saxena et al. | 2003 | 2 | 8.5% | - | 15 (out of 26) | baseline | |
| | | 3 | 11.7% | 10.1% | 10 (out of 26) | baseline | EC loss adjusted for 0,6% physiological cell loss per year |

-= 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) | pre-op ECC (cells/mm²) | post-op ECC (cells/mm²) | Notes |
|---|---|---|---|---|---|---|---|
| Guell et al. | 2008 | 2 | 3.2 endo | - | 2735±355 | 2587±551 | |
| | | 3 | 3.2 endo | - | 2735±356 | 2505±508 | |
| | | 4 | 3.2 endo | - | 2735±357 | 2560±335 | |
| | | 5 | 3.2 endo | - | 2735±358 | - | |
| Saxena et al. | 2003 | 2 | 2.6 (n.r. epi or endo) | 3.25±0.25 | 2749±348 | 2611±472 | minimum required ACD was later changed to 3,0mm |
| | | 3 | 2.6 (n.r. epi or endo) | 3.25±0.25 | 2749±348 | 2471±372 | |

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

# Appendix 5.

**Secondary Surgical Interventions in myopic eyes implanted with an IF-pIOL**

| Study | Publication | Total eyes (count) | Eyes treated (count) | Treated (%) | Reasons |
|---|---|---|---|---|---|
| Asano-Kato et al. | 2005 | 44 | 0 | 0 | - |
| Baikoff et al. | 2005 | 137 | 1 | 0.7 | 1 eye (0.7%) pIOL exchange due to pigment dispersion, note study only reporting on pigment dispersion |
| Benedetti et al. | 2007 | 49 | 0 | 0 | - |
| Benedetti et al. | 2005 | 93 | 0 | 0 | - |
| Bohac et al. | 2016 | 198 | 1 | 0.5 | 4 eyes (2%) re-enclavation due to inadequate enclavation; 1 eye (0.5%) repositioning due to decentration after trauma (after 27 months) |
| Bouheraoua et al. | 2015 | 68 | 2 | 2.9 | 1 eye (1.4%) pIOL repositioning after 3 years; 1 eye (=1.4%) pIOL exchange due to refractive error |
| Budo et al. | 2000 | 249 | 22 | 8.8 | 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 |
| Chebli et al. | 2018 | 113 | 1 | 0.9 | 1 eye (0.81%) pIOL explantation due to EC loss (after 7 years) |
| Guell et al. | 2008 | 274 | 9 | 4.5 | 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) |
| Landesz et al. | 2000 | 67 | 1 | 0.9 | 1 eye repositioning due to decentration |
| Landesz et al. | 2001 | 78 | 6 | 0.9 | 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 |
| Menezo et al. | 2004 | 137 | 2 | 1.5 | 2 eyes (1.46%) pIOL explantation due to nuclear cataract (54.83±22.12 months, at patient age 53 and 56 years) |

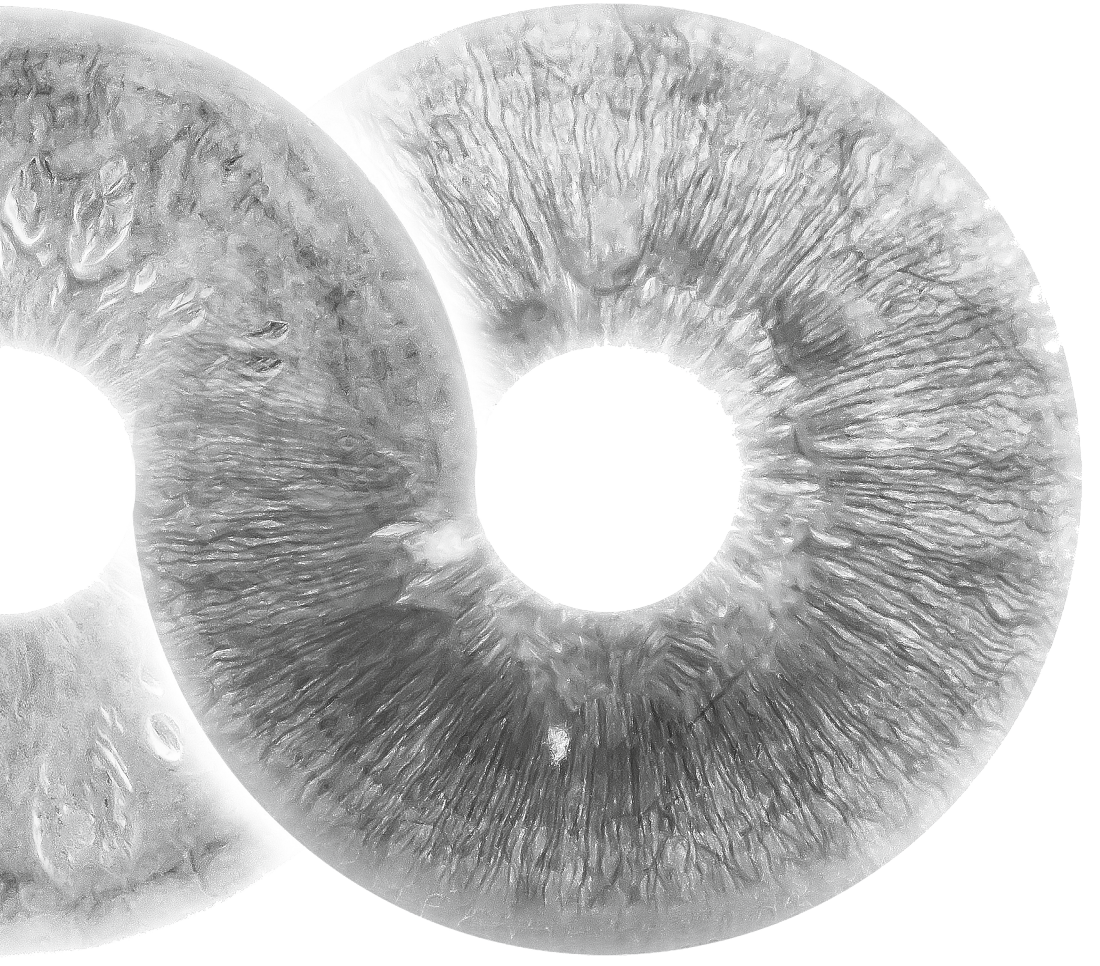
| Study | Publication | Total eyes (count) | Eyes treated (count) | Treated (%) | Reasons |
|---|---|---|---|---|---|
| Moshifar et al. | 2014 | 213 | 7 | 3.3 | 5 eyes (2.3%) pIOL explantation due to cataract (after mean of 9.3 years (R 4.0-12.6) at mean age of 55 years (R 46-62); 2 eyes (0.9%) corneal decompensation |
| Moshirfar et al. | 2007 | 85 | 5 | 5.9 | 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 |
| Qasem et al. | 2010 | 151 | 10 | 6.6 | 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 |
| Senthil et al. | 2006 | 60 | 3 | 5 | 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 |
| Shajari et al. | 2016 | 95 | 1 | 1.1 | 1 eye (1.1%) pIOL re-enclavation |
| Silva et al. | 2008 | 26 | 2 | 7.7 | 1 eye (3.88%) pIOL explantation due to cataract; 1 eye (3.8%) pIOL was explanted due to glare/ halo's |
| Stulting et al. | 2008 | 1179 | 41 | 3.5 | 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) |
| Tahzib et al. | 2007 | 89 | 3 | 3.4 | 1 eye (1.1%) ACRS; 2 eyes (2.2%) pIOL explantation cataract (at 6 years FU) |
| Titiyal, et al. | 2012 | 85 | 23 | 27.1 | 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)) |
| 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 (%) | Reasons |
|---|---|---|---|---|---|
| Baikoff et al. | 2005 | 136 | 3 | 2.2 | 3 eyes (2.2%) explanted due to severe pigment dispersion |
| Qasem et al. | 2010 | 14 | 4 | 28.6 | 4 eyes (28.6%) ACRS |
| Guell et al. | 2008 | 41 | 19 | 46 | 2 eyes (4.9%) pIOL exchange due to residual refractive error; 17 (41.4%) eyes ACRS |
| Saxena et al. | 2003 | 26 | 2 | 7.7 | 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) |

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



# CHAPTER 5.

## Differences between Scheimpflug and optical coherence tomography in determining safety distances in eyes with an iris-fixating phakic intra-ocular lens

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## 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 pre-operative screening for pIOL implantation and post-operative 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 pre-operative evaluation in combination with long-term post-operative 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 pre-operative 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 [11-13] and Scheimpflug imaging techniques [14-16] both provide high resolution images of the anterior chamber on which the pIOL position can be determined with provided software.

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. [17] and de Sousa et al. [18], he proposed a minimum distance of 1.5 mm to prevent accelerated EC loss. Later studies confirmed the importance of the central distance between the anterior surface of the pIOL and the endothelium [13,15,16,19], showing a yearly increase in EC loss with smaller distances. 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. [19] found smaller distances between the peripheral pIOL edge and endothelium to also be a significant risk factor for accelerated EC loss.

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 Optikgeräte) 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



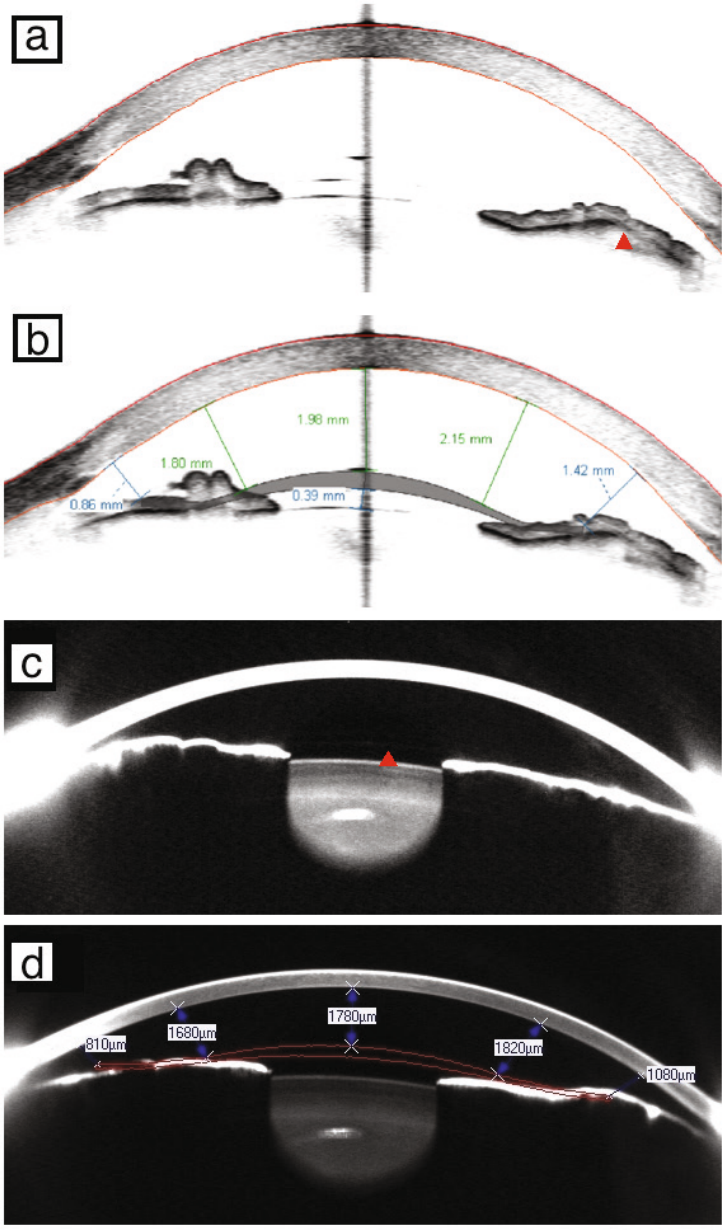
To determine the inter- and intra-observer variability, these analyses were performed separately by two independent, trained observers (ZSG, GAR). Both observers repeated the measurements at another time point, at least three months from the first measurements and without knowledge of the earlier results. 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.

**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.)



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]

## 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**.



**Table 1.** Patient characteristics

| Variable | Total | Hyperopic eyes | Myopic eyes |
|---|---|---|---|
| Eyes [count] | 62 | 25 (12 right eyes) | 37 (17 right eyes) |
| Sex (male:female) [%] | 32:68 | 64:36 | 11:89 |
| Age at examination ± SD (min-max) [years] | 49.6 ± 11.2 (24.9-76.6) | 52.6 ± 9.3 (24.9-67.4) | 47.6 ± 12.0 (25.9-76.6) |
| pIOL power ± SD (min-max) [D] | | 7.7 ± 2.6 (2.0-12.0) | -13.6 ± 4.6 (-23.5- -13.6) |
| Time interval between pIOL implantation and anterior segment examination ± SD (min-max) [years] | 9.7 ± 4.7 (0.0-18.0) | 9.8 ± 3.6 (0.0-14.0) | 9.5 ± 5.5 (0.0-18.0) |

SD: standard deviation; pIOL: phakic intraocular lens; D: diopters

### 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 Scheimplug imaging according to the Cohen's kappa classification [21], showing that a single measurement is reliable irrespective of observer or measurement occasion.

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

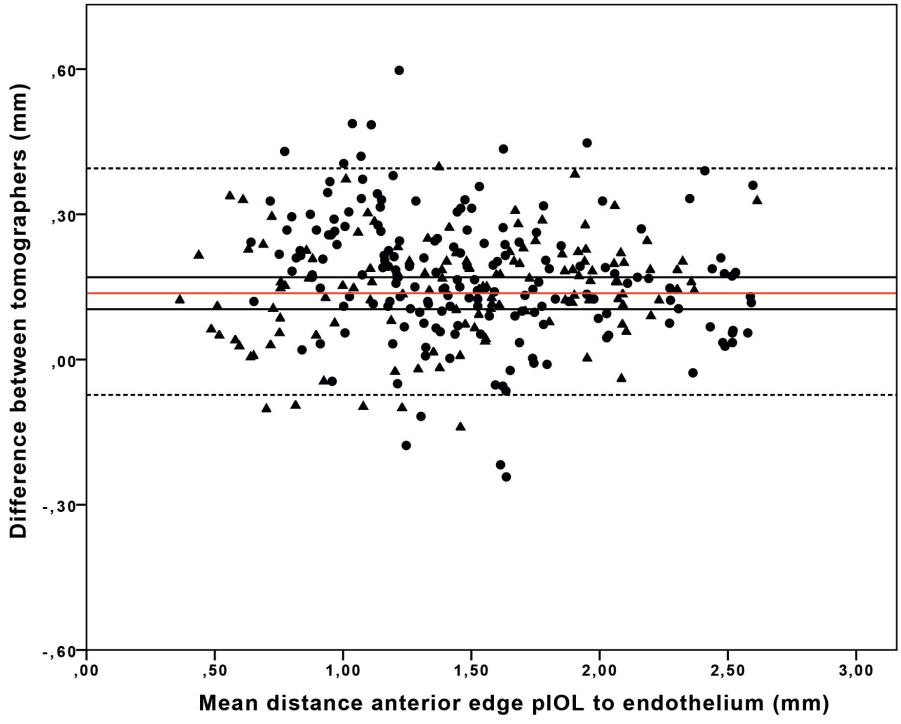
| | AS-OCT | | Scheimpflug imaging | |
|---|---|---|---|---|
| | ICC | | ICC | |
| | Inter-observer (95% CI) | Intra-observer (95% CI) | Inter-observer (95% CI) | Intra-observer (95% CI) |
| 4.0 mm nasal endothelium to pIOL | 0.944 (0.908-0.966) | 0.917 (0.882-0.942) | 0.890 (0.813-0.935) | 0.818 (0.740-0.873) |
| 2.5 mm nasal endothelium to pIOL | 0.969 (0.949-0.982) | 0.961 (0.944-0.972) | 0.958 (0.928-0.976) | 0.913 (0.875-0.939) |
| central endothelium to pIOL | 0.996 (0.994-0.998) | 0.909 (0.835-0.949) | 0.955 (0.910-0.976) | 0.991 (0.987-0.994) |
| 2.5 mm temporal endothelium to pIOL | 0.946 (0.911-0.968) | 0.930 (0.901-0.951) | 0.965 (0.940-0.979) | 0.944 (0.920-0.961) |
| 4.0 mm temporal endothelium to pIOL | 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: anterior segment optical coherence tomography; ICC: intraclass correlation coefficient; 95% CI: 95% confidence interval; pIOL: phakic intraocular lens

**Agreement between instruments**

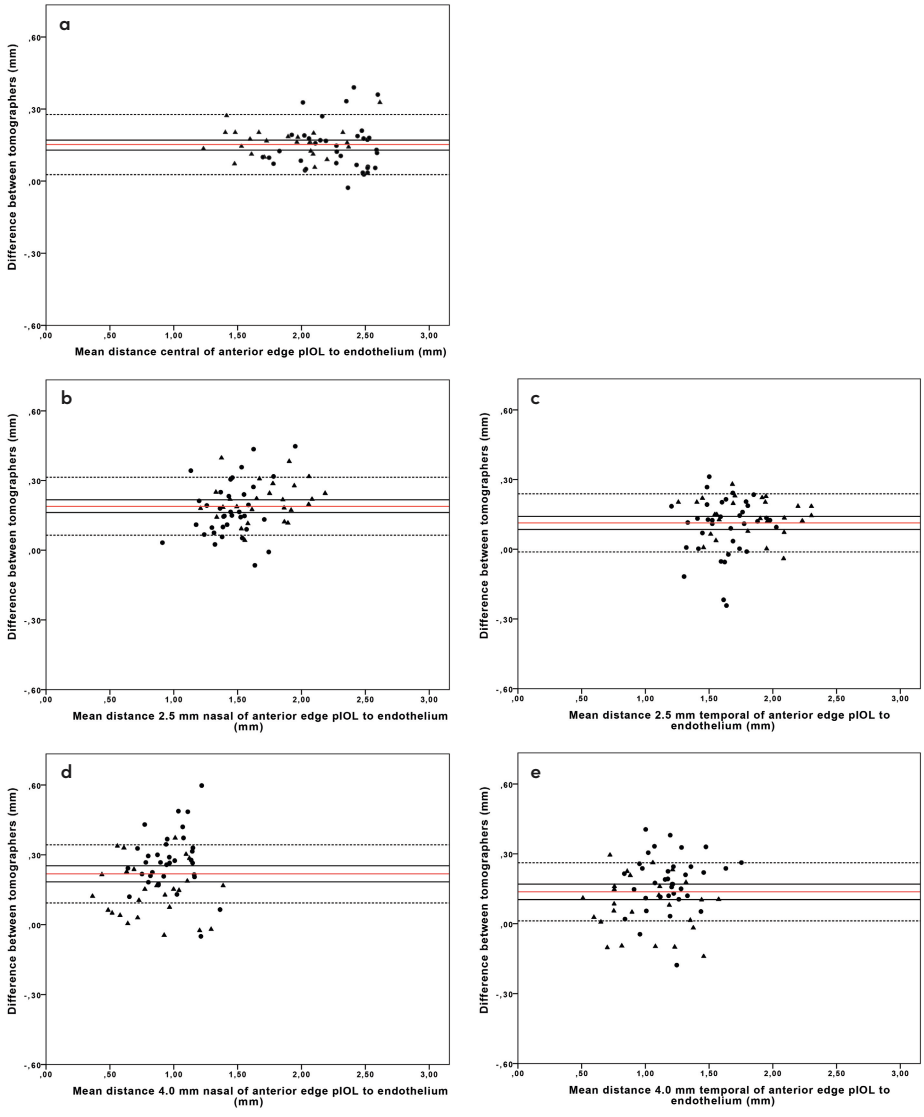
The distance from the anterior edge of the pIOL to the endothelium when measured by AS-OCT was consistently larger than when measured by Scheimpflug imaging, for all five separate positions, as listed in **Table 3**. The mean difference for all of the various positions was 0.161 (0.120) mm with a 95% 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.** 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.

**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 line 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.



**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 line 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.



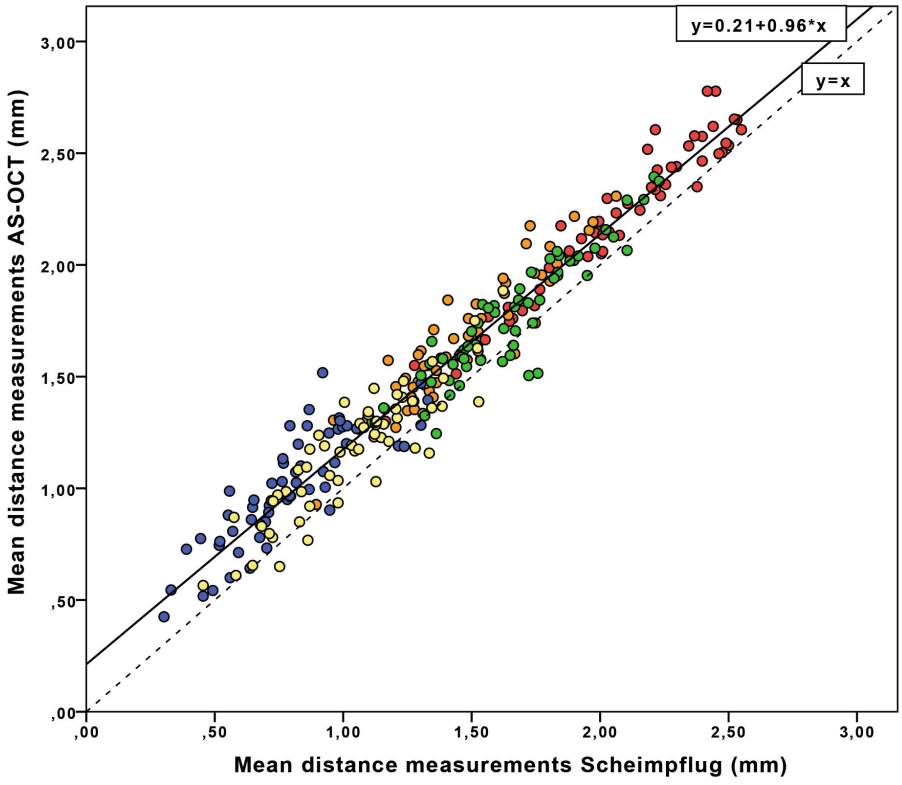
Subsequently, a general estimating equations (GEE) model was developed. In this model, we used the average of four repeated analyses (each analysis was acquired twice by both the first and the second observer) of the different distances with the average AS-OCT measurements as the dependent variable and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

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

*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.

**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 colours 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 nasal from the center; *blue:* 4.0 mm temporal 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[28] which might result in similar systematic differences in apparent pIOL-to-endothelium distances. 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 [11] 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. [12,13] evaluated pIOL clearances with the Visante OCT. Ferreira et al. [22] provided the clinicians with a new safety reference in 2014: a minimum *central* clearance distance of 1.7 mm, based on their Pentacam results. Recently, Jonker et al. [19] 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. 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 [22], when using AS-OCT. 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 Scheimplug 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.

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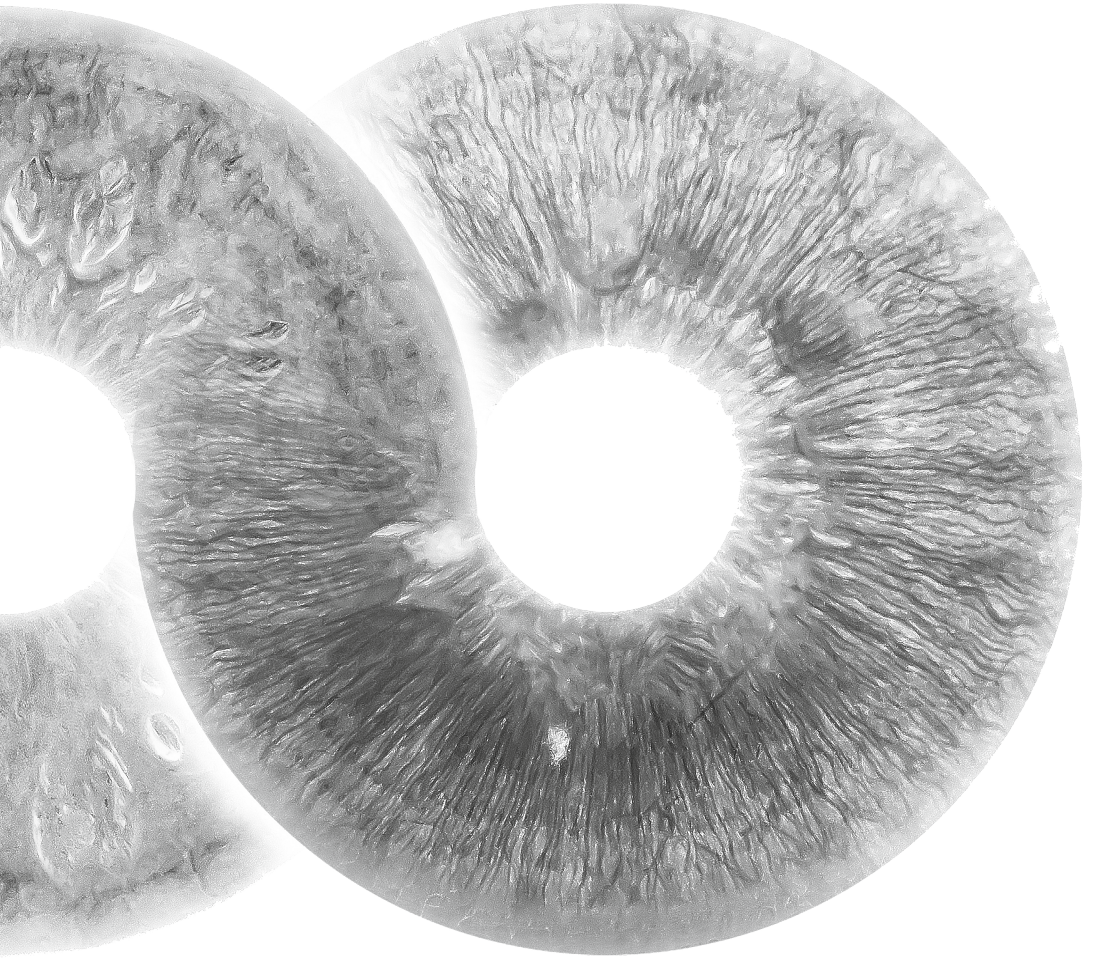

# CHAPTER 6.

## Long-term longitudinal changes in axial length in the Caucasian myopic and hyperopic population with a phakic intraocular lens

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## Abstract

Purpose: To determine the long-term longitudinal axial length changes in myopic and hyperopic adults with an iris-fixated phakic intraocular lens (pIOL).

Methods: The medical records of patients aged ≥ 18 years with myopia or hyperopia who were treated with pIOL implantation between 1996 and 2011 for refractive correction with a minimum follow-up of 5 years after pIOL implantation, were analyzed. The main outcome measure was change in ocular axial length over time.

Results: 149 eyes of 149 myopic patients and 27 hyperopic eyes of 27 patients were included in this study. Mean patients age was 37.1 ± 10.4 years (35% male) in the myopic group and 39.4 ± 9.4 years (4% male) in the hyperopic group. The eyes of the myopic patients showed a significant mean increase in axial length of 0.45 ± 0.61 mm after a mean follow-up time of 144 ± 38 months ($P < 0.001$). In 26 eyes (17%), the axial length had increased by ≥ 1 mm. The mean annual axial length increase was 0.04 ± 0.06 mm. Axial elongation was associated with a higher degree of myopia ($P < 0.001$) and younger age ($P = 0.02$). The eyes of the hyperopic patients showed no change in axial length over time.

Conclusions: Myopic eyes corrected with an iris-fixated pIOL show continuous increase in axial length at an adult age. Although this study is limited to subjects with a pIOL, this is the first time myopization in Caucasian adults has been reported in a large long-term longitudinal study.

## Introduction

Ocular axial length is the most important biometric value determining refractive errors. During the process of emmetropization in infancy, the axial length increases in line with the focal length of the eye's optics until it reaches the adult axial length at the age of 13 years, and is thought to remain stable thereafter [1,2]. It was not until the end of the nineteenth century that myopic shifts in adults were firstly described, but these refractive changes appear to primarily reflect changes in the optical power of the lens rather than in axial length [2]. Adults without cataract and with myopia, especially high myopia (at least -6 diopters), may show myopic progression, ultimately carrying risks of serious vision-threatening complications [3-5]. Given the increasing prevalence of myopia worldwide [6], a better understanding of the progression might help its prevention.

Ocular axial elongation has been reported in a few long-term longitudinal studies. In myopic Asian adults, yearly increase ranged from 0.04 to 0.30 mm with mean follow-up periods varying from two to eight years [5,7,8]. In Asian countries, (high) myopia is more prevalent than in Caucasian countries [9,10], but the ethnical differences in axial length progression are unknown. It might therefore be inaccurate to extrapolate the longitudinal findings on axial length progression to myopic adults in Caucasian countries or other regions outside of Asia. No longitudinal literature is available on axial length in adults with hyperopia.

High ametropia can successfully be corrected with phakic intraocular lens (pIOL) implantation. In our clinics, implantation of the phakic iris-fixating Artisan lens (Ophtec BV, Groningen, the Netherlands) has been performed since 1996.

The main purpose of this study is to assess long-term longitudinal axial length changes in myopes and hyperopes after phakic Artisan lens implantation. To our knowledge, this is the first study that solely focuses on long-term longitudinal data on axial length changes in Caucasian adults.

## Materials and methods

**Case selection**

This longitudinal observational study adhered to the tenets of the Declaration of Helsinki and was approved by the medical ethical committee of the Leiden University Medical Center (LUMC). Informed consent was obtained from all patients. Medical records from 1996 to 2018 were searched at our clinics for patients with a history of pIOL implantation for refractive correction of myopia or hyperopia and a follow-up time of ≥ 5 years after surgery. All surgeries were performed by one surgeon (GL) in two different clinics: Erasmus Medical Center, Rotterdam and LUMC, Leiden. If the patient had undergone pIOL implantation in both eyes, only one eye was randomly selected and included. If the medical history showed a second operation during follow-up, such as a cataract extraction, only the last data before the second surgery were used. The eyes were divided into two groups: myopes (patients corrected with Artisan Myopia Model 204 or 206 pIOL) and hyperopes (patients corrected with Artisan Hyperopia model 203 pIOL).

**Medical record review**

Detailed medical history was reviewed to gather information on the following: the axial length (AL) obtained by one experienced examiner with the immersion A-scan using the mean of three measurements (Alcon Biophysic OcuScan Version 3.02 Forth Worth, Texas, USA), Lenstar LS 900 (Haag-Streit AG, Koeniz, Switzerland) or IOLMaster (Carl Zeiss Meditec AG, Jena, Germany); spherical equivalent (SE); keratometry measured by automated keratometry (the average of dioptric power of the steepest and flattest meridian, $K_{avg}$, was calculated for analysis) using the Topcon RM-A2000 (Tokyo Optical Co., Tokyo, Japan) or Topcon KR8900 Ref (Tokyo Optical Co., Tokyo, Japan); central corneal thickness (CCT) and anterior chamber depth (ACD) measured by immersion A-scan and after 2003 by Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany). Measurements were recorded at the first preoperative visit and the last follow-up visit. For SE, in addition to the preoperative and the last measurement, also three months postoperative records were recorded and used for comparison with last visit SE. Furthermore, when present, fundus photographs taken at baseline were collected to record the presence or absence of posterior staphyloma in myopes. Using the International Photographic Classification and Grading System for Myopic Maculopathy [11], the photograph was carefully screened on features of posterior staphyloma by one examiner and either scored 'present' or 'absent'.

The primary endpoint was the change in AL over time. The secondary endpoint was to identify predictors of possible AL changes.

**Statistical analysis**

The myopic and the hyperopic study groups were analyzed separately with IBM SPSS Statistics version 25 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics, including means, standard deviations, proportions, and frequency distributions, were generated for subject characteristics. Scatter plots and box plots were used to visualize the data. The change of AL over time in each eye was analysed by examining the difference between preoperative and last visit AL measurement for statistical significance using the Wilcoxon signed rank test. In the majority of the study eyes, different biometry devices were used over time to obtain preoperative and last visit AL. To assess if the use of different biometry devices affected the AL measurements, the nonparametric Kruskal-Wallis Test (due to the limited sample size in the different groups) was performed to compare each combination of devices.

Univariate and multivariate regression analyses were used to assess possible predictors of AL changes including age, sex, right/left eye, SE at baseline, AL at baseline, $K_{avg}$, ACD, CCT and the presence of a staphyloma posterior. In addition, to compare AL change in myopic eyes with and without staphyloma posterior, an independent T-test was used.

The change in SE over time was analysed with a paired T-test (SE 3 months postoperative versus SE at last visit).

$P < 0.05$ was considered statistically significant.

## Results

**Patient characteristics**

**Table 1** shows demographic and clinical features of the study subjects in the two study groups. The myopic group included 149 eyes of 149 patients and the hyperopic group 27 eyes of 27 patients. The mean age was 37.1 ± 10.4 years and 39.4 ± 9.5 years in the myopic and hyperopic groups, respectively. The mean AL at the first visit was 28.06 ± 2.20 mm and 21.19 ± 0.81 mm, and the mean follow-up time was 144 ± 38 months and 146 ± 41 months, respectively. There were no significant differences in sex, age or postoperative SE or mean follow-up time between the two groups.

**Table 1.**
Patient characteristics

| Variable | Myopic group | Hyperopic group | P-value |
|---|---|---|---|
| Eyes (count) | 149 (77 right, 72 left) | 27 (13 right, 14 left) | |
| Sex (male:female, %) | 35:65 | 48:52 | 0.109 |
| Mean age at first visit ± SD (min-max, years) | 37.1 ± 10.4 (18-58) | 39.4 ± 9.4 (18-56) | 0.561 |
| Mean SE at first visit ± SD (min-max, D) | -12.26 ± 4.87 (-2.75 - -32.50) | +6.63 ± 1.77 (+1.75 - +10.50) | <0.001 |
| Mean SE 3 months after pIOL implantation ± SD (min-max, D) | -0.28 ± 0.83 (-6.63 - +1.00) | -0.11 ± 0.57 (-1.13 - +1.50) | 0.994 |
| Mean AL at first visit (min-max, mm) | 28.06±2.20 (24.80-37.27) | 21.18±0.81 (19.71-22.76) | <0.001 |
| Mean follow-up time ± SD (min-max, months) | 144 ± 38 (56-243) | 146 ± 41 (75-238) | 0.680 |

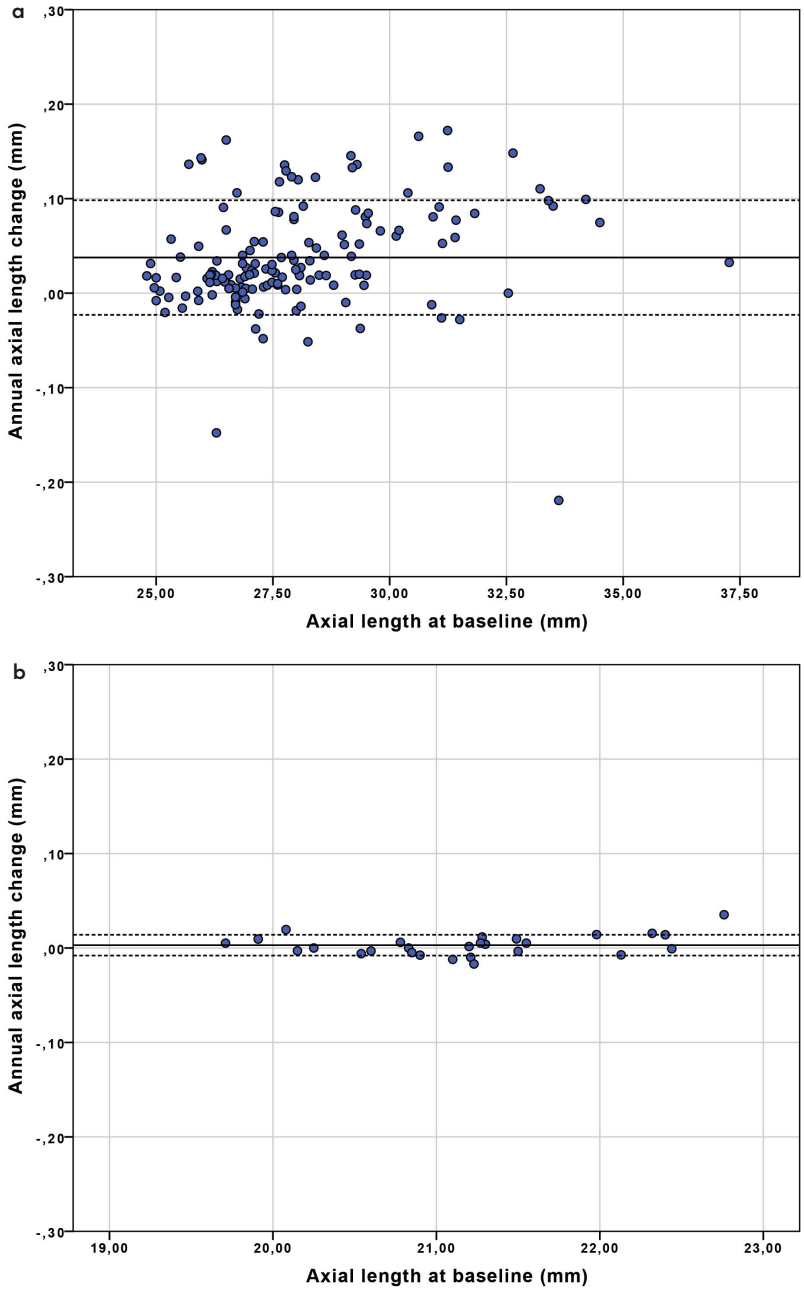
SE: spherical equivalent, SD: standard deviation, min: minimum, max: maximum, D: diopters, AL: axial length, mm: millimeters

### Axial length

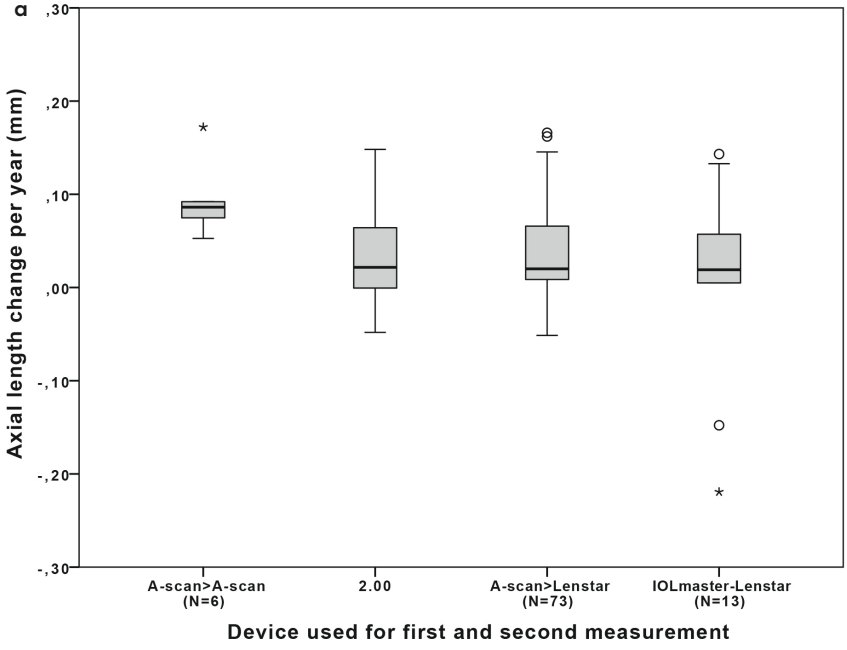
In the myopic group, a significant difference was found between the first and last visit AL measurement of 0.45 ± 0.61 after a mean follow-up time of 144 ± 38 months ($P < 0.001$). In 26 myopic eyes (17.4%), the AL had increased by ≥ 1 mm. The annual AL change was 0.038 ± 0.055 mm, inferring a 0.38 mm AL increase over a 10-year time span. In the hyperopic group, no significant difference was found between the first and last AL measurement ($P = 0.231$). As shown in the scatter plot in **Figure 1**, the AL increases over time in myopic eyes with a pIOL (A) and is stable in the hyperopic eyes with a pIOL (B).

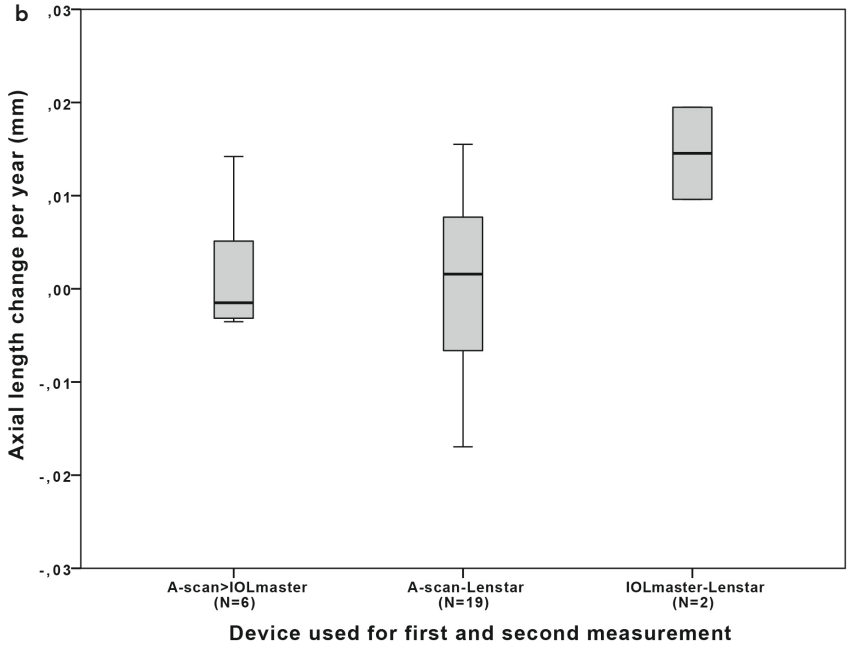
Different devices were used for the AL measurements made preoperatively and at final visit because of the more recent introduction of optical biometry. More than 90% of the preoperative AL measurements were obtained with the A-scan in both groups, in contrast to the AL measurements at the last visit, which were obtained with the Lenstar or IOLMaster in 95% of the cases in the myopic group and in all of the cases in the hyperopic group. The Kruskal-Wallis Test revealed no difference in AL change among the different combinations of device used for preoperative and final measurement in the myopic (Chi square = 8.25, $P = 0.083$, df = 4) and hyperopic group (Chi square = 3.10, $P = 0.213$, df = 2), as seen in **Supplementary figure 1**.

**Figure 1.**
Scatter plot showing differences in axial length (AL) changes over time in A) myopic eyes and B) hyperopic eyes with a pIOL in millimeters (mm). A positive difference responds to an increase in AL between the first and last measurement. *Black line*: mean. *Black dashed lines*: 95% confidence interval of the limits of agreement.



**Supplementary Figure 1.**
Box plot of axial length change for the different combinations of biometry device used for preoperative and final measurement in (A) myopic eyes and (B) hyperopic eyes.



**Risk factors for AL progression in myopia**

In order to identify the risk factors for AL change in myopic eyes with an pIOL, univariate and multivariate regression analyses were used to examine baseline variables affecting AL including age, sex, right/left eye, SE at baseline, AL at baseline, $K_{avg}$, ACD, CCT and the presence of a staphyloma posterior (**Table 2**). SE at baseline was found to be the most important risk factor for AL progression: eyes with higher degrees of myopia were associated with accelerated AL progression. A younger age was also a significant risk factor, although the effect on AL change was only small. The other factors were not found to be predictors for AL change. **Figure 2** shows a box plot of AL change per year for different age groups and axial length at baseline. The largest increase in AL over time is seen in the youngest group (16-30 years of age) with an AL of ≥ 30 mm at baseline.

In patients who had fundus photographs taken preoperatively (81 of 149 myopic eyes. Of these 81 eyes, 43 % had a posterior staphyloma and 57 % had a normal fundus. Univariate analysis showed posterior staphyloma to be a significant risk factor for AL progression (P = 0.024), but this variable was not included in the multivariate analysis because of a possible selection bias. An independent samples T-test showed no difference of AL change in the eyes with a staphyloma versus eyes without a staphyloma (P = 0.129).



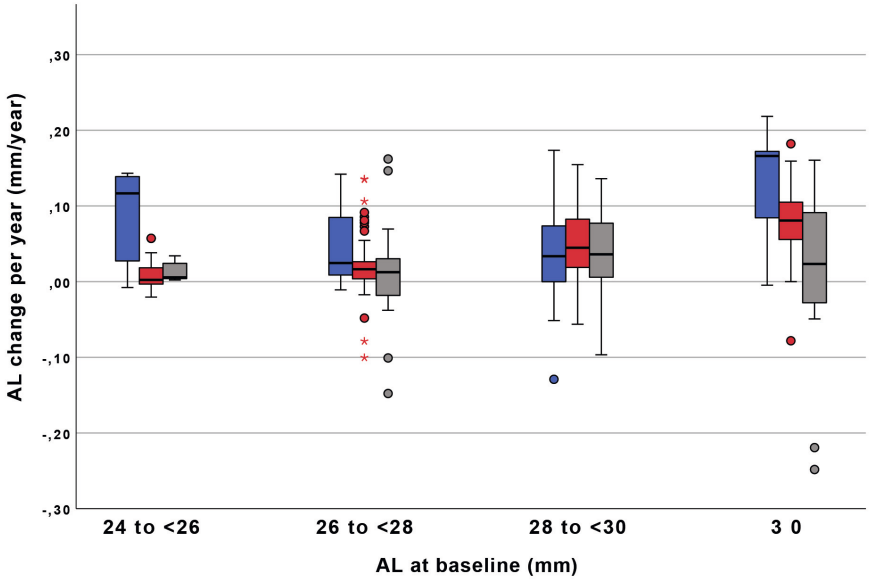
**Table 2.**
Univariate and multivariate analyses for axial length (AL) change in myopic eyes with a phakic intraocular lens.

| **Variables** | **Univariate Analysis** | | | **Multivariate Analysis** | | |
|---|---|---|---|---|---|---|
| | β coefficient | 95% CI | p-value | β coefficient | 95% CI | p-value |
| Age (years) | -0.001 | (-0.002;0.000) | **<0.001** | -0.001 | (-0.002;0.000) | **0.024** |
| Female sex | 0.010 | (-0.009;0.029) | 0.290 | | | |
| SE | -0.004 | (-0.005;-0.002) | **<0.001** | -0.003 | (-0.005;-0.001) | **<0.001** |
| AL at baseline | 0.007 | (0.004;0.010) | **<0.001** | | | |
| $K_{avg}$ (D) | 0.002 | (-0.003;0.008) | 0.577 | | | |
| ACD (mm) | 0.009 | (-0.016;0.034) | 0.482 | | | |
| CCT (µm) | 0.000 | (0.000;0.001) | **0.039** | 0.000 | (0.000;0.001) | **0.060** |
| Posterior staphyloma* | 0.023 | (0.003;0.042) | **0.024** | | | |

*Univariate analysis performed on 158 of 296 myopic eyes with a preoperative fundus photograph.

95% CI: 95% confidence interval SE: spherical equivalent, mm: millimeters, Kavg: average keratometry, D: diopters, ACD: anterior chamber depth, CCT: central corneal thickness, mm: millimeters, µm: micrometers

**Figure 2.**
Box plot showing axial length (AL) change per year in millimeters (mm) associated with axial length at baseline with respect to age at baseline. *blue*: 18-30 years, *red*: 31-45 years, *gray*: 46-60 years.




**AL progression and change in SE**

Myopic eyes showed a significant difference in SE of -0.24 ± 0.90 D ($P < 0.001$) between the first and second measurement over the mean follow-up of 144 ± 38 months using a paired T-test. The mean annual SE change was a myopisation of 0.07 ± 0.12 D per year and showed a moderate correlation with the annual AL increase ($P < 0.001$, Pearson's coefficient: -0.334).

There was no significant change in SE in the hyperopic group.

## Discussion

In this study, we investigated longitudinal changes in AL in adults with myopia and hyperopia, with an iris-fixated pIOL, during a mean follow-up time of 12 years. The myopic eyes were found to have significant AL elongation over time with a mean increase of 0.38 mm/10 years, but eyes with higher myopic errors tend to grow even more. The AL in hyperopic eyes did not change over time.

In literature, a few longitudinal studies on AL progression have been performed in myopic Asian adults: Saka et al. [5] found a median increase of AL per year of 0.08 mm (range, −0.16 to 0.43 mm/year) using A-scan ultrasonography in high myopes during a mean follow-up period of 8.2 years in 184 eyes, which is twice the increase we found in our study population. Similar to our findings, no difference in AL change was found between eyes with posterior staphyloma (58%) and those without. Using IOLMaster, Torii et al. [8] reported a similar rate of AL elongation of 0.38 mm/5 years in highly myopic adult patients without staphyloma posterior after pIOL implantation. Recently, Chen et al. [12] presented an even more dramatic increase in AL of 0.30 mm/year in Chinese adults with high myopia during a follow-up period of 5.4 years. However, the study group consisted of only 12 eyes of 7 patients with a higher degree of myopia (mean of -16.4 D), compared to our study population. Ohsugi et al. [7] reported significant axial elongation in myopic eyes with and without macular complications by using the IOLMaster. They examined four different groups: the non-highly myopic group, the group with no complications, the myopic traction maculopathy group, and the myopic choroidal neovascularization (CNV) group, with yearly AL changes of 0.007 ± 0.02 mm, 0.041 ± 0.05 mm, 0.040 ± 0.05 mm and 0.081 ± 0.04 mm, respectively. In this study, the rate of AL increase in the high myopic groups without CNV is similar to our myopic study population, although our patients were younger. In Caucasians, long-term longitudinal AL change was only earlier described by Jonker et al. [13] in a subset of Dutch patients after pIOL implantation. With a follow-up of up to 10 years, they reported an AL change of 0.11 mm/year in a subset of 24 eyes using optical biometry. The reason the previous studies reported more AL change is not clear. Our longer follow-up, bigger sample size and ethnical differences may have influenced the results.

The study of Ohsugi et al. [7] also mentioned the most important implication of AL progression in myopic adults, namely the development of visual impairment as a result of pathologic myopia. In particular, CNV eyes showed greater increases, indicating that larger changes in AL may require careful follow-up [7]. Also, in the myopic European population, longer AL is associated with visual impairment [14]. In our myopic study population, 17% of the eyes show an AL increase of ≥ 1 mm over time, and the most accelerated AL increase appears to occur in adults of 18-30 years with a baseline AL of ≥ 30 mm (Figure 2). These individuals who do not have myopic complications yet may have the greatest risk of developing visual impairment and may benefit from possible preventive therapies in future. With regards to the effect on refraction, the change in SE over time of -0.07 D we found in our study is smaller than average relation of -2.0 to -2.5 D per mm change in axial length, which can be attributed to the relatively long eyes in our myopic population [15,16].

In addition, our findings of accelerated AL change in younger adults, raises the question in what manner the rate of progression develops over time in highly myopic eyes. The 5-year AL changes, documented in the previously mentioned Asian studies[5,8,12], may suggest that a great part of AL increase occurs at a younger age. In our study, follow-up time (ranging from 5 up to 20 years) was not found to be a significant risk factor for AL elongation, which further support this hypothesis. To explore the exact process of AL progression over time, additional research on longitudinal AL changes measured at several time points is indicated.

Although this study is performed in Caucasian eyes with a pIOL, it is expected that these results can be extrapolated to the general Caucasian myopic and hyperopic population without pIOL. The results of our study show a stable AL in hyperopic patients with a similar pIOL and there is no known effect of Artisan pIOL implantation on the process of axial elongation from literature. Previous studies showed that changes in AL measurement before and after pIOL by A-scan are insignificant [17], while measurements by IOLMaster are described to be longer postoperative Artisan pIOL implantation with differences of 0.03 [18] to 0.12 mm [17]. However, the latter findings cannot explain the much greater difference of 0.45 mm, found in our study.

In myopic patients corrected with laser refractive surgery, such as laser-assisted in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK), myopic regression has widely been observed [19-22] and seems to increase with higher corrections [22]. Multiple factors may lead to myopic regression in these patients such as epithelial hyperplasia, changes in the biomechanical properties of the cornea and the increase of central corneal power [23,24]. Additionally, an increase in AL in these eyes may partially explain the myopic regression. More longitudinal studies are needed to examine this hypothesis.

In the univariate analysis, besides the degree of myopia and younger age, the presence of a staphyloma posterior was found to be a predictor of AL increase, though the extent of AL elongation did not differ between eyes without staphyloma and eyes with staphyloma. In the latter, especially in higher degrees of myopia, the sclera is often thinner than usual [25] and one might expect more elongation. Further in-depth studies are needed on the relation between posterior staphyloma and AL change, preferably using three-dimensional MRI or B-scan for more accurate identification of (types of) posterior staphyloma.

The exact aetiology of myopia progression in adults is not well understood. McBrien [25,26] states that there is an important role for the sclera in the development of myopia and progression towards pathologic myopia and the development of posterior staphyloma.

These changes are probably caused by both nature and nurture. Genome-wide association studies have provided evidence of genetic predisposition of AL and refraction [27]. In addition, environmental and behavioural factors, such as urbanization, education, socio-economic status, and near work, which have well-established links with AL elongation in children [28,29], may play a role in further elongation later in life.

Nevertheless, the fact that different biometers were used for the first and last AL measurement is a limitation of this study. This was unavoidable because the first data were collected more than 10 years ago when ultrasonography was the only clinical method available to measure AL. In our study, three different biometers were unavoidably used to measure AL throughout time. Though it is a limitation of our study, statistical analysis revealed no significant effect on our data in the myopic and hyperopic group. The fact that hyperopic eyes did not show AL changes, further support that the AL changes in myopic eyes cannot be explained by the use of different biometry devices. The IOLMaster and Lenstar strongly concur in measuring AL [30]. Although AL measurements made with the immersion A-scan also generally concur with those of the IOLMaster and Lenstar [31,32], there are some studies describing a difference of -0.11 to -0.25 mm [33-35]. Although this small difference might explain the negative AL changes in the myopic and hyperopic eyes (Figure 1), possibly caused by a misalignment of the A-scan probe, it is too small to explain the overall change in AL in the myopic group. This is further confirmed by the lack of any statistically significant change in AL in the hyperopic eyes. It is also noteworthy that the preoperative AL measurement was excluded from the multivariate analysis because of its high correlation with SE (Pierson correlation coefficient = -0,940 with $P < 0.001$).

In conclusion, Caucasian patients with myopia, corrected with an iris-fixated pIOL, show continuous AL elongation at an adult age. In 17% of the patients, ocular axial length growth was more than 1 mm over a mean time span of 12 years. The most important risk factor for AL progression is a higher degree of myopia, but also younger age was found to be a risk factor. The AL in hyperopic adults, corrected with an iris-fixated pIOL, remains stable over time. Despite the fact that all patients were corrected with a pIOL, we assume myopic eyes in general may elongate in the same manner.

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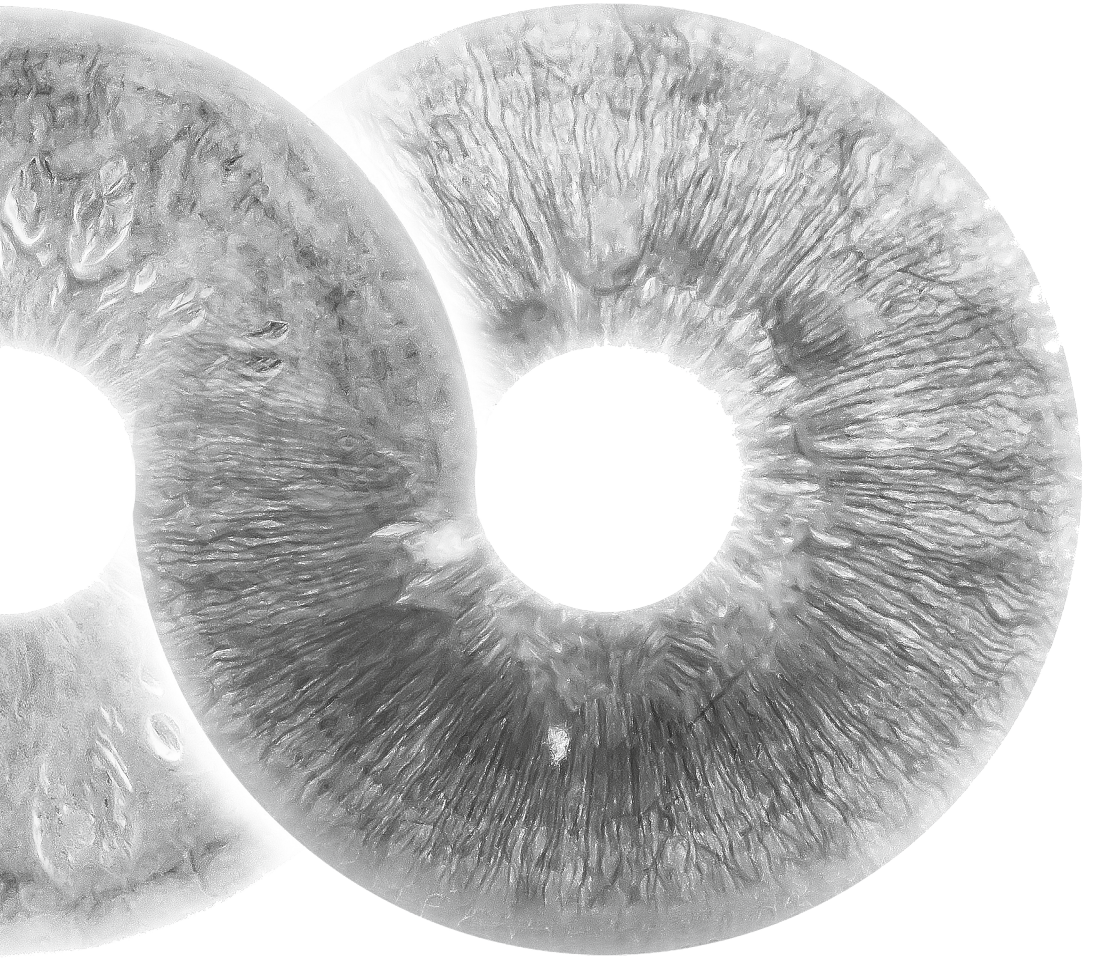

# CHAPTER 7.

## Two-year results after combined phaco-emulsification and iris-fixated phakic intraocular lens removal

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## Abstract

*Purpose:* To describe and present results after a technique for cataract surgery combined with explantation of an iris-fixated phakic intraocular lens (IF-pIOL).

*Methods:* The medical records of all patients, who had undergone cataract surgery combined with IF-pIOL explantation and subsequent implantation of a posterior chamber IOL by the Single Incision Technique (SIT), were reviewed. Data collection included preoperative and postoperative corrected distance visual acuity (CDVA), manifest refraction and endothelial cell density (ECD) up to a follow-up time of 24 months.

*Results:* 50 myopic eyes (34 patients) and 9 hyperopic eyes (6 patients) had undergone a SIT procedure mainly because of cataract (67%). Postoperative CDVA improved in both the myopic eyes to 0.16 ± 0.37 logMAR, as in the hyperopic eyes to -0.10 ± 0.55 logMAR with no eyes having loss of Snellen lines. Mean postoperative spherical equivalent was: -0.34 ± 0.72 D and -0.10 ± 0.55 D, respectively. ECD loss 6 months after surgery was 5% and remained stable thereafter.

*Conclusion:* SIT for combined phacoemulsification and IF-pIOL removal yields good visual and refractive results and is a safe procedure in regards to ECD loss. The technique has advantages over the conventional procedure and is easy to perform.

## Introduction

The implantation of a phakic intraocular lens (pIOL) allows treatment of (high) refractive errors, with the advantage of sparing the crystalline lens. One of the most common anterior chamber pIOLs is the iris-fixated (IF) Artisan pIOL[1] and has been demonstrated to be an effective, predictable and stable procedure for all models [1-3]. However, regular lifetime follow-up is needed, as increased endothelial cell density (ECD) loss remains a concern after any type of anterior chamber pIOL. Different studies have been demonstrated ECD loss to be the most important risk factor in patients with an IF-pIOL [4-8]. Excessive ECD loss and cataract formation are the main reasons for explantation of IF-pIOL. Explantation of the pIOL is then combined with phacoemulsification and placement of a posterior IOL[9,10]. This procedure carries the risk of additional ECD loss due to the phacoemulsification[11,12] and manipulation of the pIOL in the anterior chamber.

Most surgeons will first remove the IF-pIOL and sequentially perform the phacoemulsification through a separate incision, inserting a posterior chamber IOL in the capsular bag at the end[13,14]. Khokhar et al.[15] recently described an alternative surgical approach, which is already applied in our clinic since 2000. This technique consists of performing phacoemulsification underneath the pIOL through a main corneoscleral incision. The same incision is then further opened to remove the IF-pIOL as a last step before placing the posterior chamber IOL in the capsular bag. Using the latter technique, it is thought that the pIOL shields for ECD damage during cataract surgery and the anterior chamber is better maintained with less risk for iris prolapse during phacoemulsification.

In this study, we describe the surgical technique of performing cataract surgery underneath the pIOL in patients, previously treated with an (toric) Artisan or Artiflex (Ophtec BV) IF-pIOL and we present the safety and visual and refractive outcomes of this procedure.

## Methods

This retrospective case study adhered to the tenets of the Declaration of Helsinki and was approved by the medical ethical committee of the Leiden University Medical Center (LUMC). All eligible patients signed an informed consent. Medical records from our clinics were reviewed of all patients with a history of IF-pIOL implantation for refractive correction of myopia or hyperopia between 2000 and 2019 and who had undergone the Single Incision Technique for combined phacoemulsification, pIOL explantation and IOL implantation (hereafter referred as to "SIT") during follow-up. All SIT surgeries have been performed by an experienced surgeon (GL/YC) at the LUMC, Leiden. The pIOL used for refractive correction included the Artisan Myopia pIOL model 204 or 206, Artisan Hyperopia pIOL model 203, Artisan toric pIOL and Artiflex myopia pIOL. Calculation of posterior chamber IOL power was performed with the SRK/T formula [16], with the exception of short eyes (22.0 mm or shorter), for which the Holladay 2 formula was used [17]. The IOL model chosen for implantation depended on the availability and the surgeon's preference and included Tecnis ZCB00, PCB00, or ZA9003, and Sensar AR40 (Johnson&Johnson); AcrySof MA60MA and SA60AT (Alcon Laboratories); Bigbag (Carl Zeiss Meditec AG).

**Preoperative evaluation**

A detailed medical history was reviewed including patient's age at the time of the pIOL implantation and at the time of the SIT procedure, the type and power of pIOL implant, the indication for phacoemulsification, the type and power of posterior chamber IOL power implanted. Preoperative ocular examination included: corrected distance visual acuity (CDVA) determined using Snellen charts, manifest refraction, ECD measured by Topcon SP-2000P or Topcon SP-3000P noncontact specular microscope (Topcon Corporation). Data recorded on ECD included the ECD count (1) preoperative to pIOL implantation and (2) preoperative to the SIT and (3) postoperative to the SIT procedure. Preoperative axial length measurement was obtained with the Lenstar LS 900 (Haag-Streit AG) or IOLMaster (Carl Zeiss Meditec).

**Surgical technique**

**Video 1** (published online) shows the surgical procedure. After the pupil was fully dilated, the patient was prepped and draped. A main 3.0 mm limbal incision and 2 clear corneal side ports were created. The main incision was attempted to place at the steep axis to minimize postoperative astigmatism. The ophthalmic viscosurgical device (OVD) (Healon, Johnson & Johnson Vision Surgical) was injected into the anterior chamber to separate

the pIOL from the crystalline lens and a continuous curvilinear capsulorhexis was created using forceps, followed by hydrodissection, phacoemulsification and combined irrigation/aspiration (I/A). The OVD was then injected in the capsular bag, and anterior chamber. The main incision was then enlarged to 6.0 mm (except in the case of the Artiflex) and the pIOL was removed after de-enclavation of the haptics with the Budo forceps and disposable enclavation needle (Ophtec BV). Once the pIOL was removed, the posterior IOL was implanted in the capsular bag followed by closure of the main incision with one running or multiple intermittent 10-0 nylon sutures. Intraocular OVD was removed and the wounds were checked for closure. At the end of the surgery intracameral cefuroxime and parabulbar betamethasone was administered. All surgeries were performed under either general or local anesthesia.

**Postoperative management**

Follow-up examinations were typically scheduled at 1 month, 3 months, 6 months, 1 and 2 years. Postoperative examinations included CDVA and manifest refraction. Within the first 3 months, sutures were removed in case of residual corneal astigmatism. Postoperative ECD count was recorded at two follow-up points: within 6 months or between 6 to 24 months, to differentiate between ECD loss due to surgical trauma and ECD loss thereafter. For comparison of the ECD counts over time we applied the recently proposed method, described by van Rijn et al.[18], to correct for systematic differences as result of the use of these different microscopes,

**Statistical analysis**

Data was analyzed with IBM SPSS Statistics version 25 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were generated: quantitative variables were expressed in means and standard deviations; qualitative variables were expressed as percentages and proportions of the total number of cases. Histograms and line diagrams were used to visualize data.

For visual and refractive outcomes, myopic and hyperopic results were listed separately and data recorded at the last follow-up was used as postoperative value for comparative analysis. Decimal CDVA values were converted to logarithm of minimum angle of resolution (logMAR) notation for calculations. We used paired Student's *t* test to compare preoperative and postoperative visual acuity and refraction.

EC change was defined as the difference between the preoperative and postoperative examination and expressed as a percentage of the preoperative cell density. For analysis, a distinction is made between 2 groups: 1. eyes with low preoperative ECD (1000 cells/mm$^2$ or less) and 2. eyes with a preoperative ECD of above 1000 cells/mm$^2$. One-way analysis of variance (ANOVA) was used for overall comparison of the pre- and two postoperative ECD counts and post hoc comparisons were done with the Tukey test.

A p-value of $< 0.05$ was considered statistically significant.

## Results

**Patient characteristics**

SIT was performed in 59 eyes of 40 patients of which 50 myopic eyes (34 patients) and 9 hyperopic eyes (6 patients). Mean axial length was 29.1 ± 2.3 mm and 21.4 ± 0.6 mm, respectively. The age at time of the procedure was 56.1 ± 14.1 years, after having the pIOL in situ for 145 ± 60 months. Mean ECD count preoperative to pIOL implantation was 2644 ± 412 in the myopic eyes and 2834 ± 502 in the hyperopic eyes. Independent sample T-test showed no significant difference between these two groups ($p = 0.052$). Of the myopic eyes, 2 eyes had retinal detachment surgery during follow-up between pIOL implantation and cataract surgery. Overall, cataract was the main reason for the SIT procedure in 42 eyes (71 %), followed by EC loss in 17 eyes (29%). In the hyperopic eyes EC loss was the main reason (67%) for pIOL explantation and cataract extraction. The implanted spherical pIOL power was -12.2 ± 4.2 diopters (D) in the myopic and +7.6 ± 1.6 D in the hyperopic eyes. In 8 out of 50 myopic eyes and 2 out of 9 hyperopic eyes a toric Artisan and in 4 myopic eyes an Artiflex was implanted. The rest of the eyes were implanted with an Artisan lens model 203, 204 or 206. Target refraction for the posterior IOL was emmetropia, except for 4 myopic eyes. These patients had chosen a target refraction of -2.0 D. To reach target refraction, 4 myopic eyes had received a toric IOL; the remainder received a monofocal lens.

*Visual acuity and refraction*

**Table 1** shows the preoperative and postoperative clinical features of the study eyes at postoperative pIOL implantation and pre- and postoperative SIT.

Preoperative to the SIT procedure, both groups showed an overall myopization and improved CDVA.

**Table 1.**
Visual acuity and refractive results preoperative and postoperative Single incision technique

| Parameter | Postoperative pIOL | Preoperative SIT | Postoperative SIT |
|---|---|---|---|
| **Myopic eyes**<br>**N=50** | *Mean time to*<br>*SIT = 140 ± 62 months* | *Mean time to*<br>*SIT = 5 ± 7 months* | *Mean time from*<br>*SIT = 14 ± 9 months* |
| Mean CDVA (logMAR) | 0.08 ± 0.16 | 0.23 ± 0.40 | 0.09 ± 0.39* |
| Mean MRSE (D) | -0.59 ± 0.92 | -1.62 ± 1.84 | -0.34 ± 0.72** |
| Mean deviation SE from target refraction (D) | | | -0.08 ± 0.57 |
| SE refraction within ±0.5 D of intended (%) | | | 72 |
| SE refraction within ±1.0 D of intended (%) | | | 94 |
| **Hyperopic eyes**<br>**N=9** | *Mean time to*<br>*SIT = 172 ± 45 months* | *Mean time to*<br>*SIT = 7 ± 5 months* | *Mean time from*<br>*SIT = 18 ± 10 months* |
| CDVA (logMAR) | 0.07 ± 0.11 | 0.12 ± 0.18 | -0.02 ± 0.11* |
| MRSE (D) | -0.03 ± 0.64 | -0.59 ± 1.77 | -0.10 ± 0.55 |
| Mean deviation SE from target refraction (D) | | | -0.23 ± 0.34 |
| SE refraction within ±0.5 D of intended (%) | | | 89 |
| SE refraction within ±1.0 D of intended (%) | | | 100 |

CDVA: corrected distance visual acuity; D: diopters; logMAR: logarithm of minimum angle of resolution; MRSE: manifest refraction spherical equivalent; pIOL: phakic intraocular lens; SE: spherical equivalent; SIT: single incision technique.
* p-value <0.05, paired samples t-test pre- and postoperative SIT
** p-value <0.001, paired samples t-test pre- and postoperative SIT

Compared to preoperative results, the mean difference in CDVA in the myopic group was 0.16 ± 0.37 logMAR ($p$ = 0.003) and -0.05 ± 0.11 logMAR ($p$ = 0.210) in the hyperopic group (**Figure 1**). No eyes showed visual acuity loss of Snellen lines (**Figure 2**). A satisfactory mean manifest refraction spherical equivalent (MRSE) of -0.34 ± 0.72 logMAR and -0.10 ± 0.55 logMAR was achieved in myopic and hyperopic eyes, respectively. The MRSE was less myopic postoperatively, in both groups: -0.34 ± 0.72 D ($p$ < 0.001) and -0.10 ± 0.55 D ($p$ = 0.385), respectively (**Figure 3, 4**). Postoperative refractive cylinder was within ≤ 0.50 D in 24/50 eyes (48%) and ≤ 1.00 D in 33/50 eyes (66%); compared to 27% and 56% preoperatively.

**Figure 1.**
Preoperative (*grey bars*) and postoperative (*black bars*) corrected distance visual acuity (CDVA) after the Single Incision Technique of all eyes (N=59) showing an overall gain in postoperative CDVA.

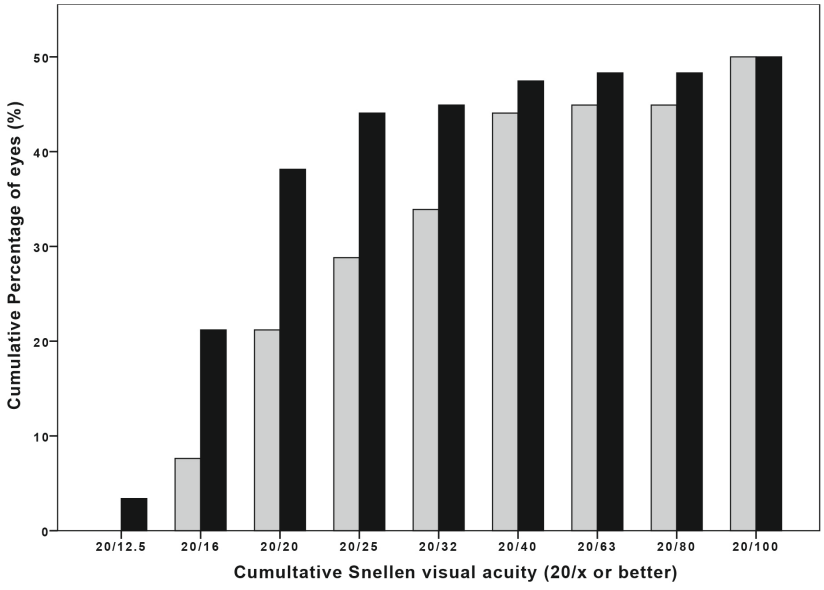



**Figure 2.**
Difference between preoperative and postoperative corrected distance visual acuity after the Single Incision Technique (N = 59) for myopic (*grey bars*) and hyperopic (*black bars*) eyes. No eyes showed loss of Snellen visual acuity lines.

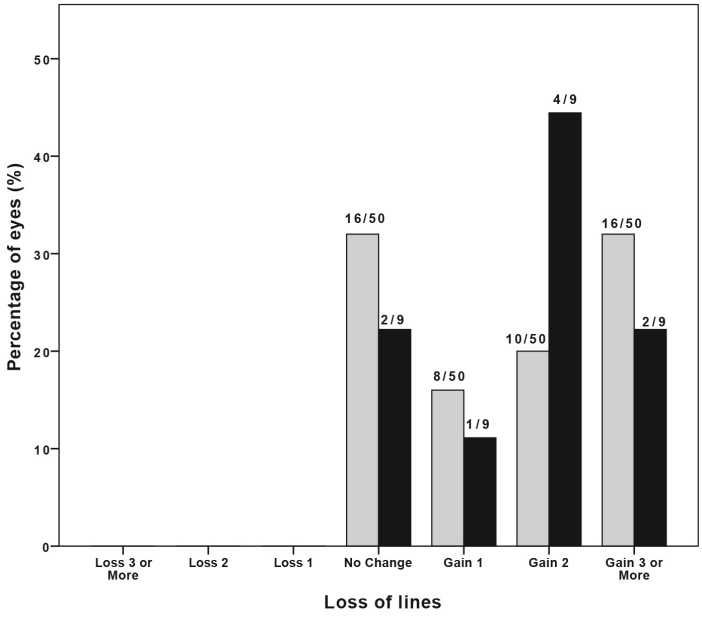


**Figure 3.**
Spherical equivalent (SE) refractive accuracy after the Single Incision Technique (N = 59) for all myopic (*grey bars*) and hyperopic (*black bars*) eyes. 94% of the myopic eyes and 100% of the hyperopic eyes reached SE refraction within ±1.0 D of intended.

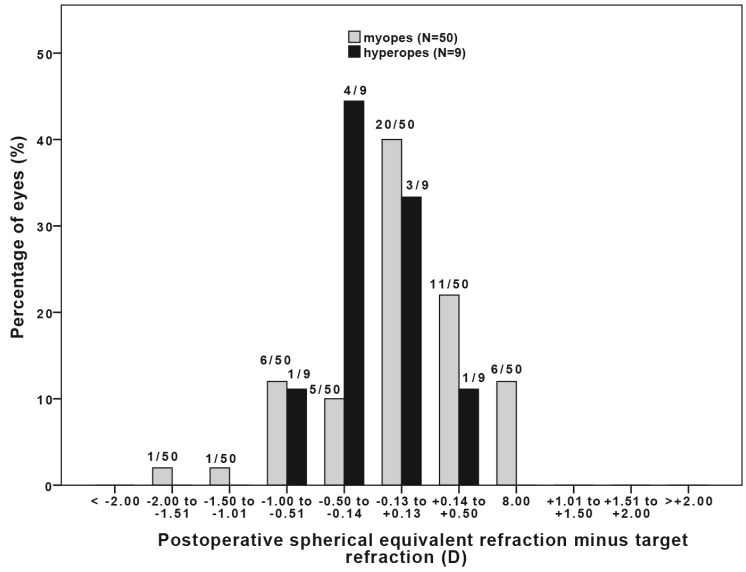
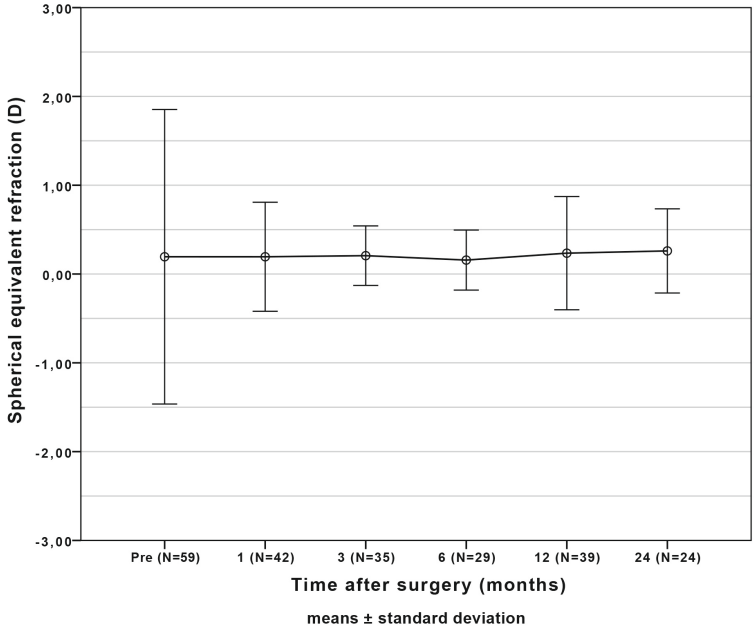



**Figure 4.**
Stability of spherical equivalent refraction of all eyes (N=59) showing stable postoperative refraction after the Single Incision Technique.



### Endothelial cell density

Overall postoperative ECD loss was -5.4 ± 11.8 % after 6 months and -9.4 ± 17.0 % after 6-24 months, compared to preoperative ECD. For a more detailed analysis of the ECD loss, a distinction is made between eyes with 1) a low preoperative ECD (less than 1000 cells/mm$^2$), 2) a preoperative ECD of 1000 to 1999 cells/mm$^2$ and 3) a preoperative ECD of 2000 or more cells/mm$^2$, as seen in **Table 2**. ECD loss developed within the first 6 months postoperative, to be interpreted as a result of surgical trauma, was -4.7 ± 12.0 % in the first group -4.0 ± 17.6 % in the second group and -3.5 ± 7.3 % in the third group. ECD loss developed 6 to 24 months postoperative was -0.8 ± 23.8 %, -16.8 ± 22.7 % and -7.7 ± 6.5 %, respectively (**Figure 5**). Using one-way ANOVA, there was no significant difference between the preoperative and postoperative ECD counts ($p$ = 0.100).

**Table 2.** Endothelial cell results preoperative and postoperative Single incision technique

| Parameter | Preoperative | Postoperative (6 months) | Postoperative (6-24 months) |
|---|---|---|---|
| **ECD < 1000 cells/mm$^2$** | **N=8** | **N=6** | **N=6** |
| Time interval to SIT (months) | -6 ± 4 | 3 ± 2 | 14 ± 5 |
| ECD (cells/mm$^2$) | 847 ± 148 | 785 ± 148 | 791 ± 138 |
| ECD loss (%) | | -8.3 ± 10.8 | -0.8 ± 23.8 |
| **ECD 1000 to 1999 cells/mm$^2$** | **N=21** | **N=11** | **N=11** |
| Time interval to SIT (months) | -7 ± 11 | 3 ± 2 | 15 ± 7 |
| ECD (cells/mm$^2$) | 1543 ± 355 | 1326 ± 385 | 1226 ± 339 |
| ECD loss (%) | | -4.0 ± 17.6 | -16.8 ± 22.7 |
| **ECD ≥ 2000 cells/mm$^2$** | **N=30** | **N=13** | **N=18** |
| Time interval to SIT (months) | -11 ± 14 | 4 ± 4 | 22 ± 10 |
| ECD (cells/mm$^2$) | 2466 ± 334 | 2269 ± 301 | 2260 ± 244 |
| ECD loss (%) | | -3.5 ± 7.3 | -7.7 ± 6.5 |

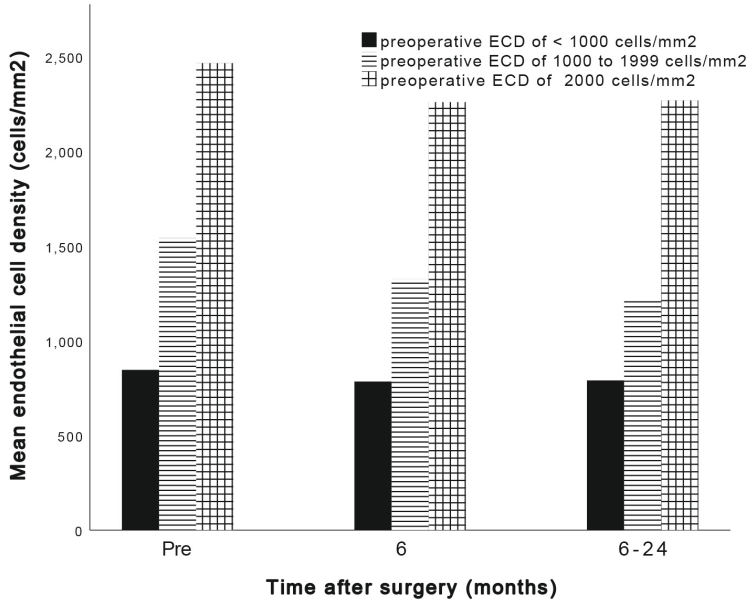
ECD: endothelial cell density; SIT: single incision technique

### Safety

The postoperative spherical equivalent of one eye (2%) deviated -1.78 D from target refraction. This concerned a patient with keratoconus after toric IF-pIOL implantation. At time of the SIT a monofocal IOL was placed. Because of this unsatisfactory refractive outcome, patient received an additional toric IF-pIOL 3 months after SIT, with good visual and refractive outcome.

Cataract surgery was complicated by a posterior capsular rupture in three eyes (5%) of which two eyes with vitreous loss. One myopic patient presented with a rhegmatogenous retinal detachment in one eye (2%) within 2 years after the SIT procedure.

**Figure 5.**
Bar graph of preoperative and postoperative endothelial cell density (ECD).




## Discussion

In this paper, we describe an alternative surgical approach, the SIT, for cataract removal in patients with an (toric) IF-pIOL in situ for myopia or hyperopia. We evaluated in 59 eyes the efficacy and safety including the course of EC loss of this technique during a follow-up of 2 years. All eyes had a stable or gain in CDVA post-SIT, no eyes had a loss of Snellen lines. The postoperative MRSE was stable during follow-up and was within ±1.00 D of intended refraction in 94.0% in the myopic and 100.0% in the hyperopic group. We found an acceptable ECD loss of less than 10% 6 months postoperative.

The main reasons for explantation of IF-pIOL in our study was formation of visually significant age-related cataract in myopic and ECD loss in hyperopic eyes. These findings are in line with previous literature [10,19,20]. Pigment dispersion has been reported as a complication of Artisan pIOL[21,22] and was present in one hyperopic eye but was not the reason for the SIT procedure. The results of removal of IF-pIOL, combined with phacoemulsification has been described in a study[13] by de Vries et al. who report a comparable effect in 36 eyes on CDVA and postoperative SE using the conventional surgical technique. That study found a smaller rate of ECD loss at 6 months of 3.5 ± 13.2 cells/mm$^2$. However, the endothelial damage after

routine cataract surgery in 'virgin' eyes are similar to our findings.[23,24] Comparable results on CDVA and postoperative SE are described in a more recent study by Vargas et al. [25] including 43 eyes. In this study the pIOL is removed through a scleral incision which was sutured before performing phacoemulsification through a 2.8 mm clear corneal incision. This study found significant postoperative ECD loss compared to preoperative of 20.7% ($p$ = 0.002). The larger amount of ECD loss in this study compared to our findings might be the result of a lower mean preoperative ECD mean ECD of 1408 cells/mm$^2$ compared to our study (1918 cells/mm$^2$). In our study we discuss the results of a combined procedure of pIOL explantation and phaco-emulsification. However, it is worth noticing that alternatively the pIOL explantation and phacoemulsification can also be performed in two individual sequential procedures. The advantages of this method are that it is less complex and phacoemulsification can be performed using sutureless incisions. The disadvantage is that it is more time-consuming and more burdensome for the patient.

To our knowledge, this retrospective study is the first to evaluate results of the SIT for combined phacoemulsification at which cataract is removed while the pIOL is still in situ. The procedure is easy to perform and has some advantages[15] over the conventional method. First of all, by performing the phacoemulsification through a 2.2-mm incision, anterior chamber stability is well controlled. Secondly, the OVD above and beneath the IF-pIOL protects the cornea endothelium during phacoemulsification.

Nevertheless, EC damage due to surgical trauma remains an important parameter for this procedure. Our results yielded an acceptable ECD loss due to surgical trauma, but some cases show unreal gains (and drops) in ECD as the result of measurement error. The reliability of EC analysis is a well-discussed topic[26-29] with count errors of up to 9% with the SP2000P[29]. In addition, in our study both the Topcon SP-2000P as the SP-3000P specular microscope was used during follow-up. We therefore applied the recently proposed method, described by van Rijn et al.[18], to correct for systematic differences as result of the use of these different microscopes.

It should further be noted that a bigger sample size and a prospective study design, would improve the strength of our findings. Typically, patients missed some of the follow-up visits. To still optimally analyze the available data, data of the last available postoperative follow-up visit was used for comparison. Furthermore, it is noteworthy that patients with pIOL having cataract surgery followed by pars plana vitrectomy at the same day due to

retinal detachment were not included in this analysis as the retinal surgeons did not use the described SIT procedure.

In conclusion, it can be stated that phacoemulsification beneath the IF-pIOL is an effective and safe procedure in regards for patients in need of IF-pIOL removal. Good visual outcomes, predictable refractive outcomes and acceptable ECD loss at 6 months of less than 10% are achieved. The technique is easy to perform and has the advantages over conventional combined surgery that the pIOL functions as a protective shield for the endothelium and the anterior chamber is better maintained.

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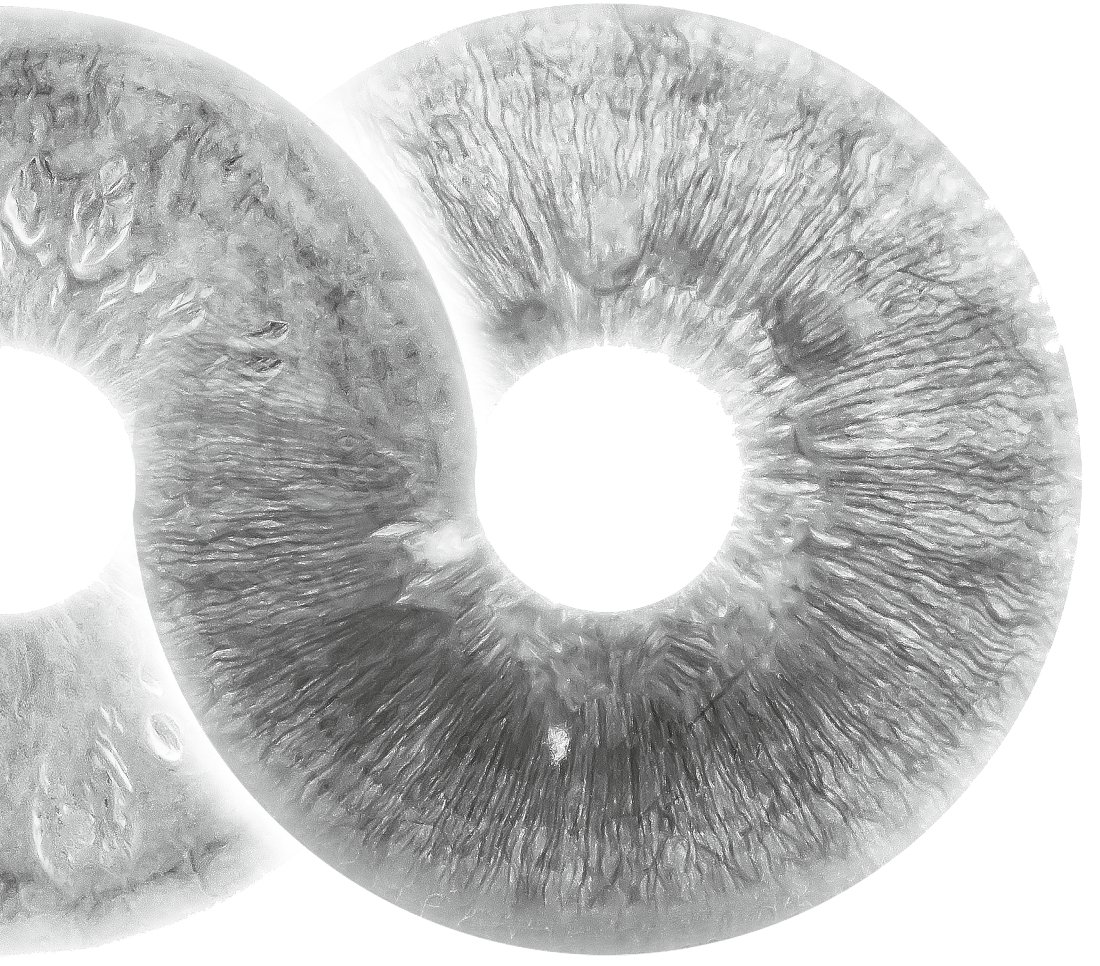


# CHAPTER 8.

Summary

Myopia (nearsightedness) is one of the most common diseases of the eye. Myopia causes impaired vision which can be corrected with glasses, contact lenses or refractive (laser) surgery. Wearing corrective eye glasses for a high refractive power can be very disabling for patients, both in the case of high myopia and high hyperopia (farsightedness). This is mainly due to the image distortion that these glasses induce. For the group of patients who are not qualified for correction by contact lenses or refractive laser surgery, it is possible to implant an artificial correction lens in the eye, while preserving the natural crystalline lens. This dissertation describes clinical aspects that are important when applying this treatment method: implantation of the phakic iris-fixated intraocular Artisan lens in myopic and hyperopic patients. Professor Jan Worst from Groningen introduced this iris-fixated anterior eye chamber lens in 1978. This lens is currently widely used in the Netherlands for multiple applications where correction of high refractive errors is a common indication. Since 1996, the Artisan lens has been implanted in this group of patients at the Erasmus Medical Center and Leiden University Medical Center. The follow-up of these patients in recent decades has given us valuable knowledge about the process from implantation to the removal of the Artisan lens.

**Chapter 1,** the introduction of this thesis, describes through a fictitious case the path that a patient with a high refractive error typically follows, from implantation of an Artisan lens to the removal of the lens. Topics such as the development of a refractive error and the current treatment options are discussed. This chapter also covers the indications for implanting the iris-fixated phakic lens and gives an overview of other relevant examinations and anterior segment imaging, which are important parts of the process. The most common reasons for lens explantation are also described.

In order to better understand which biometric factors are most important for the existence of a refractive disorder, the correlations between the main different anatomical structures in the eye, as described in the literature, are explained in **Chapter 2**. A total of 26 articles were used for a meta-analysis to describe the following correlations: the correlation between ocular axial length and refractive error; anterior chamber depth and refractive error; ocular axial length and anterior chamber depth; corneal curvature and refractive error; corneal curvature and ocular axial length. Each correlation was analyzed by using a pooled correlation coefficient. The size of this number showed whether there is a strong ($r \geq 0.6$), average ($0.4 \leq r < 0.6$) or weak ($r < 0.4$) correlation. As expected, we found a strong correlation between ocular axial length and refractive error ($r = 0.67$; 95% CI: 0.76, 0.56). With an increase of 1 mm in eye axis length, the refractive error decreased on average

by 2.3 diopter. Patients with a deeper anterior chamber also had a longer axial length. These 2 factors were found to have an average correlation (r = 0.49; 95% CI:0.04, 0.58). In addition, the anterior chamber depth also increased, to a weaker extent, the higher the myopic refraction was (r = 0.28; 95% CI: 0.45, 0.08). At present, what limited literature there is describes the little to no influence of corneal curvature on refractive error. This chapter provides an appendix containing a detailed overview of the literature used in this review. Although the statistical model used for this meta-analysis corrects the heterogeneity of the data (different research populations and equipment), it is important to highlight its possible impact on the results. Moreover, it is important to mention that the correlations described in this chapter also depend on multiple external factors, such as age (for example, due to the formation of cataract), ethnicity and gender.

**Chapter 3** discusses the effect of refractive correction on the degree of straylight. Straylight does not so much affect visual acuity but can have a great disabling effect on the quality of vision. An increase in light scattering is particularly seen in imperfections in media, for example in the case of unclean contact lenses or post-refractive laser surgery. This chapter describes the effect of refractive correction with glasses and contact lenses on the degree of light scattering. This was measured in both an emmetropic and a myopic patient group, each consisting of 30 eyes from 15 patients. In the first group, the effect of glasses and contact lenses of varying negatively powered lenses on straylight was measured. In the second group, the effect of negatively powered glasses and contact lenses was measured. The increase in straylight resulting from correction with highly negative glasses and lenses appears to be negligible and is not visually disturbing.



**Chapter 4** gives a complete overview of the medium and long-term (2-10 year) results of the iris-fixated phakic Artisan lens for the correction of hyperopia and myopia described in literature. In this systematic review, the postoperative outcomes of a total of 5523 myopic (29 studies) and 217 hyperopic eyes (4 studies) are presented, including the refractive and visual results, endothelial cell loss and safety. In a pooled group of 1602 eyes, refraction fell to within 1.0 D of the intended target refraction in 65% to 93% of the eyes. The pooled median of the percentage of myopic eyes with an uncorrected visual acuity of 20/40 or better was 87% after 2 years (560 eyes) and 82% after 5 years (210 eyes). The only study with hyperopic eyes (14 eyes) reported an uncorrected visual acuity of 20/30 or better in 100% of the eyes after 2 and 3 years of follow-up. With regard to endothelial cell loss, the existing studies show varying results. In studies with a follow-up of more than 7 years, endothelial cell loss was between 4.9% and 22.5%. The most common reason for pIOL explantation in

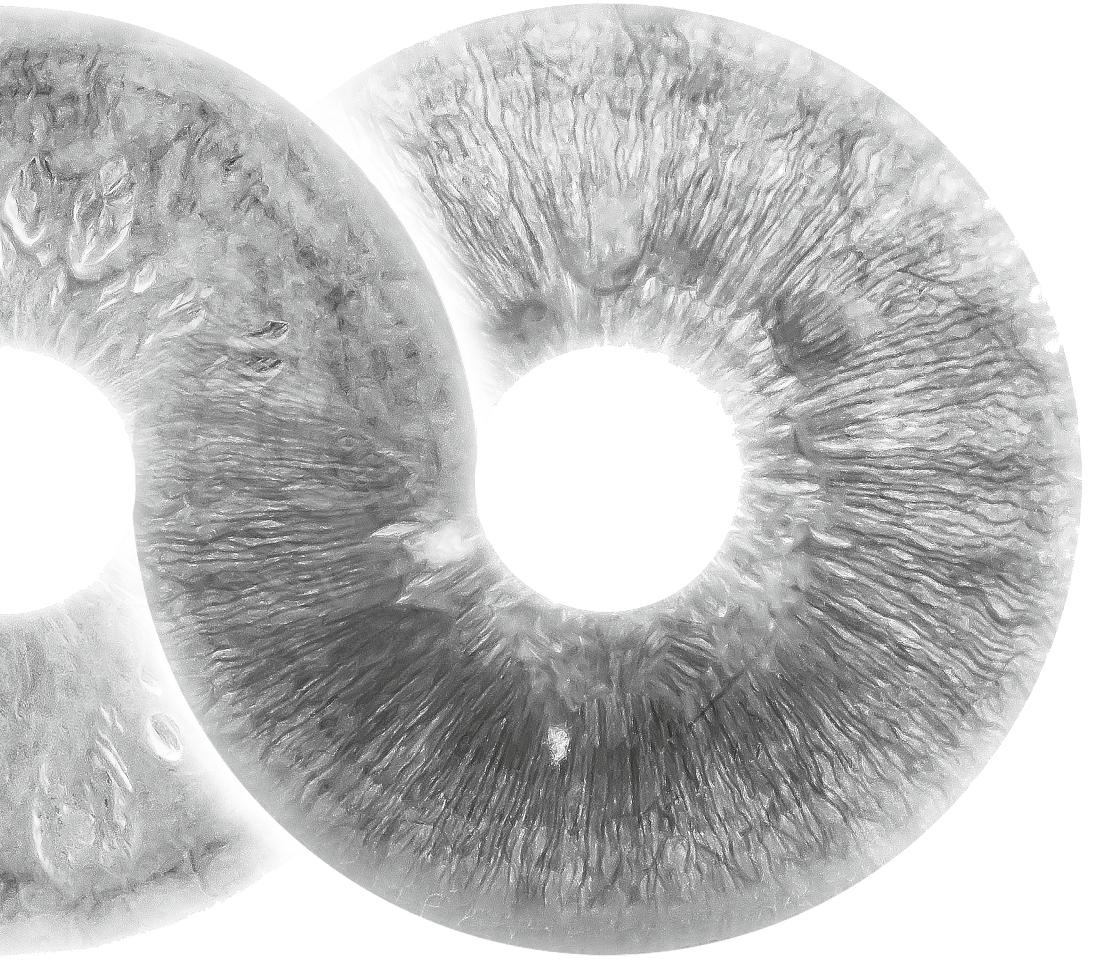
the myopic eyes was cataract. In 0.0% to 0.9% of the eyes, the pIOL was removed due to endothelial cell loss. In the hyperopic eyes, the most common reason for pIOL explantation was posterior synechiae and pigment deposition. In conclusion, the phakic Artisan lens is a suitable treatment for (high) myopia, with excellent visual and refractive outcomes and minimal risk of complications. There is no firm conclusion to be drawn about the impact of pIOL on endothelial cell loss given the discordant results. This therefore emphasizes the importance of regular follow-up. More long-term studies are needed for the hyperopic phakic Artisan lens.

**Chapter 5** describes the measurement of the minimum distance between the corneal endothelium and the anterior part of the phakic Artisan lens. In addition to the anterior chamber depth, this measurement is used to estimate the risk of increasing endothelial cell loss. To measure this distance, 2 modalities are currently being used: Scheimpflug imaging and anterior segment OCT. In this study, 62 eyes implanted with a phakic iris-fixated pIOL – 25 of which were hyperopic and 37 myopic – were scanned with both modalities. The distance between the endothelium and the pIOL was measured at 5 different positions by 2 different researchers using the provided software. The 5 positions were: central, 2.5 mm nasal and temporal, 4.0 mm nasal and temporal. For all positions, a significant difference was found between the 2 devices, with the anterior segment OCT measurements being 0.11 to 0.22 mm larger than with Scheimpflug imaging. Good intra- and inter-observer reliability was found with both modalities. The difference between the devices is clinically significant, and therefore interchangeability is not recommended. A formula is proposed for conversion between the 2 devices.

**Chapter 6** describes the long-term changes in ocular axial length of adults with a phakic iris-fixated pIOL for correction of myopia and hyperopia. The axial length of 290 myopic eyes (149 patients) and 53 hyperopic eyes (27 patients) was measured at 2 time points. In the myopic eyes, an increase in axial length was found of 0.44 ± 0.67 mm ($P < 0.001$) after an average follow-up of 12 years. In 55 eyes (19%), the axial length had increased by more than 1 mm over time. The axial length increase was mainly observed in younger patients with higher degrees of myopia. The axial length of hyperopic eyes remained stable over time.

**Chapter 7** introduces the Single Incision Technique (SIT), an alternative surgical technique to remove the iris-fixated phakic pIOL in combination with cataract extraction. Phacoemulsification is first carried out under the pIOL, after which the pIOL is removed and the posterior IOL is inserted. The theoretical advantage of this technique over the conventional method is

that the pIOL functions as a protective shield for the endothelium. Moreover, by using a 3.0 mm main port, a more stable anterior chamber can be achieved with phacoemulsification. The SIT was performed in 50 myopic eyes (34 patients) and 9 hyperopic eyes (6 patients). Postoperative corrected visual acuity was 0.16 ± 0.37 logMAR in the myopic eyes and -0.10 ± 0.55 logMAR in the hyperopic eyes. The average postoperative spherical equivalent was -0.34 ± 0.72 D and -0.10 ± 0.55 D, respectively. Six months after the procedure, an endothelial cell loss of 5% was observed which remained stable during a follow-up period of 2 years. These results are equivalent to the results of the conventional surgical technique.



# CHAPTER 9.

## Dutch summary

Myopie (bijziendheid) is een van de meest voorkomende aandoeningen van het oog. Myopie veroorzaakt verminderde visus welke te corrigeren is met een bril, contactlenzen of refractie laser/chirurgie. Het dragen van een bril voor een sterke refractieafwijking, zowel in het geval van hoge myopie als hoge hyperopie (verziendheid), kan zeer invaliderend zijn voor patiënten. Dit komt met name door de beeldvervorming die deze glazen veroorzaken. Indien contactlenzen of refractieve laser geen behandeloptie is voor deze groep patiënten, bestaat een mogelijkheid tot het implanteren van een kunstlens waarbij de natuurlijke lens behouden wordt. In dit proefschrift worden aspecten beschreven die van belang zijn bij het toepassen van deze behandelmethode. Dit proefschrift heeft betrekking op de implantatie van de iris-gefixeerde fake Artisan lens bij volwassenen met een refractieafwijking. Professor Jan Worst uit Groningen introduceerde deze iris-gefixeerde voorste oogkamerlens in 1978. Momenteel wordt in Nederland deze lens veel gebruikt voor meerdere toepassingen, waarbij correctie van hoge refractieafwijkingen een veel voorkomende indicatie is. In het Erasmus Medisch Centrum en Leiden Universitair Medisch Centrum is sinds 1996 de Artisan lens geïmplanteerd bij deze groep patiënten. De follow-up van deze patiënten in de afgelopen decennia heeft ons waardevolle kennis opgeleverd rondom het proces van implantatie tot aan het verwijderen van de Artisan lens.

**Hoofdstuk 1,** de introductie van het proefschrift, beschrijft middels een fictieve casus het pad dat een patiënt met een hoge refractieafwijking doorloopt vanaf implantatie van een Artisan lens tot aan het verwijderen van de lens. Hierbij komen onderwerpen aan bod als het ontstaan van een refractieafwijking tot aan behandelopties. De indicaties voor het implanteren van de Artisan lens worden behandeld en er wordt een overzicht gegeven over de toepassing van beeldvorming, een belangrijk onderdeel in het proces. De meest voorkomende redenen om de lens te explanteren worden beschreven.

Om beter inzicht te krijgen welke biometrische factoren het meest belangrijk zijn voor het bestaan van een refractieafwijking, wordt in **Hoofstuk 2**, de in de literatuur bekende verbanden tussen de belangrijkste verschillende anatomische structuren in het oog, beschreven. In totaal zijn 26 artikelen gebruikt voor een meta-analyse om de volgende verbanden te beschrijven; Het verband tussen de oogaslengte en refractieafwijking, de voorste oogkamer diepte en refractieafwijking, de oogaslengte en de voorste oogkamer diepte, de kromming van het hoornvlies en refractieafwijking en tot slot de kromming van het hoornvlies en de oogaslengte. Elk verband is geanalyseerd middels een gepoolde correlatie-coëfficiënt. De grootte van dit getal geeft weer of er sprake is van een sterk ($r \geq 0.6$), gemiddeld ($0.4 \leq r < 0.6$) of zwak ($r < 0.4$) verband. Zoals verwacht bestaat er een sterk verband tussen de

oogaslengte en refractieafwijking (r = 0.67; 95% CI: 0.76, 0.56). Bij een toename van 1 mm in oogaslengte, neemt de refractieafwijking gemiddeld 2.3 dioptrie af. Patiënten met een grotere voorste oogkamer diepte, hebben ook een langer oogas. Deze 2 factoren bleken een gemiddeld verband te hebben (r = 0.49; 95% CI:0.04, 0.58). Daarnaast neemt, in zwakke mate, ook de voorste oogkamer diepte toe bij een meer myope refractie (r = 0.28; 95% CI: 0.45, 0.08). Er is minder literatuur bekend over de kromming van het hoornvlies, maar deze lijkt weinig tot geen invloed te hebben op de refractieafwijking. In dit hoofdstuk wordt middels een appendix een gedetailleerd overzicht gegeven van de gebruikte literatuur. Ondanks dat in het statistisch model welke gebruikt is voor deze meta-analyse gecorrigeerd wordt voor de heterogeniteit van de data (verschillende onderzoekspopulaties en apparatuur), is het belangrijk om de mogelijke invloed op de resultaten hiervan te benadrukken. Tevens is het essentieel om te vermelden dat de gevonden verbanden ook afhankelijk zijn van externe factoren zoals leeftijd (bijvoorbeeld door de vorming van cataract), etniciteit en geslacht.

In **Hoofdstuk 3**, wordt ingegaan op het effect van het hebben van een refractieafwijking op de mate van strooilicht. Strooilicht heeft niet zozeer invloed op de gezichtsscherpte maar kan een groot invaliderend effect hebben op de kwaliteit van zien. Toename van strooilicht wordt met name gezien bij imperfecties in media bijvoorbeeld in het geval van vieze contactlenzen of status na refractie laser. Dit hoofdstuk beschrijft de invloed van de sterkte van een corrigerende bril en contactlenzen op de mate van strooilicht. Dit is gemeten in een emmetrope en myope patiëntengroep, beide bestaande uit 30 ogen van 15 patiënten. In de eerste groep is het effect op strooilicht gemeten van brillenglazen met verschillende negatieve sterktes. In de tweede groep is het effect van bril en contactlens met een negatieve sterkte gemeten. De toename in strooilicht door correctie met sterke minus glazen blijkt verwaarloosbaar klein en is niet visueel storend.

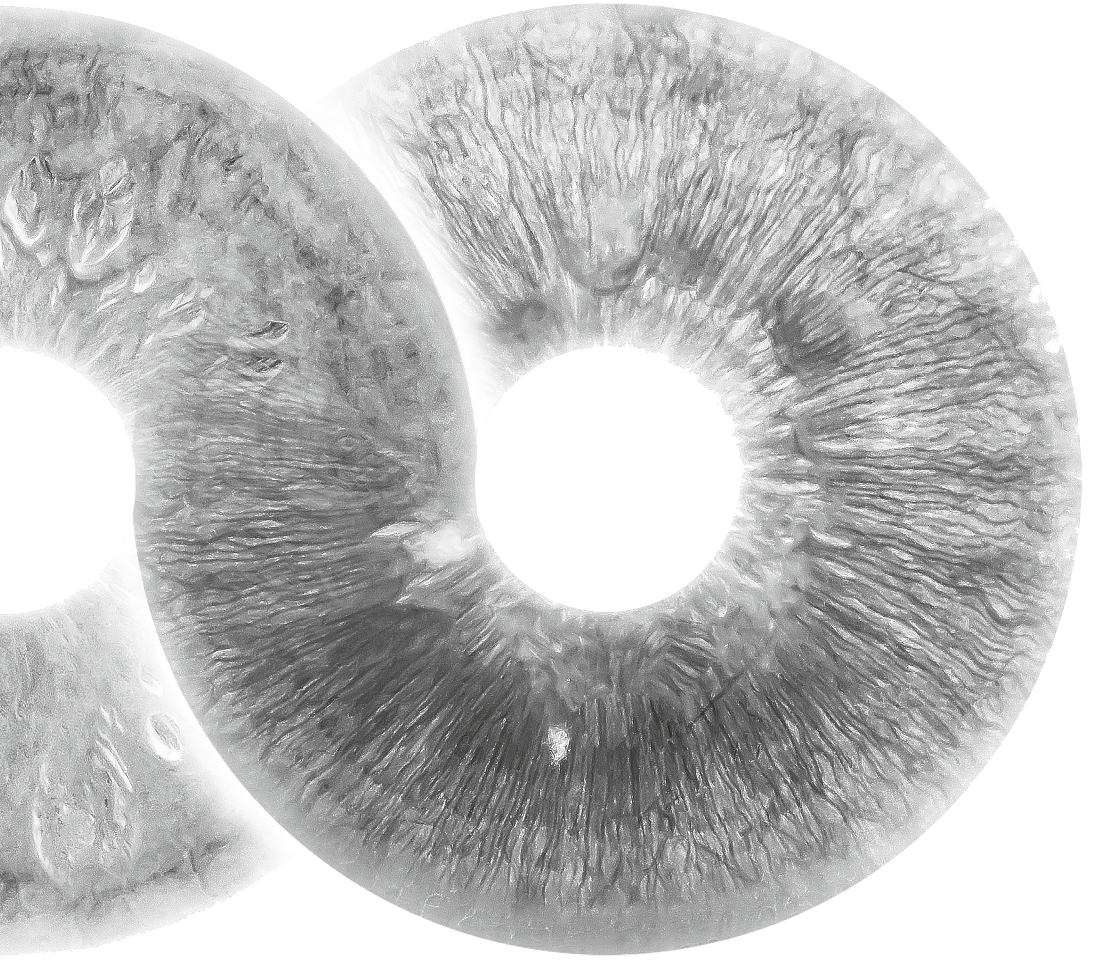
**Hoofdstuk 4** geeft een compleet overzicht van de in literatuur beschreven middellange en lange termijn (2 tot 10 jaar) resultaten van de iris-gefixeerde fake Artisan lens voor de correctie van hyperopie en myopie. Middels een systematische review worden de postoperatieve uitkomsten van in totaal 5523 myope (29 studies) en 217 hyperope ogen (4 studies) weergegeven op het gebied van refractie, visus, endotheelcelverlies en veiligheid. In een gepoolde groep van 1602 ogen vielen 65% tot 93% procent binnen 1.0 D van de beoogde target refractie. De gepoolde mediaan van het percentage van myope ogen met een ongecorrigeerde visus van 20/40 of beter, is 87% na 2 jaar (560 ogen) en 82% na 5 jaar (210 ogen). De enige studie met een 14 hyperope ogen rapporteerde een ongecorrigeerde visus van

20/30 of beter bij 100% van de ogen na 2 en 3 jaar follow-up. Wat betreft endotheelcel verlies worden uiteenlopende resultaten beschreven in de verschillende studies. Bij de studies met een follow-up van langer dan 7 jaar varieerde het endotheelcel verlies tussen de 4.9% en 22.5%. De meest voorkomende reden voor pIOL explantatie in de myope ogen was cataract. In 0.0% tot 0.9% van de ogen werd de pIOL verwijderd vanwege endotheelcel verlies. In de hyperope ogen was de meest voorkomende reden voor pIOL explantatie het bestaan van synechiae posteriores en pigmentceldeposities. In conclusie, de fake Artisan lens is een geschikte behandeling voor (hoge) myopie met uitstekende visus en refractie uitkomsten en lage complicatie risico. Over de invloed van de pIOL op het endotheelcelverlies is er geen harde conclusie te trekken gezien de zeer uiteenlopende resultaten. Dit legt dan ook de nadruk op het belang van reguliere follow-up. Voor de hyperope fake Artisan zijn meer lange termijn studies nodig.

In **Hoofdstuk 5** wordt ingegaan op de meting van minimale afstand tussen het cornea endotheel en het anterieure deel van de fake Artisan lens. Deze meting wordt naast het meten van de voorste oogkamer diepte gebruikt om een inschatting te maken van het risico op versneld endotheelcelverlies. Voor het meten van deze afstand wordt er momenteel gebruik gemaakt van 2 modaliteiten: Scheimpflug imaging en voorsegment OCT. In deze studie zijn 62 ogen met een fake iris-gefixeerde pIOL, waarvan 25 hyperoop en 37 myoop, gescand met beide apparaten. De afstand tussen het endotheel en de pIOL is gemeten met de bijgeleverde software door 2 verschillende onderzoekers op 5 verschillende posities: centraal, 2.5 mm nasaal/temporaal, 4.0 mm nasaal/temporaal. Voor alle posities werd een significant verschil in meting gevonden tussen de 2 apparaten waarbij met de voorsegment OCT de meting 0.11 tot 0.22 mm groter werd gemeten dan met Scheimpflug imaging. Er werd bij beide modaliteiten een goede intra-beoordelaars betrouwbaarheid gevonden. Dit geeft een klinisch relevant verschil waardoor de apparaten niet uitwisselbaar zijn. Er wordt een formule gegeven die omrekenen tussen de 2 apparaten mogelijk maakt.

**Hoofdstuk 6** beschrijft de lange termijn veranderingen in aslengte van volwassenen met een fake iris-gefixeerde pIOL voor myopie en hyperopie. De aslengte van 290 myope ogen (149 patiënten) en 53 hyperope ogen van 27 patiënten werd op 2 tijdspunten gemeten. In de myope ogen werd een toename in aslengte gevonden van 0.44 ± 0.67 mm ($P < 0.001$) na een gemiddelde follow-up van 12 jaar. Bij 55 ogen (19%) was de aslengte meer dan 1 mm toegenomen over de tijd. Aslengte toename werd voornamelijk waargenomen bij jongere patiënten met een hogere myopie. De aslengte van hyperope ogen bleef onveranderd over de tijd.

In **Hoofdstuk 7** wordt de Single Incision Technique (SIT) geïntroduceerd, een alternatieve chirurgische techniek om de iris-gefixeerde fake pIOL te verwijderen in combinatie met cataractextractie. Hierbij wordt eerst de phaco-emulsificatie verricht onder de pIOL, waarna de pIOL wordt verwijderd en de posterieure IOL wordt ingebracht. De theoretische voordelen van deze techniek ten opzichte van de conventionele manier is een bescherming van het endotheel door de pIOL en een meer stabiele voorste oogkamer door een 3.0 mm hoofdpoort tijdens phaco-emulsificatie. De SIT werd uitgevoerd bij 50 myope ogen (34 patiënten) en 9 hyperope ogen (6 patiënten). Postoperatieve gecorrigeerde visus was 0.16 ± 0.37 logMAR in de myope en -0.10 ± 0.55 logMAR in de hyperope ogen. Gemiddelde postoperatieve sferisch equivalent was -0.34 ± 0.72 D en -0.10 ± 0.55 D, respectievelijk. Zes maanden na de ingreep werd een endotheelcel verlies van 5% vastgesteld welke stabiel bleef tijdens een follow-up tijd van 2 jaar. Deze resultaten zijn gelijkwaardig aan de resultaten van de conventionele techniek.



# CHAPTER 10.

## General Discussion

With the incidence of refractive errors[1] on the rise, correcting such errors has never been such a great public health concern, especially with respect to myopia, which has also been severely progressing in the last decades[2]. Phakic intraocular lens (pIOL) implantation is effective in treating high refractive errors, and is widely used to treat younger patients who are not suitable for refractive laser surgery[3]. Different types of pIOLs have different associated risks. Thorough preoperative assessment and periodical postoperative monitoring are necessary to detect unsuitable patients and to deal with such risks on time[3]. The aim of this thesis was to gain knowledge on topics that an ophthalmologist will encounter when considering and treating a patient with an iris-fixated pIOL implant. In Chapter 1, we introduced you to Ms. Jansen: A young woman treated for her high myopia with an iris-fixated pIOL. After surgery, she was satisfied with the results. Now, more than 10 years after pIOL implantation, technologies have evolved to be faster and more efficient, and patients might currently have higher expectations than before. Long-term data of patients such as Ms. Jansen was collected in this thesis. We will reflect on some of the interesting findings, and on how to exploit them further to achieve improved patient care.

**Biometry in pIOL power calculation**

It is essential to have a basic understanding of biometric parameters and their correlations with refractive errors in order to provide personalized eye care in the field of refractive surgery. This thesis provides a clear overview of previous literature assessing the basic biometric correlations in regard to the refractive status of the eye. We present strong evidence that the refractive status is mainly determined by the axial length. Anterior chamber depth (ACD) tends to increase accordingly with increasing axial length, but to a lesser extent. Corneal curvature appears to have a clinically insignificant role. These three clinical biometric parameters are part of the Van der Heijde Formula, used for the iris claw pIOL calculation: mean corneal curve, adjusted ACD (ACD – 0.8 mm), and spherical equivalent of the patient's spectacle correction at a 12.0 mm vertex [4]. The formula provides fairly predictable refractive outcomes: in Chapter 4 we showed that the percentage of myopic eyes 65% to 93% of eyes were within 1.0 D of the intended correction (14 studies, 1602 eyes) with an overall pooled median of eyes of 78.8%. Advances in current diagnostic techniques provide accurate measurements of corneal curvature and ACD. To further improve the outcome of the Van der Heijde Formule care should be taken to measure patient's refraction. These patients are often contact lens wearers which can cause fluctuations in refraction. As well as manifest as cycloplegic refraction should be measured in all patients, preferably at 2 time points, Furthermore, it would be interesting to investigate whether and which patients would benefit from slight overcorrection of the myopia, as this thesis showed that axial length might further increase over time in (high) myopes.

**Biometry in IOL power calculation after prior pIOL implantation**

In this thesis we have learned that removal of the pIOL combined with cataract surgery resulted in satisfactory refractive results (mean manifest refraction spherical equivalent (MRSE) of – 0.34 ± 0.72 logMAR and – 0.10 ± 0.55 logMAR in myopic and hyperopic eyes, respectively). For calculation of the posterior IOL power the SRK/T formula was used (and the Holladay formula in eyes of 22.0 mm or shorter). We can therefore conclude that pIOL implantation did not affect IOL power calculation. However, the following points should be highlighted in order to achieve good refractive results.

First of all, we have learned that factors such as age[5,6], sex[7,8] and ethnicity[9,10] can alter interactions between different biometric parameters. For example, anterior chamber depth generally decreases with age due to an increased lens thickness[11], and this thesis showed us that axial length might further increase in (high) myopes. From all of these observations, we can deduce that biometric correlations are very complex and subjected to time. It is therefore recommended to repeat biometric assessment in patients who have had an interval of longer than 2 years between initial biometric assessment and surgery for optimal refractive outcomes. In addition, care should be taken in recognizing a faulty ACD measurement in which the biometric device measures the distance between the cornea and pIOL edge (instead of the crystalline lens surface)[12].

Secondly, a high surgically induced astigmatism (SIA) could be induced by the combined procedure. If prefered by the surgeon, creating a corneoscleral incision for pIOL explantation can reduce SIA.

Finally, which formula should be used for more accurate IOL power prediction in high myopes? Previously, ultrasound measurements often produced a falsely longer axial length as a result of eccentric measurements in patients with posterior staphyloma. Nowadays, despite more accurate measurements by optical interferometry, consistent hyperopic errors are still reported using third-generation formulas.[13-15] Currently, the effective lens position (ELP) is the only variable that cannot be measured directly by biometry and is estimated using other eye dimensions measured. Recently, a study of 325 myopic eyes reported that a combination of modified Wang-Koch axial length adjustment and Holladay 1 formula showed comparable results to the Barret Universal II and produced one of the best results for long axial length (25.0 mm to 27.0 mm). Recent advances for improving formulas i.e. ELP prediction is the application of artificial intelligence based formulas and ray tracing calculation.[16] And so the search continues. However, it is worth noticing that more accurate

refractive outcomes are archived in eyes with long axial lengths compared with eyes with short axial lengths because errors in axial length measurement or ELP estimation are minimized by the lower dioptric power of these IOLs.[17]

**Ancillary tests**

Various technologies have been developed over time for measuring the anterior segment and axial length. Many papers have been published focusing on device interchangeability to measure ACD[18-22] and AL[23-26]. Some of these studies show discrepancies in their findings. **Table 1** gives a concise overview of the methods most frequently used today for measuring the anterior chamber depth. The main reason for the differences among the devices is that each device uses a different method of measurement. This thesis demonstrates clinically important differences in measuring anterior chamber depth with the Scheimpflug imaging device versus anterior segment optical coherence tomography; the latter provides consistently greater measurements than the Scheimpflug imaging device. Based on the conversion equation, provided in Chapter 5, the minimum safety distance would be 1.84 mm when using anterior segment optical coherence tomography instead of 1.7 mm as proposed by Ferreira[27]. Theoretically, this means that 17% of our patients should not have had surgery. It would be interesting to find out whether these patients did indeed have more endothelial cell loss, as predicted by the model. In conclusion, using these two imaging modalities interchangeably for this purpose during follow-up should be avoided. As various 'minimum safety pIOL-to-endothelium distances' are in circulation, attention should be paid to which method is used for determining that norm, as conversion might be needed. In this thesis, we also found progressive axial length measurements in adult myopic patients over time. Previous longitudinal studies have also shown even more dramatic ocular axial elongation in myopic Asian adults, with annual increases ranging from 0.04 to 0.30 mm[28-30]. Unavoidably, different biometric devices were used, which affect the findings. Differences found in endothelial cell density over time, described in Chapters 4 and 7 of this thesis, are also partially subject to device interchangeability as measurements of various specular or confocal microscopes were used. Van Rijn[31] described statistically significant differences in endothelial cell counts when different specular microscopes of the same manufacturer (TopCon SP-2000P and SP-3000P) were used.

It is extremely important to recognize the impact of the differences arising from device interchangeability. Access to new technologies progresses fast, and especially patients who require long-term follow-up may be the victim of incorrect comparisons. More modifications are needed to achieve greater compatibility of the devices. Ideally, one golden

standard should be the norm. Two emerging imaging modalities are magnetic resonance imaging (MRI)[32] and photoacoustic imaging (PA)[33]. MRI provides 3-dimensional computer modeling images of the adult eye[34]. The advantage is that the image is undistorted. PA imaging forms images based on the photoacoustic effect of tissues[35]. The latter technique is still time consuming and provides lower resolution images. Recent developments in MRI technology, however, have enabled the acquisition of high-resolution images without disturbing eye-motion related artefacts[36,37]. Recently, Van Vught et al.[38] demonstrated accurate evaluation of the in-the-bag intraocular position in high-resolution ocular MRI scans. In ocular oncology, the application of ocular MRI has already been proven useful in clinical practice[39,40] as a diagnostic imaging technique in uveal melanoma. Using a dedicated protocol and eye-coil, high-resolution 3D images have been generated, improving the diagnosis, treatment plan and follow-up of patients with uveal melanoma.

**Table 1.**
Device description for ACD measurement

| Device | Technology | How ACD is measured | Pros and cons |
|---|---|---|---|
| A-scan | Ultrasonography | By measuring the time it takes for ultrasound waves to reflect back on the receiver from the posterior corneal surface and anterior lens surface. | (+) Allows imaging of regions obscured by overlying optically opaque structures<br>(-) Reproducible measurements require an experienced operater |
| Orbscan | Slit scanning | Calculates a mathematical three-dimensional model of the cornea and anterior segment. To calculate the ACD, the software automatically detects the corneal endothelium surface and anterior surface of the crystalline lens. | (+) Non-contact examination<br>(-) Unreliable corneal topography in post-LASIK eyes<br>(-) Less accurate than more recent devices as named below |
| Orbscan II | Combines the slit scanning beam system with a placido disk | Calculates ACD like the Orbscan | Same as the Orbscan |
| Pentacam | Scheimpflug imaging | Internal software creates a three-dimensional reconstruction of the anterior segment using the elevation data of these images, which gives information about the anterior and posterior surface of the cornea, and ACD from endothelium to crystalline lens. | (+) Non-contact examination<br>(+) Minimal experience is required for image acquisition<br>(-) Software is used to construct 3D images which may lead to distortion |

| | | | |
|---|---|---|---|
| Visante OCT | Time-domain OCT | Acquires multiple A-scans and aligns them to construct two-dimensional images. | (+) Non-contact examination<br>(+) Scan is acquired faster that the nearly 2 seconds required by the Pentacam<br>(-) Pigmented posterior layer of the iris hinders light penetration and might cause poor visualization |
| Lenstar | Low coherence reflectometry | Detects anterior and posterior corneal, and crystalline lens peaks in optical low coherence reflectometry waveform to measure the ACD, AL and corneal thickness. | (+) Non-contact examination<br>(+) Provides AL<br>(-) No 2D analysis of the anterior segment |

**The journey does end**

The title of this thesis is in fact incorrect. Yes, patients treated with an iris-fixated pIOL to correct a refractive error need to be frequently monitored, often for a very long time, but not life-long. When phaco-emulsification and pIOL explantation are performed, endothelial cell counts remain stable over time, as described in Chapter 7. Hereafter, follow-up is generally not indicated. Theoretically, the surgical technique described in this thesis has the following advantages over conventional surgery: The phakic intraocular lens functions as a protective shield for the endothelium, and the anterior chamber is better maintained. After explantation, the rate of endothelial cell loss was stable during a 2-year follow-up. The question remains as to when pIOL explantation, especially premature explantation, should be performed. In our clinic, the threshold for pIOL explantation due to a low endothelial cell count is set at 1000 cells/mm$^2$ in order to facilitate explantation and cataract surgery without compromising the long-term integrity of the corneal endothelium. Nevertheless, corneal integrity does not solely depend on the absolute number of cells. And endothelial cell counting can sometimes be misleading. Therefore, other factors, such as the morphology of the endothelial cells in confocal microscopy, have to be taken into account when considering pIOL explantation.

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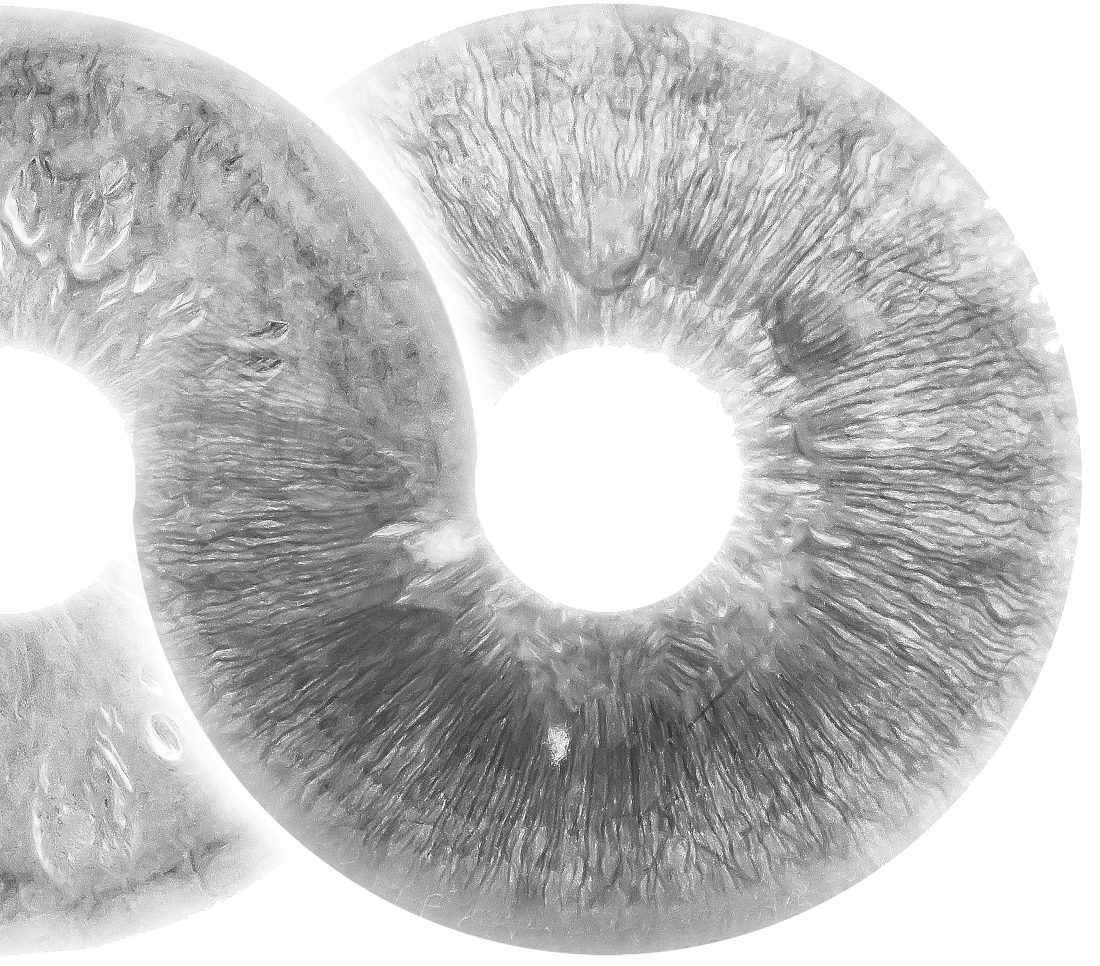

# CHAPTER 11.

Acknowledgements
Curriculum vitae
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# Curriculum vitae

Zoraida Solaiga Gaurisankar is geboren op 24 november 1988 in Paramaribo, Suriname. Op vierjarige leeftijd verhuisde zij naar Amsterdam. In 2007 rondde zij cum laude de gymnasiumopleiding aan het St. Ignatius Gymnasium Amsterdam af, waarna zij geneeskunde ging studeren aan de Vrije Universiteit Amsterdam. In haar laatste jaar deed ze voor een 4 maanden lange wetenschapsstage onderzoek over strooilicht en correctie van refractieafwijkingen onder de begeleiding van drs. G.A. van Rijn en prof. dr. G.P.M. Luijten bij de afdeling Oogheelkunde in het Leiden Universitair Medisch Centrum. In december 2013 behaalde zij haar artsendiploma. In 2014, tijdens haar opleiding tot oogarts, continueerde ze haar wetenschappelijk onderzoek bij patiënten met een fake intra-oculaire lens voor correctie van refractieafwijkingen in het Leiden Universitair Medisch Centrum, onder begeleiding van prof. dr. G.P.M. Luijten en dr. J.W.M. Beenakker. De resultaten van dit onderzoek zijn in dit proefschrift beschreven. De opleiding tot oogarts rondde zij in 2020 af, waarna zij als oogarts startte in het Onze Lieve Vrouwe Gasthuis ziekenhuis te Amsterdam. Sinds 2022 werkt zij tevens als oogarts in het Jan van Goyenkliniek te Amsterdam.

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