Universitätsklinikum Düsseldorf

Klinik und Poliklinik für Augenheilkunde

Direktor: Univ.-Prof. Dr. med. Gerd Geerling

# Safety, Efficacy and Predictability of Excimer Laser Vision Correction

Kumulative Habilitationsschrift

Zur Erlangung der Venia Legendi für das Fach

Augenheilkunde

an der Medizinischen Fakultät

der Universität Düsseldorf

vorgelegt von

Dr. med. Dr. med. univ. (Graz) Andreas Frings MHBA FEBO

Düsseldorf, Dezember 2019

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***Für Verena.***

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## *List of Abbreviations*

| | |
|---|---|
| ATR | against-the-rule |
| CDVA | corrected distance visual acuity |
| CSE | cycloplegic spherical equivalent |
| D | dioptre |
| EI | efficacy index |
| Excimer | excited dimer |
| HOA | higher-order aberrations |
| Km | keratometry |
| Kmean | mean keratometry reading |
| LASER | light amplification by stimulated emission of radiation |
| LASIK | Laser in situ keratomileusis |
| logMAR | logarithm of the minimum angle of resolution |
| MCD | manifest cycloplegic difference = difference between manifest (MSE) and cycloplegic (CSE) spherical equivalent |
| MK | microkeratome |
| MSE | manifest spherical equivalent |
| OBL | oblique |
| OLS | ordinary least square |
| ORA | ocular residual astigmatism |
| OZ | optical zone |

| | |
|---|---|
| PRK | photorefractive keratectomy |
| SE | spherical equivalent |
| SI | safety index |
| UDVA | uncorrected distance visual acuity |
| WTR | with-the-rule |

## 1. Introduction

The concept that refractive errors could be corrected by sculpting corneal stromal tissue to change corneal curvature was the brainchild of José Ignacio Barraquer Moner in 1948, who developed a procedure he coined “keratomileusis” (Reinstein et al. 2012). However, only the combination of in situ keratomileusis with the emerging technology of Excimer Lasers for corneal tissue ablation resulted in the first Laser in situ keratomileusis (LASIK) procedure performed in the early 1990 (Pallikaris et al. 1990). During the past three decades, the field of Laser refractive surgery has been faced with dramatic advances introduced by new technologies (Reinstein et al. 2012). LASIK has become one of the most common elective interventions worldwide.

However, there are pitfalls when performing LASIK or any other corneal refractive procedure to correct ametropia. We have published several studies analysing pre-, intra- and postoperative parameters based on data of approximately 125.000 refractive treatments. This thesis will introduce five studies analysing pre-, intra- and postoperative parameters and their impact on safety, efficacy and predictability of Excimer Laser vision correction.

### *1.1 Corneal Anatomy*

The cornea is a transparent avascular connective tissue that acts as the primary infectious and structural barrier of the eye and, together with the overlying tear film, it also provides a proper anterior refractive surface for the eye (DelMonte and Kim 2011).

The shape of the cornea is prolated flatter in the periphery and steeper centrally which creates an aspheric optical system; in the average adult, the horizontal diameter of the cornea is 11.5 to 12.0mm (Rüfer et al. 2005) and about 1.0 mm larger than the vertical diameter (DelMonte and Kim 2011).

Most medical textbooks describe the human cornea as made of five layers, the epithelium and Bowman’ s zone anteriorly and the endothelium with its basement membrane, the Descemet’ s membrane, posteriorly, sandwiching the stroma, whose anterior part is more compact than the posterior due to a different anatomical composition (Bettelheim and Plessy 1975; Bron 2001; Müller et al. 2001). Well maintained structural anatomy and physiology of corneal cellular components is of utmost importance to provide a clear anatomical barrier (DelMonte and Kim 2011).

Applying spectral-domain optical coherence tomography, López de la Fuente et al. (2016) defined corneal thickness and all its layers in healthy young adults: Mean central corneal thickness, epithelium, Bowman's layer, stroma, and Descemet–endothelium values were 555.50 ± 29.64, 54.60 ± 4.25, 16.70 ± 1.73, 467.51 ± 28.91, and 16.74 ± 1.66 μm, respectively, with the cornea gradually increasing in thickness toward the periphery (López de la Fuente et al. 2016).

Knowledge of these anatomical parameters is important to understand clinical changes induced by keratorefractive surgery. For instance, the corneal epithelium changes proportional to the stromal changes and higher myopic ablations yield more epithelial thickening in the centre after Excimer Laser ablation (Reinstein et al. 2008).

In recent years, there have been surprising and important findings influencing our understanding of corneal anatomy and physiology and thus, methods and outcomes of corneal refractive surgery. The most popular example is the description of a new Pre-Descemet's Layer, also referred to as Dua's Layer (Dua et al. 2013).

There is a lot more to learn about corneal physiology and anatomy. However, a complete review of the latest anatomical and physiological developments is beyond the scope of this introduction. Importantly, corneal refractive surgeons need to be aware of these new findings to better understand surgical results and optimize treatment principles.

### *1.2 Refractive Errors and Treatment Options*

Any refractive error (also termed optical aberration) reduces the optical image quality on the retina and impairs visual acuity. Spherical or cylindrical refractive deficits are classified as lower order aberrations. Ametropia, which includes myopia, hyperopia, regular astigmatism, and presbyopia, are the most common treatable disorders of the dioptric system and are lower-order aberrations (Kohnen 2011). On the other hand, there are aberrations that are not perceived under physiological conditions, but can still affect visual acuity. These are called higher-order aberrations. The two most important are called coma (greek: hair, tail) and spherical aberration.

If the axial length of the eye at an overall power of 58-65 D is about 23.5-24.0 mm, emmetropia is achieved. In this case, parallel rays of light are sharply imaged on the retina (Kohnen 2011).

In a myopic eye, the axial length of the eye is usually too long at normal refractive power or the refractive power is too high at normal axial length. Parallel rays of light entering the eye are no longer united on, but in front of the retina. While objects in the distance are perceived blurry, nearby objects can be seen sharply by increasing the refractive power.

Myopia is corrected by reducing the refractive power. The treatment is achieved by concave lenses or contact lenses (negative glasses with negative refractive power) or by flattening the central cornea with an Excimer Laser as discussed in this thesis (Kohnen 2011).

In hyperopia, the axial length of the eye is usually too short at normal refractive power, or the refractive power is too weak at normal axis length. Consequently, rays of light are no longer united on, but behind the retina. Even when looking into the far distance, the entire accommodation capacity of the eye is “consumed” in order to shift the focal point to the retina. Low to moderate hyperopia can be compensated in younger, pre-presbyopic years by principles of accommodation. The correction of hyperopia is achieved by convex lenses or contact lenses (positive glasses with positive refractive power) or by steepening the central cornea with an Excimer Laser (Kohnen 2011).

If the cornea has an asymmetrical, non-spherical but rather “egg-like” surface shape – which is frequently the case – parallel light rays do not have a focal point on the retina. Instead, they form a focal line and result in a blurry image. This condition is called astigmatism. In regular astigmatism, the meridians are perpendicular to each other. Depending on the orientation of the meridian with the stronger refractive power, with-the-rule (WTR), against-the-rule (ATR) and oblique (OBL) astigmatism are defined. The treatment is achieved by cylindrical lenses or toric contact lenses that transmit light in just one plane (omitting the other refractive plane the astigmatic eye would normally have), or by refractive surgical procedures (Kohnen 2011).

### *1.3 Short History of Laser Vision Correction*

Corneal refractive surgery had its breakthrough in the early 1990s with the commercial introduction of the Excimer Laser. By applying Laser pulses in the ultraviolet light range, it became possible to precisely remove corneal tissue in the micron- and submicron range without clinically relevant thermal destruction of surrounding tissue structures. Not only unintended tissue remodeling and scarring could be reduced, but treatment predictability and reproducibility were improved. The Argon Fluoride Excimer Laser is an ultraviolet “cold” Laser, which operates in the wavelength range of 193 nm. According to the principles of photoablation, the cornea is ablated both in a defined plane and in depth by application of many juxtaposed impulses (Kohnen 2011).

The principle of the Excimer Laser was first published in 1983 by Trokel et al. presented in animal experimental studies. Photorefractive keratectomy (PRK) was the first surface treatment with an Excimer Laser and was first performed by Marguerite McDonald in the human eye in 1988 (McDonald et al. 1989). The principles of PRK are based on the mechanical removal of the corneal epithelium and subsequent Excimer Laser ablation. Until the introduction of LASIK in the 1990s, PRK was successfully used as the standard procedure in refractive corneal surgery and today remains a reliable treatment option.

The concept of LASIK is based on a lamellar cutting technique (Keratomileusis in situ), which was developed by the ophthalmologist Ignatio Barraquer in 1949. With the help of a microkeratome Barraquer prepared a corneal flap that remained connected to the residual stroma via a tissue bridge. As the incision was placed within the stroma, below the Bowman´s membrane, the tissue healed without scarring. However, the second step, which was the precise removal of corneal tissue in the micrometer range, was faced by technical limitations in the 1950s. Only with the introduction of the Excimer Laser, this technique regained attention in 1990 when the ophthalmologist Pallikaris first combined the advantages of Barraquer's lamellar cutting technique with those of the Excimer Laser (Pallikaris et al. 1990). Since then, LASIK has been the most widely used procedure for the surgical correction of ametropia. LASIK is recommended for corrections of myopia up to -8 D, hyperopia up to +3 D and astigmatism up to 5 D.

### *1.4 Study Population and Clinical Measures*

Our Refractive Database is derived from a study population consisting of currently 125.000 eyes treated for ametropia in refractive clinics in Germany and Austria (Care Vision GmbH, Clínica Baviera, AIER Eye Hospital Group). Due to a selection bias there is a deficit of both the number of pre- and teenage subjects (<18 years) as well as older individuals (> 50 years). Most patients were eligible for refractive surgery with Excimer Laser, either LASIK or PRK. Subjects exceeding the range for Laser vision correction or those seeking a presbyopia correction were usually candidates for phakic intraocular surgery or clear lens extraction and were excluded from the Laser refractive surgery database. All indications and treatment procedures followed standard operating procedures (not published) which have been improved by various clinical studies and quality analyses like the studies that are included in this thesis.

The study protocol followed the tenets of the Declaration of Helsinki of the World Medical Association regarding scientific research on human subjects. Informed consent for data analysis and publication was obtained from all subjects during the preoperative recruiting process after explanation of the nature and possible consequences of using pseudonymized personal and medical data for scientific purposes. All studies were approved by the local institutional review board of Ärztekammer Hamburg (no. 2882).

### *1.5 Study Purposes*

LASIK and PRK have become popular methods of surgical vision correction. Minimal to moderate discomfort, rapid to intermediate recovery of visual acuity, high efficacy, and a minimal to low wound-healing response are major advantages of these techniques. However, there are some hurdles to be taken when full refractive correction is the goal of treatment. Different subgroups of patients with different types of ametropia should be addressed individually and thus, treatment planning is highly demanding. There is no one fits all solution.

This thesis discusses distinct parameters that have an influence on treatment planning, the surgery itself and refractive outcome. Among these parameters are the preoperative ocular residual astigmatism (ORA) and preoperative topographic astigmatism, the method of LASIK flap creation, the difference between manifest and cycloplegic refraction in hyperopic eyes and parameters related to retreatment settings for hyperopia. All of these aforementioned parameters take influence on treatment safety, efficacy and predictability, which are standardized parameters to discuss and compare the outcome of refractive procedures. In our context, the following definitions were applied (Dupps et al. 2011, Frings et al. 2013):

- Safety Index (SI): Mean of ratio of postoperative corrected distance visual acuity (CDVA) to preoperative CDVA.

- Efficacy Index (EI): Mean of ratio of postoperative uncorrected distance visual acuity (UDVA) to preoperative CDVA.

- Predictability: Attempted versus achieved refractive change. Usually, groups are formed based on deviation from attempted spherical equivalent (SE), i.e. ±0.5 D. Similarly, surgeons can calculate the predictability of the astigmatic power change.

This thesis aims at improving the way Excimer Laser vision correction is planned and performed to improve treatment safety, efficacy and predictability.

## 2. Study I

**Frings A*[#], Katz T*, Steinberg J, Druchkiv V, Richard G, Linke SJ.**

**Ocular residual astigmatism: effects of demographic and ocular parameters in myopic laser in situ keratomileusis.**

**J Cataract Refract Surg. 2014;40:232-238.**

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*Introduction*

There are commonly known pitfalls when choosing the appropriate treatment strategy in corneal refractive surgery. One of them is the conflict between treatment models that are based only either on the topographic astigmatism or subjective preoperative cylinder to plan refractive treatment (Alpins et al. 2012; Alpins and Stamatelatos 2007). Previous studies have suggested that treating astigmatism with LASIK based on manifest subjective refraction results in a successful outcome only if the preoperative refractive astigmatism arises primarily from the anterior corneal surface (Alpins 1997; Kugler et al. 2010).

The contributors to refractive cylinder are the anterior cornea and the ocular residual astigmatism (ORA). The latter mainly results from the posterior corneal surface, the crystalline lens and some perceptual unknown “retinal” components (Tejedor and Guirao 2013). ORA is defined as the vectorial difference between the corneal topographic astigmatism and the refractive cylinder (Alpins et al. 2012; Alpins and Stamatelatos 2007; Kugler et al. 2010). This difference can be significant and may lead to suboptimal visual outcomes after refractive corneal surgery (Kugler et al. 2010). Unfortunately, a discrepancy between corneal astigmatism and refractive cylinder is a common clinical finding (Alpins and Stamatelatos 2008). This is a pitfall when planning corneal refractive treatments as uncorrected astigmatism, even as low as 1.00 D or less, has been identified to cause significantly decreased vision and visual symptoms (Wolffsohn et al. 2011). The better the correlation between the magnitude and the orientation of the corneal astigmatism and refractive cylinder, the less astigmatism will be left remaining in the optical system of the eye as a whole after treatment (Alpins 1998; Alpins et al. 2012; Alpins and Stamatelatos 2007).

The ORA can be high in more irregular corneas such as in those with keratoconus (Alpins and Stamatelatos 2007). As there is a direct proportional relationship between increasing ORA and topographic disparity (= the vectorial difference between the two opposite semimeridian values for magnitude and axis in each corneal part) (Alpins 1998), it is therefore of crucial importance when treating high astigmatism that the topography data for astigmatism be incorporated into the treatment plan as treatment based on the manifest refraction alone leaves the cornea with excess avoidable astigmatism (Alpins and Stamatelatos 2007).

Study I of this thesis was initiated to analyse the influence of epidemiologic, anatomical and refractive parameters on the pre-existing ORA in patients scheduled for LASIK to treat myopic astigmatism thereby identifying patients that are at high risk of having a significant difference between subjective cylinder and topographic astigmatism.

*Methods*

*Patients*

Consecutive myopic patients were recruited between October 2011 and June 2012 from a chain of private refractive surgery centres in Germany. All data were based on the Hamburg Refractive Data Base (data retrieved from Care Vision Germany GmbH). Before the refractive treatment, patients provided informed consent for retrospective data analysis and a local ethics committee (no. 2882) approved the study. The study adhered to the tenets of the Declaration of Helsinki.

One eye of each patient was randomly selected for analysis. Studied were the effects of demographic and ocular parameters on ORA. Demographic (nonocular) parameters were the patients' age and sex. The dominant eye, manifest cylinder, topographic astigmatism, manifest sphere, and the mesopic pupil size were defined as ocular parameters. The dominant eye was determined using the hole-in-the card test.

To determine the amount of ORA before LASIK, standard double-angle vector analysis was performed. The magnitude and orientation of ORA were determined in a double-angle vector diagram by the vector difference between the preoperative refractive cylinder (R) and the topographic (simulated keratometry [K]) astigmatism (Alpins 1997; Kugler et al. 2010). Following Kugler et al. (2010) the R value was obtained from the manifest refraction and the simulated K value was calculated from corneal topography (Orbscan II, Bausch & Lomb) based on the difference between the steepest meridian and the flattest meridian oriented 90 degrees from each other. ORA is the amount of the vector difference between R and simulated K (ie, R – K) with its orientation directed to the refractive cylinder value from the cornea and was calculated using a previously described formula (Alpins 1997; Kugler et al. 2010). Calculations for Alpins vector analysis were performed using Excel software (Version 2007, Microsoft Corp.).

Patients were assigned to 1 of 2 groups according to the ratio of ORA to preoperative refractive cylinder (R) as follows. The groups were ORA:R ≥1.0 and ORA:R <1.0. All results were based on data from the preoperative examination.

The spherical and cylindrical refractions were acquired by subjective refraction, and topographic astigmatism was obtained using the corneal topographic system. The mesopic pupil size was determined by Colvard pupillometry (Oasis Medical, Inc.).

To assess whether the preoperative cylinder meridian had an influence on ORA, subgroups were defined according to the preoperative astigmatism meridian as follows: with-the-rule (WTR), axis at 0 ± 22.5 degrees; against-the-rule (ATR), axis at 90 ± 22.5 degrees; or oblique (OBL), axis at 45 ± 22.5 degrees.

*Statistical Analysis*

Once the data were compiled, they were entered into an Excel spreadsheet program (Hamburg Refractive Data Base) and were statistically analysed using predictive analytical software (SPSS, version 17.0, SPSS, Inc.). For statistical analysis, data description was based on ordinary least square (OLS) estimation and odds ratios (ORs) obtained from logistic model analysis. Regression analysis was applied based on robust regression methods. The idea of robust regression is to weigh observations based on their leverage or deviation from prediction obtained by OLS estimation analysis. It is a form of weighted and reweighted least-squares regression.

*Results*

The mean ORA was 0.75 ±0.39 D (range, 0 to 2.00 D). 1372 (46%) eyes had an ORA of 1.00 D or more.

The OLS-Estimation (Table 1) found that subjective sphere (P = 0.02) and male sex (P < 0.001) were statistically significant negative predictors for the degree of preoperative ORA. On the other hand, WTR astigmatism meridian was more likely in eyes with low ORA while OBL (P < 0.001) and ATR (P < 0.001) meridia were connected with high ORA.

Eyes with low ORA had significantly (P < 0.001) higher magnitudes of subjective cylinder and topographic astigmatism (= cylinder arising from the anterior cornea). Moreover, a statistically significant (P = 0.015) difference of 0.20 D in subjective sphere was found between low and high ORA groups thereby indicating that eyes with high ORA were more myopic.

Table 1. Ordinary-Least-Square-Estimation ($R^2$ = 0.0653) (Table taken from Frings et al. J Cataract Refract Surg. 2014;40:232-238; permission to reuse obtained)

| Parameter | Coefficient* | SE | *t* | *P*>*t* | 95% CI |
|---|---|---|---|---|---|
| Age (y) | −0.002 | 0.002 | −1.070 | .285 | −0.007, 0.002 |
| Subjective sphere (D) | −0.024 | 0.010 | −2.330 | .020 | −0.045, −0.004 |
| Mesopic pupil size (mm) | 0.000 | 0.028 | 0.000 | .999 | −0.055, 0.055 |
| Sex (male) | −0.244 | 0.041 | −5.930 | .000 | −0.325, −0.163 |
| Dominant eye | −0.041 | 0.041 | −0.990 | .324 | −0.121, 0.040 |
| Eye (right) | 0.033 | 0.041 | 0.810 | .419 | −0.047, 0.112 |
| OBL vs WTR | 0.558 | 0.047 | 11.870 | .000 | 0.466, 0.650 |
| ATR vs WTR | 0.498 | 0.051 | 9.760 | .000 | 0.398, 0.598 |
| Constant | 1.071 | 0.225 | 4.750 | .000 | 0.629, 1.513 |

ATR = against the rule; CI = confidence interval; Coefficient = influence of the individual parameter; OBL = oblique; *P*>*t* = significance; SE = standard error; *t* = empirical *t* value (coefficient/SE); WTR = with the rule

*Comparable to the slope of a regression. For example, to be male means to have a regression with a coefficient of −0.244, which is a negative predictor for having lower ocular residual astigmatism (ORA). (On the other hand, the ATR astigmatism meridian goes along with high ORA because its coefficient is positive). The coefficients show the mean differences depending on the relationship between ORA and the subjective manifest cylinder.

This was confirmed by odds ratios obtained from logistic model analysis, because it indicated that subjective sphere, male sex, and the dominant eye were at lower probability to have ORA of 1.00 D or more (Table 2). However, the predictability to have high ORA was only slightly dependent on increasing age and larger mesopic pupil size, as these parameters had odds ratios of 1.003 and 1.076. This means increasing age is 0.3% and the mesopic pupil size is 7.6% at higher risk of having high preoperative ORA.

Independent of low or high ORA, the prevalence of cylinder meridia distribution was WTR>OBL>ATR, with WTR dominating. To rule out systematic differences between the ORA groups that arise by definition of high and low ORA, manifest cylinder as an explanatory variable was added in our models.

Table 2. Logistic Model (pseudo $R^2$ = 0.0059) (Table taken from Frings et al. J Cataract Refract Surg. 2014;40:232-238; permission to reuse obtained)

| Parameter | Odds Ratio | SE | 95% CI |
|---|---|---|---|
| Age (y) | 1.003 | 0.004 | 0.995, 1.012 |
| Subjective sphere (D) | 0.964 | 0.019 | 0.928, 1.002 |
| Mesopic pupil size (mm) | 1.076 | 0.057 | 0.971, 1.193 |
| Sex (male) | 0.740 | 0.057 | 0.637, 0.860 |
| Dominant eye | 0.946 | 0.071 | 0.817, 1.096 |

CI = confidence interval; OR = odds ratio; SE = standard error
Example: The probability that older people have higher ocular residual astigmatism (ORA) is estimated by the factor 1.003. This means older people are 0.3% at higher risk for having higher ORA. If the OR were 1.0, age would not have had an influence on ORA. On the other hand, males had an OR of 0.740, which signifies that their probability of having high ORA is statistically 26% less than that of their female counterparts.

*Discussion*

In summary, the present results indicate that subjective sphere (P = 0.02) and male sex (P < 0.001) were statistically significant negative predictors for the degree of preoperative ORA, while increasing age and larger mesopic pupil sizes did not indicate an orientation of preoperative ORA. WTR astigmatism meridian was more likely in eyes with low ORA while OBL and ATR meridia were common in high ORA.

Several studies have reported age-related changes of astigmatism with conflicting results (Hoffmann and Hütz 2010; Khan and Muhtaseb 2011; Riley et al. 2001). As previous studies have shown, both the net value and the prevalence of total and corneal astigmatism increase with age. According to Asano et al. (2005) the age-related change in astigmatism is mainly associated with changes in the cornea. Others see the lens as main contributor of increasing astigmatism with age. Older patients may thus have higher amount of ORA. However, the included subjects must have healthy eyes to be planned for a LASIK surgery. Older subjects with clinically significant cataracts have changing lens induced refraction and require cataract surgery first.

For low ORA eyes, the total refractive cylinder arises principally from the anterior corneal surface (Alpins and Stamatelatos 2007 and 2008; Kugler et al. 2010). As expected, the current study supports this observation, shown by mean magnitudes of topographic astigmatism and subjective cylinder of eyes with low ORA.

This analysis further aimed to estimate the relation between sex and ORA. In the current study, 61% of refractive surgery candidates were female. A statistically significant ($P < 0.001$) difference between both females and men was found as men had lower ORA, indicated by OLS and odds ratio. For statistical analysis, data description was based on OLS estimation and odds ratios obtained from logistic model analysis. Regression analysis was applied based on robust regression methods. The idea of robust regression is to weight observations based on their leverage or deviation from prediction obtained by OLS estimation analysis. It is a form of weighted and reweighted least-squares regression.

The effect of pupil size on uncorrected visual acuity in astigmatic eyes has been analysed thereby revealing preoperative UDVA to be better in eyes with smaller pupil sizes (Kamiya et al. 2012). The patient's pupil size and especially, pupil centre position is of utmost importance for maintaining a predictable and safe treatment setting (Applegate et al. 2010). Cakmak et al. (2010) and Linke et al. (2012) reported that age and magnitude of both spherical and cylindrical refractive error are the strongest determinative factors on mesopic pupil size. Myopia goes along with larger pupil size. Accordingly, the relation between ORA and pupil size was analysed. The odds ratio of 7.6% indicates that eyes with larger mesopic pupil size tend to have higher ORA, indicating that those should be assessed more closely in order to acquire excellent visual outcome. However, as mentioned previously, age is a confirmed parameter that influences the mesopic pupil size, with a smaller pupil size as the age advances (Cakmak et al. 2010). Accordingly, pupil size is influenced by other factors and therefore, it may be difficult to conclude whether one factor, e.g. large pupil size, or another factor that goes along with large pupil size is indicating high ORA.

Both corneal and non-corneal astigmatism are usually balanced. In a recent study, the amount of aberration of both the cornea and internal optics was found to be larger than for the complete eye, indicating that the first surface of the cornea and internal optics partially compensate for each other's aberrations and produce an improved retinal image (Artal et al. 2001). As a consequence, topographic astigmatism and refractive cylinder do not necessarily coincide in magnitude and axis (Alpins 1997; Alpins and Stamatelatos 2007 and 2008). Our data supports this finding (mean magnitude of topographic astigmatism -1.18 D (±0.73D) versus subjective cylinder -0.99 D (±0.78D)). This further corroborates to the notion that full correction of low myopic manifest cylinder could result in astigmatic overcorrection (Katz et al. 2013).

Moreover, on average, 40% less of the ORA being corrected on the cornea would reduce the corneal astigmatism significantly without compromising the refractive cylinder outcome (Alpins and Stamatelatos 2007 and 2008). According to Alpins and Stamatelatos (2007) using vector planning that integrates topographic values can more effectively reduce overall remaining astigmatism. Integrating the topography parameters with the wavefront aberrometry results in greater reduction in corneal astigmatism and better visual outcomes under mesopic conditions (Alpins and Stamatelatos 2008). Alpins' (1997) initial study of 100 patients found a mean ORA magnitude of 0.81 D; 34% of patients had a magnitude greater than 1.00 D. Our results support these previous data as a mean ORA of 0.75D (±0.39D; range 0 to 2.00 D) was obtained. The summated vector mean of the ORA for both the subgroups was 0.32 D x 141° (low ORA) and 0.76 D x 138° (high ORA).

Assumingly, the crystalline lens is the most important contributor as in the vast majority of young eyes, the posterior corneal surface compensates for astigmatism arising from the anterior corneal surface and thus, the remaining net astigmatism is mainly induced by lenticular aberration (Ho et al. 2010). Moreover interestingly, the subjective cylinder did not correlate with the amount of ORA. By contrast, the mean values of subjective cylinders indicate that high ORA was connected to lower magnitudes of mean subjective cylinder. This difference was statistically significant ($P < 0.001$).

Different methods to determine the magnitude of cylinder and its associated axis can lead to different results (Visser et al. 2012). A comparison of corneal astigmatism and axis location in cataract patients measured by total corneal power, automated keratometry, and simulated keratometry revealed the magnitude of astigmatism and axis location are different when measured differently (Visser et al. 2012). This is of importance when treating eyes with low ORA, as low magnitudes of astigmatism are usually more affected by inaccuracies/ differences in measurement.

The current analysis of astigmatism meridia suggests that 66.76% of patients with WTR astigmatism meridian have low ORA. This finding is supported by epidemiologic evidence which means the corneal astigmatism has traditionally been associated with a WTR astigmatism meridian thereby confirming that in these eyes the corneal cylinder is dominating the total net astigmatism. This was confirmed by OLS analysis.

In this study, we did not differentiate between any variability in the ORA magnitude depending on different measuring techniques (such as manual K, simulated K from the 3.0 mm zone alone, or corneal wavefront, Pentacam vs. Orbscan Data).

The contributors to refractive cylinder are the anterior cornea and the ocular residual astigmatism, which is defined as the vectorial difference between the corneal topographic astigmatism and the refractive cylinder (Alpins et al. 2012; Alpins and Stamatelatos 2007; Kugler et al. 2010). This difference can be significant and may lead to suboptimal visual outcomes after refractive corneal surgery (Kugler et al. 2010). Unfortunately, a discrepancy between corneal astigmatism and refractive cylinder is a common clinical finding (Alpins and Stamatelatos 2008). This is a pitfall when planning corneal refractive treatment.

To conclude, the better the correlation between the magnitude and the orientation of the corneal astigmatism and refractive cylinder, the less astigmatism will be left remaining in the optical system of the eye as a whole after treatment (Alpins 1998; Alpins et al. 2012; Alpins and Stamatelatos 2007). The preoperative assessment of refractive surgery candidates should consider the interaction between topographic, refractive and ocular residual astigmatism. The current data can help identify patients at high risk for having a significant difference between subjective cylinder and topographic astigmatism thereby improving safety, efficacy and predictability of the Excimer Laser treatment.

## 3. Study II

**Frings A, Richard G, Steinberg J, Skevas C, Druchkiv V, Katz T, Linke SJ.**

**LASIK for spherical refractive myopia: effect of topographic astigmatism (ocular residual astigmatism, ORA) on refractive outcome.**

**PLoS One. 2015; 10: e0124313.**

*Introduction*

The results of previous studies (Alpins 1993 and 1997; Kugler et al. 2010) have suggested that treating astigmatism with LASIK based on manifest subjective refraction results in a more successful outcome if the preoperative refractive cylinder arises primarily from the anterior corneal surface. However, in eyes with a preoperative plano refractive cylinder there is no rationale for astigmatic treatment and, therefore, any postoperative refractive cylinder is either induced by the ablation, the flap preparation or both.

In Study I, the influence of specific parameters on pre-existing ocular residual astigmatism (ORA) in patients scheduled for LASIK to treat myopic astigmatism was assessed. To determine the amount of ORA before LASIK, we performed a standard double-angle vector analysis in which the magnitude and orientation of ORA were determined by the vector difference between the preoperative refractive cylinder (R) and the topographic (simulated keratometry [K]) astigmatism (Alpins 1993 and 1997; Kugler et al. 2010) Following Kugler et al. (2010), the R value was obtained from the manifest refraction, and the simulated K value was calculated from corneal topography based on the difference between the steepest meridian and the flattest meridian oriented at 90 degrees to each other. The ratio of ORA to preoperative refractive cylinder (R) was calculated for each patient.

However, in eyes without preoperative refractive cylinder this approach cannot be applied. The aim of Study II was to determine the magnitude of topographic astigmatism (= the magnitude of ORA *in refractive plano eyes*) that results in reduced efficacy after myopic LASIK. This study was set up to investigate the effect of applying the new definition of high and low ORA for eyes with pre-existing plano refractive cylinder using receiver operating characteristic (ROC) analysis.

*Methods*

This retrospective study included 267 eyes from 267 consecutive myopic patients treated between December 2010 and March 2013, and was based on the Hamburg Refractive Database (data retrieved from Care Vision Refractive Centres in Germany). In all eyes a refractive plano cylinder was present preoperatively. Patients with a significant pre-existing complication of the ocular surface or tear film, and eyes with intra- and postoperative flap complications were excluded from analysis. The latter included eyes with postoperatively dislocated flap, epithelial ingrowth, diffuse lamellar keratitis and central toxic keratopathy. Written informed consent for retrospective data analysis was obtained from refractive surgery candidates during their recruiting process. The study and consent procedure were approved by the local ethics committee of the University of Hamburg, Germany (no. 2882), and adhered to the tenets of the Declaration of Helsinki.

Manifest spherical and cylindrical refractions, as well as visual acuity with and without correction were assessed preoperatively and 1 day, and 1, 3–4, and 6 months postoperatively, and recorded electronically. All outcome results reported here are based on the data from the 1-month follow-up. The spherical and cylindrical refractions were acquired by subjective refraction, and topographic astigmatism was obtained using Pentacam Scheimpflug tomography (Oculus, Wetzlar, Germany). All refractions were acquired by subjective refraction by expert optometrists in different refractive centres using the same refractometers, visus tables and documentation protocol. Each patient was examined pre- and postoperatively by the same optometrist under standardized ambient conditions.

The Alpins vector method (Alpins 1993, 1997 and 2001) was applied to describe the effects of LASIK on refractive cylinder. The following definitions were applied: Target induced astigmatic vector (TIA) is the astigmatic change (by magnitude and axis) the surgery is intended to induce. Surgically induced astigmatic vector (SIA) is the amount and axis of astigmatic change the surgery actually induces. It ideally should equal the TIA and can also be described as vector of the real change achieved by surgery (Alpins 1993, 1997 and 2001).

*Surgical Treatment*

The LASIK procedure included mechanical flap preparation using automated microkeratomes (MK) from Moria, France. Each MK uses single-use heads with a pre-defined distance of 90µm between the footplate and the oscillating blade. All have one oscillating motor and a second forward/ backward advancing motor operated by the surgeon with foot pedals. The MKs are attached to a pump-driven vacuum ring fixed to the limbus. The ring size and blade-progression-stop point were chosen by the surgeon according to the corneal keratometry, the desired flap diameter and hinge-width recommended by the manufacturer. Both eyes of the same patient were operated using the same MK and the same head.

Excimer ablation for all eyes was performed using an Allegretto Excimer Laser platform

(Eye-Q 200 Hertz (Hz) or 400 Hz, WaveLight GmbH, Erlangen, Germany) under constant eye tracking (250 Hz). To minimize the induced spherical higher-order aberration (HOA), an aspherical “wavefront-optimized” profile was used with an optical zone of 6.0, 6.5 or 7.0 mm depending on the mesopic pupil diameter and expected residual stromal bed. The manufacturer-recommended “WaveLight myopic astigmatic nomogram” was implemented to compensate for very short or long ablation time and for a cylinder-sphere coupling effect. However, cylinder magnitudes of 0.25 D or less are not addressed by this nomogram. Cyclotorsion was minimized using a “NeuroTrack” system (WaveLight GmbH) in which four built-in blinking light sources eliminate cyclotorsion at its source by controlling optokinesis.

The Laser treatments were performed in eight Refractive Centres located in Berlin, Cologne, Frankfurt/ Main, Hamburg, Hanover, Munich, Nuremberg, and Stuttgart. All refractive surgeons were senior consultants who had performed at least 500 LASIK surgeries and who followed a standard protocol of indications, and preoperative, intraoperative and postoperative management.

Postoperative preservative-free medication after LASIK included ofloxacin four times a day for 1 week, and dexamethasone four times a day for the 1st week, and two times a day for the 2nd and 3rd weeks. Hyaluronic acid artificial tears (Hylolasop, Ursapharm GmbH, Germany) were applied to all eyes for 1– 4 months.

*Statistical analysis*

ROC analysis was used to find the cut-off magnitudes of preoperative ORA (which has the same magnitude as the topographic astigmatism in eyes with a preoperative plano refractive cylinder) that can best discriminate between the groups of efficacy (EI) and safety (SI) indices in preoperative plano refractive cylinder eyes. For EI, these groups were ≤ 0.7 vs. >0.7; ≤0.8 vs. >0.8; ≤0.9 vs. >0.9 and ≤1.0 vs. >1.0. For SI, these groups were ≤0.9 vs. >0.9; ≤1.0 vs >1.0; ≤1.1 vs >1.1 and ≤1.2 vs 1.2. EI was defined as the mean of ratio of postoperative UDVA to preoperative CDVA; SI was defined as the mean of ratio of postoperative CDVA to preoperative CDVA.

The area under the curve (AUC), sensitivity and specificity for the given cut-off magnitudes are shown in Table 3. The hypothesis that the AUC is significantly different from 0.5 was tested and the P values were reported. A P value <0.05 was considered as statistically significant. Differences in preoperative and postoperative parameters between the groups of high and low ORA (determined by ROC analysis) were tested using the t-test for independent samples. The differences in nominal scaled parameters such as sex (male, female), eye dominance (dominant, non-dominant), and eye side (left, right) were tested using the Chi-squared test. We also performed an OLS regression to estimate the direction and degree of correlation between preoperative ORA magnitude and EI or SI of the operative outcome.

*Results*

*ROC analysis*

The ROC analysis (Table 3) shows that eyes with a preoperative ORA (or topographic astigmatism) of ≤ 0.9 D reached an EI of at least 0.8 (best sensitivity and high specificity) statistically significantly more frequently than eyes with a preoperative ORA of > 0.9 D. If the preoperative ORA or topographic astigmatism was maximally 0.8 D, then an EI of at least 0.9 (statistically significant) or > 0.9 (probable) was possible, although with a lower sensitivity and specificity. Therefore, an ORA cut-off of 0.9 was chosen for the comparison of groups with high and low preoperative ORA (topographic astigmatism). For an SI of 0.9 or more, the preoperative ORA (topographic astigmatism) should be maximally 0.8. Sex, eye dominance and side were equally distributed among the groups (Table 4).

Table 3. ROC (receiver operating characteristic) analysis (Table taken from Frings et al. PLoS One. 2015; 10: e0124313; permission to reuse obtained)

| Cut-off | ORA(1) cut-off | AUC(2) | SE(3) | Sensitivity | Specificity | P(4) |
|---|---|---|---|---|---|---|
| **EI(5)** | | | | | | |
| 0.7 | 0.900 | 0.354 | 0.061 | 0.397 | 0.280 | 0.016 |
| 0.8 | 0.900 | 0.376 | 0.049 | 0.382 | 0.362 | 0.013 |
| 0.9 | 0.800 | 0.407 | 0.039 | 0.473 | 0.434 | 0.017 |
| 1.0 | 0.800 | 0.456 | 0.039 | 0.480 | 0.490 | 0.260 |
| **SI(6)** | | | | | | |
| 0.9 | 0.8 | 0.511 | 0.068 | 0.508 | 0.552 | 0.872 |
| 1 | 0.8 | 0.463 | 0.036 | 0.496 | 0.493 | 0.304 |
| 1.1 | 0.8 | 0.509 | 0.045 | 0.537 | 0.507 | 0.847 |
| 1.2 | 0.8 | 0.493 | 0.061 | 0.583 | 0.506 | 0.915 |

1 = ocular residual astigmatism; 2 = Area under the curve; 3 = Spherical Equivalent; 4 = P value <0.05 was considered as significant; 5 = Efficacy Index; 6 = Safety Index.

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Table 4. Descriptives (Table taken from Frings et al. PLoS One. 2015; 10: e0124313; permission to reuse obtained)

| Preoperative ORA(1) | Low (<0.9) ORA (n = 153) | | High (≥0.9) ORA (n = 114) | | Total (N = 267) | | P(2) |
|---|---|---|---|---|---|---|---|
| | Min/Max | Mean (SD) | Min/Max | Mean (SD) | Min/Max | Mean (SD) | |
| age (y) | 19/68 | 33(±10) | 19/63 | 35(±10) | 19/68 | 34(±10) | 0.236 |
| Scotopic pupil size (mm) | 4.0/8.0 | 6.5(±0.7) | 4.5/9.0 | 6.5(±0.7) | 4.0/9.0 | 6.5(±0.7) | 0.513 |
| **Preop refractive data** | | | | | | | |
| CDVA(3) (LogMar) | -0.12/0.15 | -0.03(±0.05) | -0.14/0.34 | -0.02(±0.06) | -0.14/0.34 | -0.02(±0.05) | 0.077 |
| UDVA(4) (LogMAr) | 0.00/2.00 | 1.18(±0.67) | 0.00/2.00 | 1.18(±0.62) | 0.00/2.00 | 1.18(±0.65) | 0.995 |
| sphere (D) | -8.00/-0.75 | -3.58(±1.49) | -8.00/-1.00 | -3.74(±1.77) | -8.00/-0.75 | -3.65(±1.62) | 0.413 |
| topographic cyl (D) (= ORA magnitude (D)) | -0.80/-0.10 | -0.50(±0.21) | -2.00/-0.90 | -1.11(±0.22) | -2.00/-0.10 | -0.76(±0.37) | 0.000 |
| ORA axis (°) | 5/174 | 88(±31) | 21/178 | 89(±14) | 5/178 | 89(±25) | 0.796 |
| **Postop refractive data** | | | | | | | |
| CDVA (LogMar) | -0.20/0.10 | -0.04(±0.05) | -0.18/0.19 | -0.02(±0.07) | -0.20/0.19 | -0.03(±0.06) | 0.010 |
| UDVA (LogMAr) | -0.20/0.44 | -0.01(±0.08) | -0.16/2.00 | 0.05(±0.22) | -0.20/2.00 | 0.01(±0.16) | 0.001 |
| sphere (D) | -0.75/2.50 | 0.24(±0.46) | -1.75/2.50 | 0.22(±0.56) | -1.75/2.50 | 0.23(±0.51) | 0.793 |
| subjective cyl (D) | -1.25/-0.25 | -0.40(±0.19) | -2.00/-0.25 | -0.47(±0.33) | -2.00/-0.25 | -0.43(±0.26) | 0.030 |
| topographic cyl (D) | -1.90/0.00 | -0.65(±0.37) | -2.10/-0.20 | -1.13(±0.38) | -2.10/0.00 | -0.86(±0.44) | 0.000 |
| Spherical Equivalent (D) | -1.00/2.13 | 0.04(±0.43) | -2.00/2.13 | -0.01(±0.56) | -2.00/2.13 | 0.02(±0.49) | 0.400 |
| ORA magnitude (D) | 0.05/1.54 | 0.55(±0.31) | 0.05/2.46 | 0.95(±0.42) | 0.05/2.46 | 0.72(±0.41) | 0.000 |
| ORA axis (°) | 3/175 | 91(±34) | 9/152 | 93(±20) | 3/175 | 92(±29) | 0.606 |
| Refractive SIA(5) magnitude (D) | 0.25/1.25 | 0.40(±0.19) | 0.25/2.00 | 0.47(±0.33) | 0.25/2.00 | 0.43(±0.26) | 0.030 |
| Refractive SIA (°) | 4/180 | 83(±46) | 5/180 | 81(±36) | 4/180 | 83(±42) | 0.721 |
| Refractive TSIA(6) magnitude (D) | 0.03/1.73 | 0.43(±0.30) | 0.00/3.09 | 0.50(±0.45) | 0.00/3.09 | 0.46(±0.37) | 0.111 |
| Refractive TSIA (°) | 1/180 | 86(±47) | 0/177 | 93(±55) | 0/180 | 89(±51) | 0.273 |
| Efficacy Index | 0.36/1.33 | 0.98(±0.15) | 0.01/1.25 | 0.91(±0.21) | 0.01/1.33 | 0.95(±0.18) | 0.002 |
| Safety Index | 0.70/1.39 | 1.04(±0.12) | 0.64/1.39 | 1.02(±0.12) | 0.64/1.39 | 1.03(±0.12) | 0.255 |

1 = Ocular residual astigmatism; 2 = P value <0.05 was considered as significant; 3 = corrected distance visual acuity; 4 = uncorrected distance visual acuity; 5 = refractive surgically induced astigmatism (subjectively manifest SIA); 6 = topographic SIA; Means of astigmatism were calculated by arithmetic means.

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*Crosstabulation*

The crosstabulation (Table 5) shows that smaller magnitudes of preoperative ORA (= topographic astigmatism) resulted in a statistically significantly better EI (Chi-Square = 10.41, P = 0.001). Table 5 also shows that in 62% of the observed cases higher ORA magnitudes (≥ 0.9) were correlated with a low EI (true positive).

Table 5. Ordinary least square regression (OLS) analysis (Table taken from Frings et al. PLoS One. 2015; 10: e0124313; permission to reuse obtained)

| | | True class | | |
|---|---|---|---|---|
| | | **Low (EI(1) 0.01–0.8)** | **High (EI 0.82–1.33)** | **Total** |
| **Predicted class** | **Low (ORA(2) 0.1–0.9)** | 17 | 136 | 153 |
| | **High (ORA 0.91–2)** | 30 | 84 | 114 |
| | **Total** | 47 | 220 | 267 |
| | *True positive* | 0.38 | | |
| | *False positive rate* | 0.64 | | |
| | *Sensitivity* | 0.38 | | |
| | *Specificity* | 0.36 | | |
| | *Correctly classified* | 0.38 | | |

1 = Efficacy Index; 2 = ocular residual astigmatism

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*Refractive results I: Sphere, ORA and Visual Acuity*

No statistically significant difference was found in the preoperative manifest sphere (Table 4). On average, ORA was 0.51±0.21 D (range 0.1–0.8 D) in the low ORA group and 1.11±0.22 D (range 0.9–2.00 D) in the high ORA group; this difference was statistically significant (P < 0.001). There were also no statistically significant differences in the postoperative manifest sphere, but statistically significant differences were found for the postoperative corrected (CDVA) and uncorrected (UDVA) distance visual acuity between eyes with low and high preoperative ORA (Table 4) – although these differences may not be clinically relevant.

*Refractive results II: Manifest SIA and topographic SIA*

The difference in the postoperative subjective cylinder or refractive surgically induced astigmatism (RSIA) was statistically significant (P = 0.03), since the eyes of the group with preoperatively higher ORA had, on average, a higher postoperative subjective cylinder (RSIA) with a wider range in terms of min/max. Eyes with a high ORA preoperatively also had a high ORA postoperatively; the difference in post-op ORA magnitude between the low and high ORA groups was statistically significant (P < 0.001). The difference in the postoperative topographic astigmatism was also significant (P < 0.001) since the eyes of the group with a high ORA preoperatively had, on average, a higher postoperative topographic astigmatism. The RSIA mostly corresponded in magnitude and alignment to the postoperative topographic SIA (TSIA). Eyes with a preoperatively higher ORA had a higher RSIA and TSIA postoperatively, which was statistically significant for RSIA (P = 0.030).

*Refractive efficacy*

Pre- and postoperatively, differences in ORA were statistically significant (P < 0.001; Table 4). In addition, the difference in EI was statistically significantly higher (P = 0.002) for low ORA eyes. The bivariate OLS regression (Table 6) shows that there was a statistically significant negative correlation between preoperative ORA magnitude and EI. Each dioptre (D) of preoperative ORA reduced efficiency by 0.07. The correlation between preoperative ORA and SI was not significant.

Table 6. Bivariate ordinary least square regression (OLS) analysis (Table taken from Frings et al. PLoS One. 2015; 10: e0124313; permission to reuse obtained)

| | Coefficient | Std. Err. | t(2) | P(3) | 95% Conf. Interval | |
|---|---|---|---|---|---|---|
| **EI(1)** | | | | | | |
| **ORA(4) mangnitude** | -0.07 | 0.03 | -2.37 | 0.02 | -0.13 | -0.01 |
| **_cons** | 1.00 | 0.03 | 39.73 | 0.00 | 0.95 | 1.05 |
| **SI(5)** | | | | | | |
| **ORA mangnitude** | -0.02 | 0.02 | -0.80 | 0.43 | -0.05 | 0.02 |
| **_cons** | 1.04 | 0.02 | 62.22 | 0.00 | 1.01 | 1.07 |

1 = Efficacy Index; 2 = empirical t value (coefficient/SE); 3 = significance; 4 = ocular residual astigmatism; 5 = Safety Index

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*Discussion*

As known from Study I, the contributors to refractive cylinder are the anterior cornea and ORA. The ORA mainly results from the posterior corneal surface, the crystalline lens and some unknown "retinal" components (Tejedor and Guirao 2013). ORA is defined as the vectorial difference between the corneal topographic astigmatism and the refractive cylinder (Kugler et al. 2010).

Study II presents treatment data of eyes with preoperatively zero refractive cylinder. In these eyes, our results show that a low preoperative ORA was correlated with a low postoperative ORA and better refractive results (EI, SI, CDVA) as low preoperative topographic astigmatism may be more precisely treated or, if demasked after the Excimer treatment, its refractive disadvantage is less powerful in eyes with low amounts of preoperative ORA compared to cases with higher cylinder magnitudes (nota bene: in eyes with zero refractive cylinder prior to keratorefractive surgery). These differences were statistically significant compared to eyes with high preoperative ORA. Therefore, our findings indicate that caution is recommended when a preoperative ORA of ≥ 0.9 D is present. This could favourably be considered in the LASIK design, even if the subjective refractive cylinder is neutral.

It was hypothesized that in order to analyse the effect on the postoperative refractive cylinder in such cases, initially, in small trial and error steps maybe a part of the preoperative corneal topographic astigmatism should be corrected. This goal can favourably be reached by applying vector analysis according to Alpins (Alpins 1997). Further prospective studies are needed to analyse this assumption and its real effect on post-LASIK refractive results.

In Study I, we analysed 2991 eyes from 2991 consecutive myopic patients scheduled to undergo LASIK to investigate the influence of age, gender, ocular dominance, subjective cylinder and topographic astigmatism, subjective sphere, and mesopic pupil size on pre-existing ORA. The ORA was determined using Alpins vector analysis. Patients were assigned to 1 of 2 subgroups defined by the ratio of ORA to preoperative refractive cylinder (R) (ORA/R of ≥1.0 vs. <1.0). Our analysis indicated that the preoperative assessment of refractive surgery candidates should consider the interaction between topographic, refractive and ocular residual astigmatism. The better the correlation between the magnitude and the orientation of the corneal astigmatism and refractive cylinder, the less astigmatism will remain in the optical system of the eye after treatment (Alpins 1998; Tejedor and Guirao 2013).

However, the definition of high or low ORA cannot be applied in eyes without preoperative refractive cylinder (because the ratio of ORA to preoperative refractive cylinder was calculated for each patient). Therefore, ROC analysis was used to find cut-off values of preoperative ORA that can best discriminate between the groups to optimize EI and SI.

The ROC analysis (Table 4) shows that eyes with a preoperative ORA and preoperative topographic astigmatism of ≤ 0.9 D attained an EI of at least 0.8 (i.e. best sensitivity and high specificity) statistically significantly more frequently than eyes with a preoperative ORA or topographic astigmatism of > 0.9. The difference between low and high ORA eyes in postoperative subjective cylinder or RSIA was statistically significant (P = 0.03) since the eyes of the patients in the group with a high ORA preoperatively on average resulted in a higher postoperative subjective cylinder or RSIA with a wider range of results in terms of min/max, because higher ORA correlates with less treatment predictability. The difference in EI was also statistically significant (P = 0.002). A statistically higher EI was obtained for eyes with a low ORA preoperatively.

Both corneal and non-corneal astigmatism are usually balanced. In a recent study, the amount of aberration of both the cornea and internal optics was found to be larger than that for the complete eye, indicating that the first surface of the cornea and internal optics partially compensate for each other’s aberrations and produce an improved retinal image (Artal 2001). Moreover, topographic astigmatism and refractive cylinder do not necessarily coincide in magnitude and axis (Alpins 1993 and 1997; Alpins and Stamatelatos 2007 and 2008). 40% less of the ORA being corrected on the cornea would reduce the corneal astigmatism significantly without compromising the refractive cylinder outcome (Alpins and Stamatelatos 2007 and 2008).

According to Alpins, using vector planning that integrates topographic data can more effectively reduce overall remaining astigmatism. Integrating the topography parameters with the wavefront aberrometry results in greater reduction in corneal astigmatism and better visual outcomes under mesopic conditions (Alpins and Stamatelatos 2008). The initial study of Alpins (1997) of 100 patients found a mean preoperative ORA magnitude of 0.81 D; 34% of patients had a magnitude greater than 1.00 D.

The strength of Study II of this thesis includes a large sample size, homogeneity of the method of measurement of refraction, and a strict exclusion of ocular pathologies. On the other hand, this study is limited by the fact that statistically significant results do not necessarily indicate clinically relevant differences. There are other factors besides those described in our study that affect the astigmatic status and ORA. These are the posterior cornea, vitreous, and retina, as well as non-optical components such as the visual cortex (Kugler et al. 2010). Of course, measurement errors in manifest cylinder cannot be fully excluded.

Accordingly, our conclusions should be carefully qualified as being determined in a sample of patients with spherical myopia by refraction but showing some anterior corneal astigmatism on topography. By definition, in an eye where the refractive cylinder was underestimated in the manifest refraction, this eye will be classified as having high ORA. Postoperatively, if the astigmatism is then picked up on the manifest refraction, this will be interpreted as having been induced by the procedure, however it seems more likely that there was an error in the preoperative manifest refraction – at least in some cases.

In conclusion, myopic eyes with preoperatively zero refractive cylinder but low topographic astigmatism and low ocular residual astigmatism are correlated with low postoperative ocular residual astigmatism and better refractive results after LASIK. The results of Study II indicate that a preoperative corneal astigmatism of 0.9 D and higher could (partially) be treated at the same time even when the subjective refractive cylinder is neutral. This goal can favourably be reached by applying vector analysis according to Alpins (Alpins 1993 and 1997; Alpins and Stamatelatos 2007 and 2008). In such cases, 50% of the preoperative corneal topographic astigmatism should be corrected initially to analyse the effect on the postoperative refractive cylinder to improve safety, efficacy and predictability of the Excimer Laser treatment.

## 4. Study III

**Katz T*, Frings A*#, Richard G, Steinberg J, Druchkiv V, Linke SJ.**

**Flap-induced astigmatism in eyes with sphere myopia correction: Superior hinge using a rotating microkeratome versus nasal hinge using a linear microkeratome.**

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*Introduction*

Study I and II of this thesis discussed that appropriately addressing astigmatism is crucial and can be a pitfall in Laser vision correction. However, there are other factors influencing postoperative astigmatism and thus, safety, efficacy and predictability of the treatment. One of those factors is the method of LASIK flap preparation.

Creating the corneal flap is a crucial step in LASIK and can be done mechanically using a microkeratome or through photodisruption using a femtosecond Laser (Slade et al. 2007). Using a microkeratome to create a hinged lamellar corneal flap has been the standard procedure for more than a decade. Continuous development of microkeratome designs aims to produce more regular and predictable flap thickness and size and stable fixation of the flap to its bed postoperatively. Results in previous studies indicate that the lamellar cut made with a microkeratome can modify the existing refractive error (Dada et al. 2001). This can induce astigmatism, which can limit uncorrected distance visual acuity (UDVA) and cause subjective symptoms such as halos and night-vision problems (Dada et al. 2001). In contrast, Pallikaris et al. (2002) reported that most undesired ocular aberrations after LASIK were caused by ablation, not by flap preparation.

A previous study (Wolffsohn et al. 2001) reported that uncorrected astigmatism as low as 1.00 D can cause significantly decreased vision. Of course, patients having LASIK usually expect high precision. Accordingly, inducing unwanted astigmatism in eyes with preoperative plano refractive myopia, whether caused by ablation or flap preparation, presents a dilemma. To our best knowledge, one of our previous studies (Frings et al. 2013) was the first to assess the astigmatic component correction in eyes with very low refractive cylinder preoperatively using a rotating superior-hinged microkeratome. Study III of this thesis compared the changes in the astigmatic component in eyes with preoperative plano refractive myopia (zero cylinder) between a rotating microkeratome that creates a superior hinge (M2, Moria SA) and a linear microkeratome that creates a nasal hinge (SBK, Moria SA).

*Methods*

*Patients*

This study evaluated myopic eyes of consecutive patients from March 1, 2011, to September 30, 2012, and was based on the Hamburg Refractive Database (data retrieved from Care Vision Refractive Centres in Germany and Austria). Informed consent for retrospective data analysis was obtained from refractive surgery candidates during their recruiting process. The study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee (no. 2882).

In some patients, the study evaluated both eyes because a refractive plano cylinder was present in both eyes preoperatively. Patients were assigned to the linear microkeratome group (Group 1) or the rotating microkeratome group (Group 2), depending on their LASIK centre and the microkeratome type available. Internal standard documentation was used to define groups of eyes having moderate myopic astigmatism and high myopic astigmatism.

Eyes with a significantly compromised ocular surface and tear film and eyes with intraoperative or postoperative flap complications were excluded from analysis. The latter group included eyes with a postoperatively dislocated flap, epithelial ingrowth, diffuse lamellar keratitis, or central toxic keratopathy. Also excluded were eyes with flap buttonhole or dry-eye syndrome, which can influence refractive outcomes.

The manifest spherical and cylindrical refractions, corrected distance visual acuity (CDVA), and UDVA were assessed and electronically recorded preoperatively and 1 day and 1, 3, 4, and 6 months postoperatively. All outcome results are based on the data from the last follow-up examination. The postoperative spherical and cylindrical refractions were acquired using subjective refraction, and the topographic astigmatism was obtained using an Orbscan II system (Bausch & Lomb). The refractive outcomes were analysed according to standard graphs for reporting the results of refractive surgery (Dupps et al. 2011).

The Alpins vector analysis method (Alpins 1993 and 2001) was applied to describe the effect of LASIK on refractive cylinder. Clinical notations of postoperative cylinder power and cylinder axis were converted to a surgically induced astigmatic (SIA) vector and then to a difference vector. Because all eyes had a plano preoperative refractive cylinder and the target induced astigmatism (TIA) was zero, the difference vector, the SIA, and the post-LASIK refractive cylinder corresponded. The TIA vector was zero in all cases and thus had an indeterminate axis, making the angle of error not calculable. Because the magnitude of error is the SIA minus the TIA, it is equivalent to the SIA because the TIA is zero, which in this case is a measure of the error. Calculations for the Alpins vector analysis were performed using Excel software (Version 2007, Microsoft Corp.).

*Surgical Technique*

The LASIK procedure included mechanical flap preparation using an automated linear microkeratome or rotating microkeratome with a single-use 90µm head. Both microkeratomes used single-use heads with a predefined distance of 90µm between the footplate and the oscillating blade. All had an oscillating motor and a forward/backward advancing motor operated by the surgeon using footpedals. The microkeratomes were attached to a pump-driven vacuum ring affixed to the limbus. The ring size and blade progression stop point were chosen by the surgeon according to the corneal keratometry, the desired flap diameter, and the hinge width recommended by the manufacturer. In cases of bilateral surgery, the same microkeratome and the same head were for both eyes.

The microkeratomes tested differed in their intended flap thickness and their oscillating blade line of progression. The linear microkeratome was attached to linear tracks on the suction ring and driven linearly from the temporal cut border to the nasal hinge and back. The pivoting microkeratome (from the surgeon’s viewpoint) was mounted on a right-sided pin on the vacuum ring and rotated from the upper right toward the lower centre, creating a superior hinge. Ultrasound pachymetry was used to measure the flap thickness on the center of the cornea before the cut and again after flap lifting. The actual flap thickness was determined by subtracting the first flap measurement from the second one.

The Allegretto Excimer Laser platform (Eye-Q 200 Hz or 400 Hz, Wavelight Laser Technologie AG) was used to perform all ablations. Constant eye tracking (250 Hz) was used. Induction of spherical higher-order aberrations (HOAs) was minimized using an aspheric wavefront-optimized profile with an optical zone of 6.0, 6.5, or 7.0 mm, depending on the mesopic pupil diameter and the expected residual stromal bed. The manufacturer-recommended nomogram was used to compensate for very short or very long ablation time and for a cylinder–sphere coupling effect; however, the nomogram did not address cylinder magnitudes of 0.25 D or less.

A Neurotrack system (Wavelight GmbH) was used to minimize cyclotorsion. The system has 4 built-in blinking light sources that eliminate cyclotorsion at its source by controlling optokinesis.

The laser treatments were performed at 9 refractive centres in Berlin, Cologne, Frankfurt am Main, Hamburg, Hanover, Munich, Nuremberg, and Stuttgart, Germany, and Vienna, Austria. All refractive surgeons were senior consultants who had performed at least 500 LASIK surgeries. The surgeons followed a standard protocol of indications and preoperative, intraoperative, and postoperative management.

A Kruskal-Wallis test was applied to rule out systematic differences between the 200 Hz lasers and 400 Hz lasers and thus between the centres (Frings et al. 2013).

*Statistical Analysis*

The compiled data were entered into a spreadsheet program (Excel, Microsoft Corp.) and the Hamburg Refractive Database and then statistically analysed using general purpose statistical software (Stata, version 11.0, Stata Corp). Analysis of variance (ANOVA) was used to compare mean values. If the overall ANOVA model results were statistically significant, the means were compared pairwise and the differences determined using a Bonferroni post hoc test. A Pearson chi-square test was applied for counted data. If significant distributions of counted data were found, the groups were compared pairwise and adjusted using the Bonferroni method. In a multivariate step, ordinary least squares (OLS) regression was used to estimate the effects of the independent variables on SIA. A P value less than 0.05 was considered statistically significant.

*Results*

Group 1 comprised 193 right eyes and 151 left eyes and Group 2, 358 eyes and 343 eyes; the difference was statistically significant (P = 0.22, chi-square test). The mean pre-LASIK ametropia and mean age were similar between the microkeratome groups (Table 7).

Postoperatively, the difference in the magnitude of the refractive cylinder between the study groups was statistically significant (Table 7). Group 1 had a higher mean magnitude of postoperative manifest refractive cylinder than Group 2 (P = 0.003). The remaining subjective sphere was statistically significantly higher in Group 2 than in Group 1 (P < 0.001).

Group 2 had a statistically significantly higher mean magnitude of preoperative topographic astigmatism than Group 1 (P = 0.23). Postoperatively, corneal astigmatism increased in both groups. The absolute increase was higher in Group 2, but not statistically significantly.

Table 8 shows the flap thickness and SIA in the 193 patients (66 in Group 1; 127 in Group 2) whose treatment was bilateral. The bilateral treatment allowed control of the influence of laterality on flap thickness (the right eye always being the first treated eye). Regardless of the microkeratome used, the fellow eyes had thinner flaps. The flap was thicker in the right eye than in the left eye in 42 patients (63.6 %) in Group 1 and in 98 patients (77.2 %) in Group 2 (Table 8). In Group 2, the flaps in the fellow eyes were statistically significantly thinner than in the first eyes. The flaps in fellow eyes were also thinner in Group 1, although the difference between eyes was not statistically significant and the standard deviation (SD) was smaller.

In addition, and again independent of the microkeratome used, the mean magnitude of the SIA was slightly higher, but differences were not statistically significant between first and fellow eyes. However, the distribution of first eyes and fellow eyes was not proportionally between the study groups (Table 7). In both study groups, more right eyes were treated and this difference was statistically significantly larger in Group 1 (P = 0.022).

There were statistically significant differences in the SIA between Group 1 and Group 2 (P = 0.002) (Table 7). The postoperative refractive cylinder (SIA) was 0.75 D or more in 116 (11.1%) of 1045 eyes (44 [12.8%] of 344 eyes in Group 1; 72 [10.3%] of 701 eyes in Group 2) (Figure 1). The mean SIA was lower in Group 2.

The postoperative refractive cylinder was 0.25 D or less in 739 eyes (70.7%) (226 eyes [65.7%] in Group 1; 513 eyes [73.2%] in Group 2). The magnitude of error was statistically significantly different between the microkeratome groups and corresponded to the SIA because of the plano preoperative refractive cylinder. The OLS analysis associated greater degrees of preoperative ametropia (high myopic astigmatism) with higher SIA in all eyes (Table 9). When controlled for the single effect of follow-up time on SIA, the analysis showed it had no statistically significant influence (Table 9).

Applying the rotating microkeratome as a reference category and analysing the effect of the microkeratome head on SIA magnitude over time showed small but statistically significant differences in the ordinary least squares coefficients (Table 10 and Figure 2). The mean SIA of 0.26 D (calculated mean, Table 7) mainly arises from the predominating number of cases that were treated using the rotating microkeratome. As Figure 2 shows, by applying the rotating microkeratome as a reference category, for eyes treated using the linear microkeratome, the SIA with time rose over a long period. In addition, all the coefficients remained stable when analysing the SIA magnitude as a dependent variable and determining the effect of follow-up times of fewer than 400 days.

Both study groups had a mean overall efficacy of approximately 1.00 (Table 7), and there was no statistically significant difference in efficacy between Group 1 and Group 2 (P = 0.741, ANOVA). The safety index (SI) in Group 1 was statistically significantly higher than in Group 2 (P = 0.020, ANOVA), although both groups had a mean SI of 1.0 or more (Table 7).

Table 7. General and refractive data displayed by study group (Table taken from Katz et al. J Cataract Refract Surg. 2015; 41: 1160–1167; permission to reuse obtained)

| | Group 1* (344 Eyes) | | Group 2† (701 Eyes) | | |
|---|---|---|---|---|---|
| Parameter | Mean ± SD | Range | Mean ± SD | Range | P Value |
| Preoperative | | | | | |
| Age (y) | 34.19 ± 9.20 | 19, 60 | 34.50 ± 9.45 | 19, 61 | .345 |
| Sphere (D) | −3.61 ± 1.78 | −9.25, −0.50 | −3.55 ± 1.83 | −9.50, −0.25 | .155 |
| Topographic astigmatism (D) | −0.69 ± 0.36 | −1.90, 0.00 | −0.76 ± 0.40 | −4.00, 0.00 | .023 |
| Topographic astigmatism (°) | 99 ± 73 | 1, 180 | 92 ± 72 | 1, 180 | .185 |
| UDVA | 1.23 ± 0.48 | 0.03, 2.00 | 1.12 ± 0.43 | −0.06, 2.00 | .000 |
| CDVA | −0.03 ± 0.05 | −0.20, 0.17 | −0.03 ± 0.08 | −0.20, 1.30 | .524 |
| Intraoperative | | | | | |
| Flap thickness (um) | 96 ± 16 | 51, 147 | 110 ± 24 | 51, 230 | <.001 |
| Postoperative | | | | | |
| Time (d) | 133 ± 71 | 50, 407 | 255 ± 141 | 50, 627 | <.001 |
| Manifest sphere (D) | 0.05 ± 0.43 | −1.25, 1.75 | 0.11 ± 0.41 | −1.50, 2.00 | <.001 |
| Manifest cylinder (D) | −0.29 ± 0.28 | −1.25, 0.00 | −0.23 ± 0.26 | −1.25, 0.00 | .003 |
| Manifest cylinder (°) | 126 ± 68 | 1, 180 | 139 ± 61 | 1, 180 | .006 |
| Topographic astigmatism (D) | −0.83 ± 0.42 | −2.30, 0.00 | −0.85 ± 0.40 | −2.60, 0.00 | .600 |
| Topographic astigmatism (°) | 97 ± 75 | 1, 180 | 0.99 ± 76 | 0, 180 | .592 |
| UDVA | −0.01 ± 0.10 | −0.20, 0.70 | −0.01 ± 0.09 | −0.20, 1.00 | .869 |
| CDVA | −0.05 ± 0.05 | −0.20, 0.10 | −0.04 ± 0.07 | −0.20, 1.00 | .001 |
| SIA (D) (magnitude of error) | 0.29 ± 0.29 | 0.00, 1.25 | 0.23 ± 0.26 | 0.00, 1.25 | .002 |
| SIA (°) | 61 ± 54 | 0, 180 | 46 ± 49 | 0, 180 | <.001 |
| Efficacy index | 0.97 ± 0.18 | 0.19, 1.39 | 0.98 ± 0.17 | 0.40, 2.00 | .741 |
| Safety index | 1.06 ± 0.11 | 0.75, 1.45 | 1.03 ± 0.14 | 0.69, 2.00 | .020 |

CDVA = corrected distance visual acuity; SIA = surgically induced astigmatism; UDVA = uncorrected distance visual acuity
*Linear microkeratome
†Rotating microkeratome

Table 8. Flap thickness and SIA vector in eyes of patients having bilateral treatment (n= 193) (Table taken from Katz et al. J Cataract Refract Surg. 2015; 41: 1160–1167; permission to reuse obtained)

| | Group 1 (n = 66) | | | Group 2 (n = 127) | | |
|---|---|---|---|---|---|---|
| Parameter | Mean ± SD | Range | Percentage | Mean ± SD | Range | Percentage |
| First (right) eye | | | | | | |
| Flap thickness (μm) | 97.29 ± 17.55 | 60.0, 147.0 | | 117.56 ± 24.60 | 58.0, 174.0 | |
| SIA (D) | 0.31 ± 0.30 | 0.0, 1.0 | | 0.20 ± 0.22 | 0.0, 0.8 | |
| Fellow (left) eye | | | | | | |
| Flap thickness (μm) | 93.77 ± 14.19 | 64.0, 138.0 | | 104.11 ± 21.01* | 59.0, 157.0 | |
| SIA (D) | 0.25 ± 0.27 | 0.0, 1.3 | | 0.19 ± 0.24 | 0.0, 1.0 | |
| Thicker flap in first eye than fellow eye | | | 63.6 | | | 77.2 |

SIA = surgically induced astigmatism
*Paired $t$ test; difference from first eye is statistically significant at $P = .05$ level

Table 9. Interaction between the linear microkeratome head and refraction for dependent variable = SIA magnitude, refractive cylinder = 0, and reference category = rotating microkeratome (Table taken from Katz et al. J Cataract Refract Surg. 2015; 41: 1160–1167; permission to reuse obtained)

| Interaction/Parameter | Coef | Std Err | *t* | *P* Value | 95% CI |
|---|---|---|---|---|---|
| Microkeratome head | | | | | |
| Linear microkeratome | 0.07 | 0.02 | 3.44 | .001 | 0.03, 0.11 |
| Postop days | 0.00 | 0.00 | 1.51 | .133 | 0.00, 0.00 |
| Refraction | | | | | |
| Moderate myopic astigmatism* | 0.06 | 0.02 | 3.41 | .001 | 0.03, 0.09 |
| High myopic astigmatism† | 0.09 | 0.03 | 3.14 | .002 | 0.03, 0.14 |
| _cons | 0.17 | 0.02 | 8.01 | .000 | 0.13, 0.22 |

CI = confidence interval; coef = coefficient (influence of the individual parameter); _cons = constant; SIA = surgically induced astigmatism; Std Err = standard error of coefficient; *t* = empirical t value
*Spherical equivalent −3.10 to −6.00 D; cylinder 0.00 to −3.00 D
†Spherical equivalent −6.10 to −13.50 D; cylinder 0.00 to −3.00 D

Table 10. Interaction between the linear microkeratome head and postoperative days for dependent variable = SIA magnitude, refractive cylinder = 0, and reference category = rotating microkeratome (Table taken from Katz et al. J Cataract Refract Surg. 2015; 41: 1160–1167; permission to reuse obtained)

| Parameter | Linear Head and <400 Postoperative Days | Linear Head and All Postoperative Days* |
|---|---|---|
| Coef | 0.001 | 0.001 |
| Std err | 0.000 | 0.000 |
| *t* | 2.490 | 2.840 |
| $P > t$ | .013 | .005 |
| 95% CI | 0.000, 0.001 | 0.000, 0.001 |

CI = confidence interval; Coef = coefficient; SIA = surgically induced astigmatism; Std err = standard error; $P > t$ = significance; *t* = empirical value
*Including those in the previous column

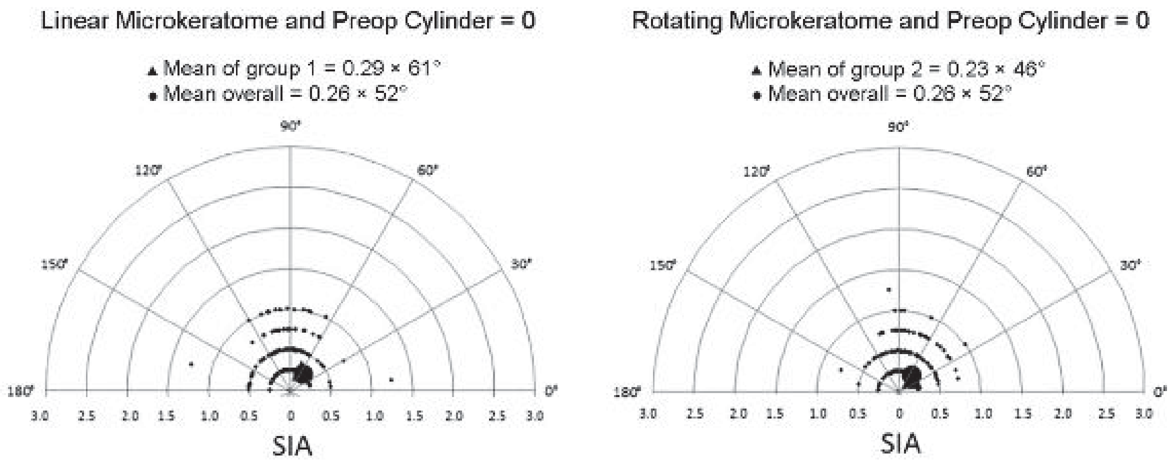



Figure 1. Clinical notations of cylinder power and cylinder axis converted to SIA vector (SIA = surgically induced astigmatism) (Figure taken from Katz et al. J Cataract Refract Surg. 2015; 41: 1160–1167; permission to reuse obtained)

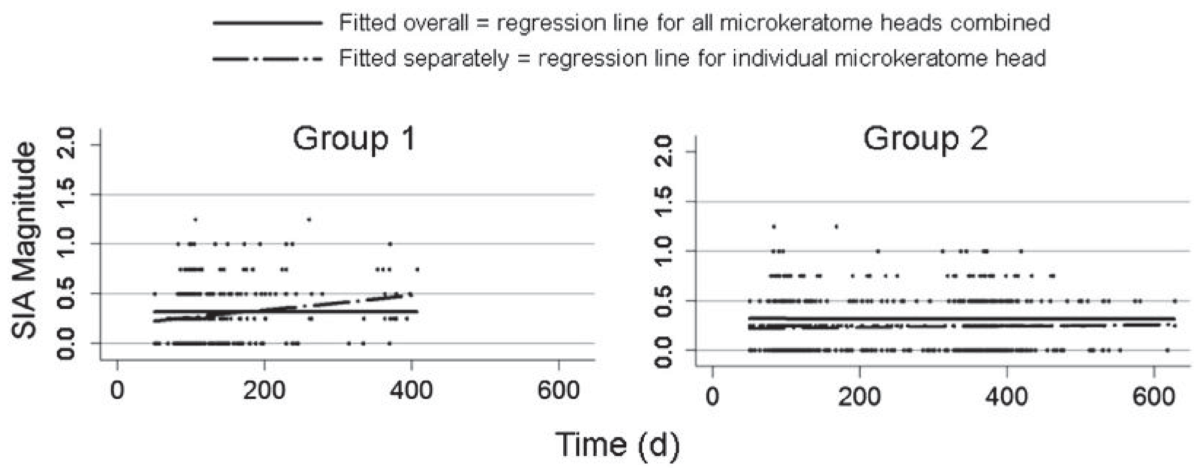



Figure 2. The SIA vector over time (SIA = surgically induced astigmatism) (Figure taken from Katz et al. J Cataract Refract Surg. 2015; 41: 1160–1167; permission to reuse obtained)

*Discussion*

Study III of this thesis compared the SIA results using a rotating microkeratome with a superior hinge and a linear microkeratome with nasal hinge position to perform

LASIK in eyes with a preoperative plano refractive cylinder. The finding was that the main contributor to SIA seems to be the rotating versus the linear mechanism of flap creation and the flap geometry inherent to each. The effect of the hinge position might be a secondary contributor.

Although the mean overall efficacy and safety indices indicate a highly precise, safe, and efficient procedure, there were statistically significant differences in the SIA ($P = 0.002$). The postoperative refractive cylinder (SIA) was 0.75 D or more in 116 (11.1%) of 1045 eyes (44 [12.8%] of 344 eyes in Group 1; 72 [10.3%] of 701 eyes in Group 2). Independent of the microkeratome used, the SIA was slightly higher in eyes that were treated first. In Group 2, the difference in flap thickness was statistically significant, whereas in Group 1, this difference was not statistically significant and the standard deviation was smaller.

The OLS coefficient differences were statistically significant but not clinically relevant. In the Group 1, the SIA significantly increased over a longer period, which was attributed to a surgical learning curve because the linear microkeratome was introduced to the clinic setting after the rotating microkeratome. However, in terms of clinical practice, the mean magnitude of induced astigmatism was 0.35 D or less, and it was independent of the microkeratome type.

The magnitude of error (the difference between the magnitudes of the achieved correction and the intended correction) indicates the SIA (all eyes having plano preoperative refractive cylinder). The OLS analysis showed that higher degrees of preoperative ametropia were connected with higher SIA in all eyes. This was expected because the flap incongruity with the stromal interface becomes important with the amount of tissue ablated, potentially inducing small deviations in postsurgical astigmatism.

Vector magnitudes can be added with regard to each vector’s orientation to obtain a summated vector mean of the group (Alpins 2001). An overall trend would be less evident with a larger difference between the summated vector mean and the mean vector magnitude (Alpins 2001). The differences in our study were similar between the microkeratome groups; therefore, the probability of random events is equal between the groups.

Waheed et al. (2005) described how creating a microkeratome flap contributes to ocular aberrations and concluded that the change in lower-order terms is microkeratome dependent. Variability between microkeratome models has been examined. Studies (Behrens et al. 2000; Flanagan and Binder 2003; Gailitis and Lagzdins 2002; Gokmen et al. 2002; Maldonado et al. 2000; Perez-Santonja et al. 1997; Yildirim et al. 2000) have shown that microkeratomes might cut thinner or thicker flaps than expected. Other studies (Azar et al. 2008; Nassaralla et al. 2005) have shown that the flap thickness can vary across the path of the blade, producing a thinner flap toward the hinge. In the present study, the mean flap thickness was calculated for each microkeratome group using intraoperative ultrasound measurements taken at the centre of the cornea. Because the microkeratomes used in the study were semiautomatic, the flap characteristics were less dependent on the individual surgeon. However, microkeratome types vary in how they cut a corneal flap. Rotating microkeratomes induce an asymmetric flap anatomy because of the geometric way they create the corneal flap. Linear microkeratomes induce a more planar, symmetric flap geometry, independent of which eye is treated. This might be important when discussing small SIA magnitudes. In one study (Muallem et al. 2004), when a rotating microkeratome was used, the flap in the fellow eye was thinner than the flap in the first eye. Because variations in flap thickness might explain SIA, their possible influence on post-LASIK refractive cylinder should be considered, especially in eyes with a small preoperative refractive cylinder.

The present study evaluated the influence of laterality (right eye or left eye = first eye or fellow eye) and found that with the rotating microkeratome, there was a statistically significant difference in flap thickness in both eyes of 1 patient. Independent of the microkeratome used, the fellow eye was associated with thinner flaps.

Roberts (2002) pointed out that any procedure that circumferentially or nearly circumferentially severs corneal lamellae will induce a biomechanical response that will alter the cornea shape less predictably (Waheed et al. 2005). However, several studies have shown that leaving an uncut posterior cornea of at least 250μm is ideal for maintaining normal corneal integrity and biomechanical strength over time (Güell et al. 2005; Holland et al. 2000; Seiler et al. 1998). From this perspective, a thinner corneal flap increases safety after the ablation; however, a thinner corneal flap is less stable and wrinkles more easily, which might lead to irregular astigmatism (Güell et al. 2005; Knorz et al. 1998). The data in our study associated thinner flaps (within a microkeratome group) with less SIA and indicated that high safety indices were independent of the microkeratome used (different flap thicknesses). However, eyes treated using the linear microkeratome (thinnest flap thickness) had a statistically significantly higher SI (P = 0.020)

The role of the hinge position on the outcomes of LASIK has been widely discussed. Huang (2003) reported that a mean of 0.12 D of astigmatism was induced by the flap creation and that hinge position was the strongest determinant of postoperative astigmatism. Lee and Joo (2003) found no difference in flap complication rates or visual outcomes in eyes of LASIK patients assigned to superior hinges and nasal hinges. Using simulated keratometry, Güell et al. (2005) also found no statistical difference from varying hinge position. On the other hand, Pallikaris et al. (2002) reported that most undesired ocular aberrations after LASIK were caused by the ablation, not by flap preparation. In their study, horizontal coma increased after using microkeratomes that created nasal hinges. However, that study compared higher-order aberrations (HOA), which the present study did not analyse.

In summary, our findings concur with those of Nassaralla et al. (2005), Güell et al. (2005), and Lee and Joo (2003), who found no clinically important differences in visual outcomes using a rotating microkeratome (superior hinge position) versus using a linear microkeratome (nasal hinge position). Our results showed that eyes treated using a linear microkeratome had statistically significantly better CDVA after LASIK; however, this finding was not clinically relevant.

Hersh and Abbassi (1999) found that induced astigmatism was generally lower and more randomly placed on the axis after LASIK than after photorefractive keratectomy. Regarding whether the microkeratome flap creation or the ablation procedure induces more refractive errors, some authors reported that the femtosecond Laser might generate more consistent and predictable flap diameters and thicknesses than microkeratomes generate (Durrie and Kezirian 2005). Results in a study by Montés-Micó et al. (2007) indicate that the geometric differences in the shape of the stromal bed between femtosecond LASIK and mechanical LASIK play a significant role. This technique could offer another method for reducing overall induced astigmatism (Durrie and Kezirian 2005; Montés-Micó 2007).

Studies (Oshika et al. 1999; Padmanabhan et al. 2010) have shown that the HOA in the cornea increase after LASIK. However, comparing the studies is difficult because of the variability in the wavefront-sensing method adopted, the spot size and beam profile of the Laser, the ablation and transition zone diameters, and the types and ranges of refractive errors treated (Padmanabhan et al. 2010). Moreover, Moshirfar et al. (2010) found that the rates for all complications were similar between the use of a femtosecond Laser and the use of a mechanical microkeratome.

We acknowledge limitations of our study. First, the effects of the individual examiner and the clinical setup could not be eliminated; however, patients were examined by the same optometrist pre- and postoperatively so that individual examination techniques should have influenced the pre- and postoperative results equally. This limitation exists in almost all refractive studies and is even more limiting in retrospective studies analysing a large patient pool. Another limitation was that HOA were not analysed. Individual healing processes, flap regularity, and postoperative dry eye can explain the difference in SIA; to help prevent the effect of these factors, artificial tears were prescribed according to our clinical standard. During the follow-up, no eye received further surgical (refractive) treatment.

In conclusion, previous studies have shown that the creation of the LASIK flap induces significant ocular aberrations (Pallikaris et al. 2002); however, other studies (Porter et al. 2003; Zhou et al. 2011) have reported that most aberrations after LASIK are induced by the ablation and not by the flap creation. The results of Study III of this thesis show that approximately 10% of preoperatively myopic eyes with preoperatively zero refractive cylinder but a topographic astigmatism of less than 1.00 D tend to be overcorrected in the astigmatic component which can affect safety, efficacy and predictability of the Excimer Laser treatment. Nevertheless, independent of the type of microkeratome, the mean magnitude of refractive cylinder after LASIK was 0.29 D or less.

## 5. Study IV

**Frings A, Steinberg J, Druchkiv V, Linke SJ, Katz T.**

**Role of preoperative cycloplegic refraction in LASIK treatment of hyperopia.**

**Graefes Arch Clin Exp Ophthalmol. 2016; 254: 1399–1404.**

*Introduction*

The preceding Studies I to III have discussed treatment difficulties in myopic and astigmatic eyes and their influence on safety, efficacy and predictability of the Excimer Laser treatment. Studies IV and V of this thesis will focus on pitfalls in hyperopic treatments.

Independent of the treatment method, the Excimer Laser corneal ablation profile for correcting hyperopia steepens the central anterior cornea, changes the corneal asphericity, and makes the cornea more prolate (Gatinel et al. 2004). With steeper cornea, the SI becomes lower as patients lose lines of CDVA, and therefore the treatment of the hyperopic correction range is commonly limited up to +3.00 D, in contrast to the more than double range for myopic correction.

Surface smoothing as a result of corneal wound healing and epithelial remodulation (Huang et al. 2003) and biomechanical changes (Roberts 2002) can contribute to less accurate refractive predictability; in these cases, unwanted regression with flattening of keratometry and, most frequently, final undercorrection occurs. Refractive stability after hyperopic corneal refractive surgery is still controversial. After LASIK, stability has been reported after 1 month (Alió et al. 2006), at 3 months (Llovet et al. 2009), and at 6 months (Waring et al. 2008). Regression represents a considerable clinical problem, demanding retreatment in a significant proportion of cases (Aslanides and Mukherjee 2013).

Previous studies (Cobo-Soriano et al. 2002; Spadea et al. 2006; Zaldivar et al. 2005) suggested that, to improve refractive predictability, preoperative cycloplegic or manifest refraction, or a combination of both (Zadok et al. 2003), could be used in the Laser nomogram. In Study IV, refractive predictability after LASIK in hyperopic astigmatic eyes was analysed. The prevalence of a high difference between manifest (MSE) and cycloplegic SE (CSE) (= manifest cycloplegic difference (MCD)) in hyperopic eyes preoperatively, and (2) the predictability of postoperative keratometry (Km) and MSE in eyes with significant MCD were targeted.

## *Methods*

### *Patients and examinations*

This retrospective study included 186 eyes from 186 consecutive hyperopic patients treated between January 2013 and January 2014, and was based on the Hamburg Refractive Database (data retrieved from Care Vision Refractive Centres in Germany). For each patient, one eye was analysed. An inclusion criterion was a follow-up period of at least 6 months and up to 1 year.

Written informed consent for retrospective data analysis was obtained from refractive surgery candidates during their recruiting process. The study and consent procedure were approved by the local ethics committee of the University of Hamburg, Germany (no. 2882), and adhered to the tenets of the Declaration of Helsinki.

The hyperopic correction was based on the manifest refraction independent of age, and is presented here as spherical equivalent.

Spherical and cylindrical refractions, as well as visual acuity with and without correction, were assessed preoperatively, at 1 day after surgery, and during three consecutive follow-up (FU) intervals (4-week, 3-month, 6-month), and were recorded electronically. All refractions were acquired by subjective refraction, the cycloplegic refraction was measured 30 min after giving cyclopentolate eye drops, and corneal topography was obtained using Scheimpflug topography (Pentacam HR, Oculus, Wetzlar, Germany). All refractions were acquired by expert optometrists using similar refractometers, visual acuity tables, and documentation protocol. Each patient was examined pre- and postoperatively by the same optometrist. Examinations were carried out according to a standardized protocol.

*Laser treatment*

The LASIK procedure included mechanical flap preparation using an automated linear microkeratome (SBK, Moria SA) that creates a nasal hinge with a single-use 90µm head between the footplate and the oscillating blade. The ring size and blade progression stop point were chosen by the surgeon according to the corneal keratometry, the desired flap diameter, and the hinge width recommended by the manufacturer. The microkeratome was attached to linear tracks on the suction ring, and driven linearly from the temporal cut border to the nasal hinge and back. Ultrasound pachymetry was used to measure the flap thickness on the centre of the cornea before the cut and again after flap lifting. The Allegretto Excimer Laser platform (Eye-Q 400 Hz, Wavelight Laser Technologie AG) with eye tracking (400 Hz) was used to perform all ablations. Induction of spherical higher-order aberrations was minimized using an aspheric wavefront- optimized profile with an optical zone of 6.0, 6.5, or 7.0 mm, depending on the mesopic pupil diameter and the expected residual stromal bed. The OZ diameter did not correlate with keratometric or refractive regression. The manufacturer-recommended nomogram was used to compensate for very short or very long ablation time and for a cylinder–sphere coupling effect. A Neurotrack system (Wavelight GmbH) was used to minimize cyclotorsion. The system has four built-in blinking light sources that eliminate cyclotorsion at its source by controlling optokinesis.

The ablation was centred on the visual axis (1st Purkinje image), which is required in hyperopic eyes with relatively large angle kappa. The patient was asked to focus on a target light offered by the Excimer platform. The 1st Purkinje image of this light and its relation to the pupil centre were documented and the eye tracker used this reference point as ablation centre (<<off-set>>).

All three refractive surgeons were experienced consultants and followed a standard protocol of indications, and pre-, intra- and postoperative management.

Pre- and postoperative keratometry (Km) readings were measured in the central 3 mm as simulated K (simK) in millimetre radius and converted to Dioptre using the air to stroma refraction index of 1: 1.367. The central 3 mm include the visual axis, and reflect the main refractive change of the whole cornea. The difference between the true anterior corneal keratometry preoperatively versus postoperatively follows quite precisely the change in manifest refraction, und hence is an appropriate parameter for the corneal and refractive development over time. The targeted Km was calculated using the preoperative Km and adding the SE that was used by the laser platform, with compensation for the vertex distance of the manifest refraction (12 mm) to corneal plane (0 mm). For example, correcting a manifest SE of +4.0 D should increase the central keratometry by $4/(1–0.012 \times 4) = 4.2$ D. In an eye with preoperative Km of 39 D and SE of +4 D, the treatment should result in Km of 43.2 D and SE of 0 D. The expected change is in Km +4.2 D and in SE +4.0 D. We calculated the postoperative actual Km and SE at each FU, and analysed changes between the FU examinations.

*Statistical analysis*

To analyse the predictability, we applied ordinary least square regression (OLS) analysis. To compare differences in slopes between the defined groups of MCD, we estimated the OLS with dummy variable for MCD groups (difference between manifest (MSE) and cycloplegic SE), preoperative SE, and the interaction between these two parameters as explanatory variables, and achieved SE as a dependent variable. The p values for the coefficients were obtained using standard OLS procedures.

*Results*

Table 11 summarizes pre- and postoperative data. Figure 3 displays the predictability of the manifest SE (Pearson correlation coefficient $r = 0.88$). Comparing groups with higher MCD of ≥ 1.00 D versus lower MCD of < 1.00 D, the difference in slopes (high MCD slope of 0.65 in 24 eyes with tendency to overcorrection in higher attempted correction vs. 162 eyes with low MCD slope of 0.93 with better predictability) was statistically significant ($p = 0.025$) (Figure 3 a and b).

Figure 4 demonstrates the dependency of the achieved MSE on the preoperative difference between MSE and CSE. Of the 186 hyperopic eyes, 24 eyes (13 %) had an MCD of ≥ 1.00D (see also Table 12). With increasing difference between MSE and CSE, the postoperative achieved SE increased up to 1 year after surgery, i.e., eyes remained rather hyperopic and regression in terms of an undercorrection was higher.

To rule out bias due to age (i.e., accommodation), in the subgroup with an MCD of ≥ 1.00 D (n = 24) the SE after at least 6 months (249 ± 72 days) was analysed, and no statistically significant effect of age (accommodation) on the postoperatively achieved SE was found. Figure 5 displays the course of postoperative SE and mean keratometry reading (Kmean) in eyes with high MCD. After 3 months, SE and Kmean approach each other, and Kmean shows a tendency towards lower mean magnitude.

Table 11. Summary of pre- and postoperative data. The postoperative data originate from the last FU (249 ± 72 days) (Table taken from Frings et al. Graefes Arch Clin Exp Ophthalmol. 2016; 254: 1399–1404; permission to reuse obtained)

| Preoperative | Min/max | Mean (SD) | Median (Q25/Q75) |
|---|---|---|---|
| Age (years) | 18/63 | 42 (±12) | 45 (18/63) |
| Manifest refraction | | | |
| Sphere (diopter, D) | 0.50/4.00 | 2.60 (±0.86) | 2.75 (0.50/4.00) |
| Cylinder (D) | −3.75/0.00 | −1.09 (±0.98) | −0.75 (−3.75/0.00) |
| Axis‡ (°) | 2/180 | 110 (±62) | 106 (2/180) |
| Spherical equivalent (SE, in D) | 0.13/4.00 | 2.05 (±0.97) | 2.25 (0.13/4.00) |
| Cycloplegic refraction | | | |
| Sphere (D) | 0.75/5.75 | 3.00 (±1.01) | 3.00 (0.75/5.75) |
| Cylinder (D) | −3.75/0.00 | −1.14 (±1.02) | −0.75 (−3.75/0.00) |
| Axis‡ (°) | 1/180 | 109 (±63) | 110 (1/180) |
| SE (D) | −0.13/5.25 | 2.43 (±1.10) | 2.50 (−0.13/5.25) |
| Visual acuity | | | |
| UDVA (logMAr) | 0.00/1.52 | 0.43 (±0.29) | 0.40 (0.00/1.52) |
| CDVA (logMar) | −0.14/0.52 | 0.00 (±0.08) | 0.00 (−0.14/0.52) |
| Pachymetry (µm) | 456/639 | 554 (±32) | 551 (456/639) |
| Postoperative | Min/max | Mean (SD) | Median (Q25/Q75) |
| Manifest refraction | | | |
| Sphere (D) | −0.75/2.25 | 0.41 (±0.55) | 0.25 (−0.75/2.25) |
| Cylinder (D) | −1.75/0.00 | −0.44 (±0.38) | −0.50 (−1.75/0.00) |
| Axis‡ (°) | 1/180 | 110 (±71) | 151 (1/180) |
| SE (D) | −1.00/2.00 | 0.19 (±0.52) | 0.13 (−1.00/2.00) |
| Visual acuity | | | |
| UDVA (logMAr) | −0.19/0.47 | 0.05 (±0.11) | 0.03 (−0.19/0.47) |
| CDVA (logMar) | −0.14/0.30 | 0.00 (±0.07) | 0.00 (−0.14/0.30) |
| EI | 0.33/1.68 | 0.91 (±0.20) | 0.91 (0.33/1.68) |
| SI | 0.62/1.67 | 1.00 (±0.14) | 1.00 (0.62/1.67) |

‡Mean direction was defined with double angle as (Arctan(S / C))/2, where S = SUM sin axis, C = SUM cos axis and axis and converted back to 0°–180°

*UDVA* uncorrected distance visual acuity, *CDVA* corrected distance visual acuity, *EI* efficacy index, *SI* safety index

Table 12. Spherical equivalent (SE) per manifest and cycloplegic refraction (in D) (Table taken from Frings et al. Graefes Arch Clin Exp Ophthalmol. 2016; 254: 1399–1404; permission to reuse obtained)

| Variable | Min | Max | Mean (SD) |
|---|---|---|---|
| | LASIK $n = 186$ | | |
| Age (years) | 18 | 63 | 42 (±12) |
| SE per manifest refraction (D) | 0.13 | 4 | 2.06 (±0.97) |
| SE per cycloplegic refraction (D) | −0.13 | 5.25 | 2.43 (±1.10) |
| MCD (D) | 0 | 2.5 | 0.42 (±0.45) |
| Eyes with high MCD ≥1.00D (*n*) | | | 24 (13.0 %) |

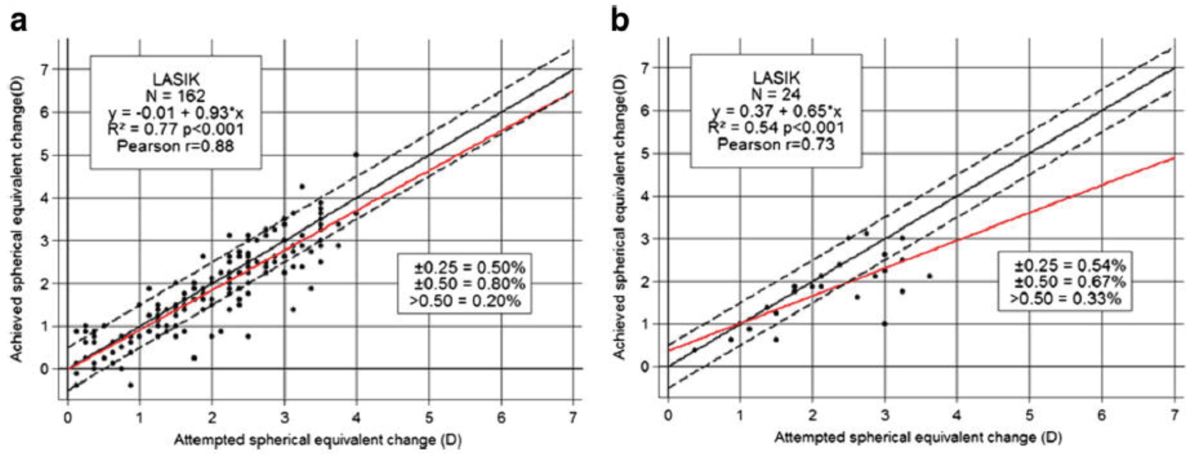



Figure 3. Predictability of change of spherical equivalent (SE). a) Eyes with preoperative MCD < 1 D. b) Eyes with preoperative MCD ≥ 1.00 D. The difference in slopes for MCD ≥ 1.00 D versus MCD < 1.00 D (0.93–0.65 = 0.28) was statistically significant ($p = 0.025$). MCD = difference between manifest (MSE) and cycloplegic (CSE) spherical equivalent (Figure taken from Frings et al. Graefes Arch Clin Exp Ophthalmol. 2016; 254: 1399–1404; permission to reuse obtained)

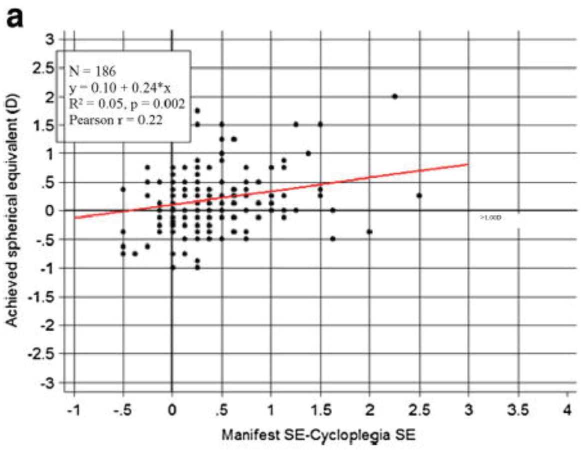



Figure 4. Difference of preoperative MSE and preoperative CSE (= MCD) in a) all LASIK-treated eyes, b) achieved SE in eyes with high MCD matched to patients' age (x-axis) (Figure taken from Frings et al. Graefes Arch Clin Exp Ophthalmol. 2016; 254: 1399–1404; permission to reuse obtained)

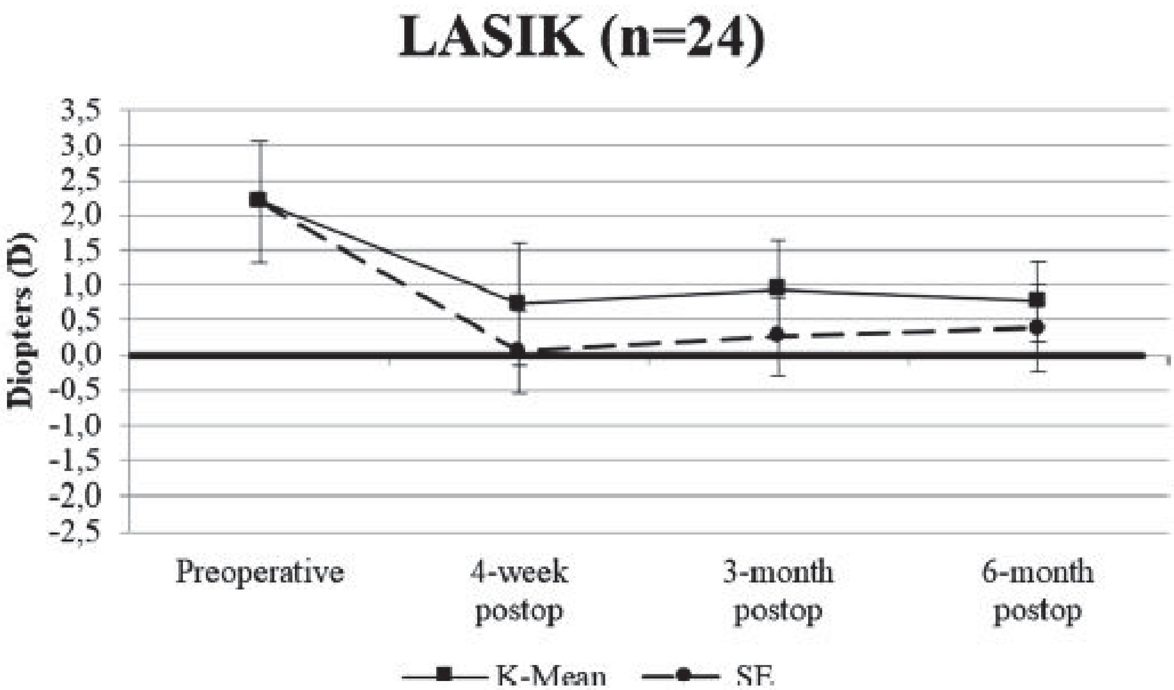



Figure 5. Refraction (SE) and keratometry (Kmean) during FU in eyes with a difference of ≥ 1.00 D between MSE and CSE. During FU, Kmean ranges from 0.75 to 1.00 D. After 3 months, SE and Kmean approach each other, and Kmean shows a tendency towards lower mean magnitude (Figure taken from Frings et al. Graefes Arch Clin Exp Ophthalmol. 2016; 254: 1399–1404; permission to reuse obtained)

*Discussion*

Study IV of this thesis analysed refractive predictability after LASIK treatments based on manifest refraction in hyperopic astigmatic eyes, investigating the prevalence of the high difference between cycloplegic (CSE) and manifest (MSE) SE preoperatively and its correlation with predictability of postoperative MSE.

Our data shows that of the 186 hyperopic eyes (from 186 hyperopic patients), 24 (13 %) had a difference of ≥ 1.00 D between MSE and CSE. With increasing difference between the MSE and CSE, the postoperative achieved SE was hyperopic after the 3-month FU, i.e., eyes remained hyperopic and/ or regression was higher. Comparing groups with an MCD of ≥ 1.00 D versus < 1.00 D, the difference (0.93 – 0.65 = 0.28) in slopes of the predictability of the manifest SE was also statistically significant (P = 0.025).

However, there was no statistically significant effect of age (accommodation) on the achieved SE (Figure 4). This point is, however, still a matter of controversy in clinical practice. For example, for younger patients (< 40 years) with a cycloplegic refraction that differed from the manifest refraction by more than 0.5 D, Spadea et al. (2006) carried out the treatment with the aim of correcting the whole cycloplegic refraction. By contrast, for older patients (> 40 years) a correction of the manifest refraction was performed. Cobo-Soriano et al. (2002) recommended a treatment with 5 % below the cycloplegic refraction for younger patients. Zaldivar et al. (2005) considered that farsighted patients between 20 and 35 embodied a population for whom the most difficulties in the correction of hyperopia occurred, and recommended that for this age group the cycloplegic and the manifest refraction should also be taken into consideration.

In our study, the manifest sphere and cylinder that were used to correct hyperopia resulted in a relatively precise adherence to the desired postoperative manifest SE for eyes with a preoperative difference of < 1.00 D between the MSE and CSE (Figure 3). As already mentioned, with increasing difference between the preoperative MSE and CSE, the postoperative hyperopic regression after LASIK became statistically significant. Nevertheless, a regression of 0.5 D hyperopia was only reached when the MCD was ~ 1.5 D or more. If this difference was 1.0 D or less (which statistically was the case for most of the eyes), the achieved SE deviated by less than 0.5 D.

Figure 5 displays the course of postoperative SE and Kmean in eyes with high preoperative MCD. After 3 months, SE and Kmean approach each other and Kmean shows a tendency towards lower mean magnitude, and thus, hyperopic regression was not caused by regression of Kmean.

We acknowledge limitations to our study. The impact of preoperative or postoperative mean corneal curvature on the visual outcomes was not studied (Torricelli et al. 2014), thereby neglecting a possible influence on SE due to varying cylinder magnitudes caused by measurements with smaller (3 mm, manifest) or larger (7 mm, cycloplegic) diameter.

To conclude, Study IV shows that a preoperative difference of 1.00 D or more between the manifest spherical equivalent and cycloplegic spherical equivalent occurs in about 13% of hyperopic eyes. Our results suggest that hyperopic correction should be based on the manifest spherical equivalent in eyes with a preoperative difference of less than 1.00 D between the manifest and the cycloplegic spherical equivalent to improve safety, efficacy and predictability of the Excimer Laser treatment. If the preoperative difference between the manifest and the cycloplegic spherical equivalent is 1.00 D or more, treatment may produce manifest undercorrection, and therefore it is advisable that the patient should be warned about lower predictability. In these cases, the arithmetic mean calculated from the preoperative manifest and cycloplegic spheres should be applied for treatment planning.

## 6. Study V

**Frings A, Intert E, Steinberg J, Druchkiv V, Linke SJ, Katz T.**

**Outcomes of retreatment after hyperopic laser in situ keratomileusis.**

**J Cataract Refract Surg. 2017; 43: 1436–1442.**

*Introduction*

In Study IV, potential pitfalls of Laser vision correction in hyperopic eyes were discussed. However, in cases where the treatment has not been planned as suggested in Study IV, Laser retreatment is an option to improve efficacy, predictability, and safety of LASIK. Therefore, Study V of this thesis discusses retreatment strategies and refractive results of hyperopic eyes following retreatment.

When searching for "LASIK retreatment and hyperopia" in the PubMed database, only 36 search results were found (04/2017), indicating that only a few studies validate the concept. In contrast, there were 3 to 4 times more studies of "LASIK retreatment and myopia." Moreover, from the 36 search results, only 8 studies were published after 2010. However, optimum treatment planning should be still a vigorous debate because the treatment results of LASIK for hyperopia are less predictable than those of myopic eyes. A recently published large-scale study (Mimouni et al. 2016) identified hyperopia as the parameter that showed the strongest association with retreatment after Excimer Laser refractive surgery.

There are several reasons for less accurate refractive predictability and, most frequently, final undercorrection after hyperopic corneal refractive surgery (Huang et al. 2003; Roberts 2002). Possible explanations are an increase in corneal optical aberrations or a higher rate of refractive regression because of peripheral epithelial proliferation (Ibrahim 1998; Suarez et al. 1996). To improve refractive predictability, preceding studies (Cobo-Soriano et al. 2002; Spadea et al. 2006; Zaldivar et al. 2005) suggested that preoperative cycloplegic or manifest refraction, or a combination of both (Zadok et al. 2003), could be used in the Laser nomogram. In Study IV, it was reported that a manifest cycloplegic difference in SE of 1.00 D or more occurs in approximately 13% of hyperopic eyes. In these cases, a correction of the manifest SE only did not appear to be adequate.

The safety of hyperopic LASIK is also inferior to myopic LASIK, possibly because of creating iatrogenic corneal conus and its location in relationship to the line of sight and to the pupil centre (Desai et al. 2008).

Although the frequency of LASIK retreatment for hyperopia and compound hyperopic astigmatism might be decreasing with the advent of better Lasers, eye trackers, and ablation profiles, retreatments are still performed daily and thus comprise a percentage of our patient profile (Bababeygyet al. 2008). In a previous study (Alió et al. 2006), femtosecond Laser-assisted hyperopic LASIK with the Excimer Laser in the tissue saving mode resulted in only a 1.0 % retreatment rate.

LASIK retreatment for hyperopia is challenging and, if considered, should ultimately fulfil patients' expectations. The purpose of Study V was thus to evaluate the efficacy, predictability, and safety of LASIK retreatment based on manifest refraction in eyes with hyperopia and compound hyperopic astigmatism.

*Methods*

*Patients and Examinations*

This retrospective multicentre study included hyperopic patients with a preoperative difference between cycloplegic and manifest refraction of 1.00 D or less. All patients had LASIK retreatment between May 2014 and October 2015. Both LASIK and retreatment were based on manifest refraction and the target refraction was emmetropia in all cases. The treatments did not include deliberate overcorrection of the hyperopia.

All data were retrieved from the Hamburg Refractive Database (University Hospital Hamburg-Eppendorf and Care Vision Refractive Centres in Germany). One randomly selected eye per patient was analysed and all patients had a follow-up of at least 6 months after retreatment. All patients gave written informed consent for data analysis during the recruiting process. The study and consent procedure were approved by the local ethics committee of the University of Hamburg, Germany, and adhered to the tenets of the Declaration of Helsinki.

Spherical and cylindrical refractions and visual acuity with and without correction, were assessed preoperatively and postoperatively, and during 3 consecutive follow-up examinations (4 weeks, 3 months, and 6 months to 1 year), and were recorded electronically. All refractions were acquired by subjective refraction. The cycloplegic refraction was measured 30 minutes after instilling cycloplegic eyedrops, and corneal topography and higher-order aberrations (HOAs) were obtained using Scheimpflug tomography (Pentacam HR, Oculus Optikgeräte GmbH). All refractions were acquired by expert optometrists using similar refractometers, visual acuity tables, and a documentation protocol. Each patient was examined preoperatively and postoperatively by the same optometrist. Examinations were performed according to a standardized protocol. The refractive outcome was analysed according to standard graphs for reporting the efficacy, predictability, and safety of refractive surgery as suggested previously (Dupps et al. 2011). The influence of preoperative manifest SE (≤2.50 D versus >2.50 D), manifest cylinder (≤1.00 D versus >1.00 D), and keratometry (≤44.00 D versus >44.00 D) on efficacy and safety were also tested.

*Laser Treatment*

The LASIK procedure included mechanical flap preparation using an automated linear microkeratome (SBK 90µm, Moria SA) that creates a nasal hinge with a single-use 90µm head. Ultrasound pachymetry was used to measure the flap thickness on the centre of the cornea before the cut and again after flap lifting. The Allegretto Excimer Laser platform (Wavelight GmbH) with eye tracking (250 Hz) was used to perform all ablations. Induction of spherical HOAs was minimized using an aspheric wavefront-optimized profile with an optical zone (OZ) depending on the mesopic pupil diameter, which was measured with a Colvard pupilometer, and the expected residual stromal bed. A Neurotrack system (Wavelight GmbH) was applied to minimize cyclotorsion. The ablation was centred on the visual axis (first Purkinje image), which is recommended in hyperopic eyes with relatively large angle kappa. The patient was asked to focus on a target light offered by the Excimer platform. The first Purkinje image of this light and its relationship to the pupil centre were documented, and the eye tracker used this reference point as the ablation centre (offset). The target ablation was based on the manifest refraction (eyes had manifest cycloplegic differences of 1.00 D or less).

All patients were treated in 4 centres by 4 refractive surgeons who were experienced consultants and followed a standard protocol of indications as well as preoperative, intraoperative, and postoperative management.

*Laser Retreatment*

Patients who were not satisfied with their uncorrected distance visual acuity (UDVA) but satisfied with their corrected distance visual acuity (CDVA), eyes that deviated by 0.50 D of SE or more from target but had stable manifest and cycloplegic refraction, and were motivated to have a retreatment were included according to the same criteria mentioned above, including manifest cycloplegic difference of less than 1.00 D. In all cases, retreatments were offered free of extra charge and the possible limitations as well as alternatives were discussed before the patient's decision for retreatment. All retreatments were performed at the same centres by the same surgeons with the same laser settings after lifting the existing flap; identical postoperative therapy was applied.

*Statistical Analysis*

To analyse changes in biometrical data from preoperative to postoperative, the paired samples t-test or the Wilcoxon matched-pairs signed-rank test was applied depending on the distribution of the differences. To analyse predictability of the treatment, linear regression was applied. A P value of 0.05 or less was defined as statistically significant.

*Results*

After applying the aforementioned inclusion criteria, this study enrolled 113 eyes of 113 consecutive hyperopic patients. The 51 men (46.0 %) and 60 women (54.0 %) (P = 0.138) had a mean age of 47 years (range 21 to 63 years). Table 13 shows the preoperative and postoperative refractive data for LASIK and retreatment. The mean follow-up after the first treatment and before the second treatment was 10.41 months ± 5.6 (SD). Analysis of the manifest refractive SE showed a statistically significant (P < 0.001) reduction in refractive error at 7.0 ± 0.8 months after retreatment (Table 13).

*Efficacy*

The mean efficacy (mean of the ratio of postoperative UDVA to preoperative CDVA) was 0.68 ± 0.21 logarithm of the minimum angle of resolution (logMAR) for LASIK and increased to 0.93 ± 0.18 logMAR comparing visual acuity before and after retreatment (Table 14). Figure 6 shows the shift to higher EI after retreatment with a postoperative UDVA equivalent to the preoperative CDVA in 85 eyes (75.0 %). Five eyes (4.0 %) still lost 2 lines after retreatment compared with 26 eyes (23.0 %) that lost 3 lines after the first treatment. Table 14 shows the effect of preoperative manifest SE (≤ 2.50 D versus > 2.50 D), manifest cylinder (≤ 1.00 D versus > 1.00 D), or keratometry (≤ 44.00 D versus > 44.00 D) on efficacy and safety. The efficacy after retreatment was statistically significantly improved (P < 0.001, Table 14) without being negatively influenced by preoperative manifest SE, manifest cylinder, or keratometry.

*Predictability*

Figure 7 shows a comparison of refractive predictability after LASIK and retreatment. After LASIK, in 92 eyes (81.0%), the results were greater than ± 0.50 D of the attempted correction. Of the 92 eyes outside this interval, 73 (79.3%) were undercorrected by 1.00 D or more in terms of attempted SE change and this was statistically significantly more common in eyes with a preoperative SE of 2.50 D or more (P = 0.005, chi-square test). In cases still showing a trend toward undercorrection (Figure 7, red lines), retreatment resulted in 88 eyes (78.0%) being within ± 0.50 D of the attempted correction. The target ablation was based on the manifest refraction (all eyes had a manifest cycloplegic difference of 1.00 D or less).

*Safety*

Safety was defined as mean of the ratio of postoperative CDVA to preoperative CDVA. The mean safety was 0.96 ± 0.12 after LASIK and increased to 0.99 ± 0.15 after retreatment (Table 14). LASIK and retreatment resulted in stability and a good SI (Figure 13). No eye had vision-threatening complications. No flap complications (epithelial defects or macrostriae) were observed. No eye developed clinically relevant epithelial ingrowth. In a study under revision at present, 18 patients (14%) had epithelial ingrowth by flap lift when treated with Sub-Bowman keratomileusis, only 3 (2%) of which extended beyond the flap border centripetally, and most of them did not need cleaning. There was no topographic indication of ectasia at the last follow-up.

Table 14 shows the effect of preoperative manifest SE (≤ 2.50 D versus > 2.50 D), manifest cylinder (≤ 1.00 D versus > 1.00 D), and keratometry (≤ 44.00 D versus > 44.00 D) on safety. The SI was statistically significantly improved by retreatment (P = 0.004) without being negatively influenced by preoperative manifest SE, manifest cylinder, or keratometry. Despite the high levels of the SI before retreatment, eyes with preoperative manifest SE of more than 2.50 D, manifest cylinder of 1.00 D or less, or keratometry of 44.00 D or less in particular did benefit from retreatment.

All Laser treatments applied an optical zone (OZ) diameter of either 6.0 mm (29 treatments [25.5 %]) or 6.5 mm (84 treatments [74.5 %]) based on mesopic pupil size. The smaller OZ in the first treatment correlated with lower SI (P = 0.019, paired-samples t-test). The OZ diameter did not correlate with efficacy, predictability, or safety achieved by retreatment. These parameters also did not show statistical significance with regard to age or sex. No patient required further retreatment.

*Discussion*

Refractive treatment planning of hyperopic LASIK is still a vigorous scientific debate. Recently, higher initial corrections, astigmatism, older age, and hyperopia have been identified as significant risk factors for LASIK retreatment (Hersh et al. 2003; Randleman et al. 2009). Among those risk factors, hyperopia has been highlighted as the parameter that showed the strongest association with retreatment after Excimer Laser refractive surgery. Therefore, the purpose of this study was to evaluate the efficacy, predictability, and safety of LASIK retreatment of eyes with hyperopia and compound hyperopic astigmatism.

For primary hyperopic LASIK, retreatment rates of 6.0 % to 20.8 % have been reported (Ghanem et al. 2007; Hersh et al. 2003). All patients in the current study reported highly subjective dissatisfaction; in these eyes, the main objective criterion for a retreatment was a difference between targeted and achieved manifest SE of

0.50 D or more after at least 6 months' follow-up. We did not retreat eyes earlier after LASIK because keratometric and refractive changes are likely to occur up to 6 months after LASIK and therefore, earlier retreatment is not advisable (Frings et al. 2016).

However, the criteria for retreatment can differ between surgeons. For myopia correction in particular, various criteria to retreat have been published (Brahma et al. 2001; Perez-Santonja et al. 1999; Rojas et al. 2002). Similar to our retreatment protocol, Netto and Wilson (2004), for example, decided to retreat based on patient dissatisfaction with UDVA from residual refractive error of at least 0.50 D. Alió et al. (2006) and Ortega-Usobiaga et al. (2007) evaluated the safety, efficacy, and predictability of wavefront-guided LASIK using the Technolas Excimer in retreatment for hyperopia. Both studies compared primary preoperative low-hyperopia and high-hyperopia groups and found that the low-hyperopia group had better predictability results, UDVA, CDVA, and postoperative SE (Bababeygy et al. 2008). Accordingly, different groups of preoperative manifest SE (≤ 2.50 D versus > 2.50 D), manifest cylinder (≤ 1.00 D versus > 1.00 D), and keratometry (≤ 44.00 D versus > 44.00 D) were tested.

Using an aspheric wavefront-optimized profile with the Allegretto Excimer Laser platform, the results of our study indicate that in hyperopic eyes with a preoperative difference between cycloplegic and manifest refraction of 1.00 D or less, a LASIK retreatment is efficient, predictable, and safe and therefore, ultimately meets patients' preoperative expectations. The EI and the SI after retreatment were not negatively influenced by preoperative manifest SE, manifest cylinder, keratometry, or OZ diameter. Treatment predictability, however, was statistically significantly worse in eyes with a preoperative SE of more than 2.50 D ($P = 0.005$, tested with chi-square test), which is similar to the results in previous studies (Alió et al. 2006; Patel et al. 2000). Our results show good UDVA and CDVA, high predictability, and especially high safety and efficacy indices, which were statistically significantly improved by the retreatment; no eye lost more than 2 CDVA lines.

As mentioned above, some recently published large-scale studies of retreatment rates after corneal refractive surgery found that retreatment rates are declining. Mimouni et al. (2016) analysed 41 504 eyes and reported retreatment rates ranging from 0.48% to 3.14%. They concluded that based on multiple logistic regression analysis, age, astigmatism, hyperopia, temperature, and surgeon' s experience significantly affected the necessity for retreatment. However, retreatment rates reaching up to 16% have been reported in the past (Mimouni et al. 2016; Yuen et al. 2010). In 2003, Hersh et al. (2003) reported a 10.5% incidence of retreatment with higher initial corrections, astigmatism, and older age being significant risk factors for LASIK retreatment. In 2009, Randleman et al. (2009) reported a 6.3% retreatment rate and found that hyperopic eyes or those with higher astigmatism were more likely to have retreatment.

Since then, surgeon experience, innovations in Laser technologies, and nomogram adjustments have led to improvements in visual and refractive outcomes (Jin and Merkley 2006; Mimouni et al. 2016). For myopic LASIK, approximately one third of the eyes that had wavefront technology in LASIK retreatments had overcorrections of more than 0.5 D (Hsu et al. 2015; Mimouni et al. 2016; Schwartz et. al. 2005). Carones et al. (2003) noted postoperative retreatment overcorrections ranging from +0.12 to +1.50 D in all 7 eyes studied, Castanera et al. (2004) reported a 38% overcorrection rate in a study of 21 eyes, and Schwartz et al. (2005) also found 29% of 14 eyes were overcorrected by 1.00 to 2.00 D. Jin and Merkley (2006) further compared the outcome of conventional and wavefront-guided LASIK retreatment and found that 30% of eyes in the wavefront-guided group showed an overcorrection of +0.5 D versus no eyes in the conventional group.

Pokroy et al. (2016) analysed the records of 9699 eyes of 9699 consecutive patients. They found that transepithelial photorefractive keratectomy (PRK) increased the odds of retreatment. Preoperative low myopia and CDVA better than 20/20 tended to increase retreatment rates, although general retreatment rates have continued to decline. Although 223 eyes (2.30%) were retreated, the 2-year retreatment rate decreased from 6.17% for primary PRK treatments performed in 2005 to 0.10% for primary PRK performed in 2012 ($P < 0.001$) (Pokroy et al. 2016). Next-generation Laser treatment applications, such as hyperopic small-incision lenticule extraction, and advanced treatment modalities, such as epithelial monitoring, are offering interesting perspectives for future retreatment rates (Reinstein, Carp et al. 2017; Reinstein, Pradhan et al. 2017).

The role of preoperative cycloplegic refraction in LASIK planning has been widely discussed. According to Study IV of this thesis, treatment might be more likely to produce manifest undercorrection and therefore, it is recommend cautioning the patient about lower predictability and suggest basing the arithmetic mean calculated from the preoperative manifest and cycloplegic SE if the preoperative difference between cycloplegic and manifest refraction (manifest-cycloplegic difference) is 1.00 D or more. A strong advantage of the current study is that only eyes with a preoperative difference between cycloplegic and manifest SE of 1.00 D or less were included and all treatments were based on manifest refraction. However, even when the preoperative difference between cycloplegic and manifest SE is 1.00 D or less (as in the current study), most eyes were beyond ± 0.50 D of the attempted SE correction after the first treatment and most of these eyes were undercorrected by 1.00 D or more. As mentioned above, this was statistically significantly more likely in eyes with preoperative SE of 2.50 D or more ($P = 0.005$, chi-square test).

In contrast to a previous study (Ortega-Usobiaga et al. 2007) in which most patients had relatively good uncorrected vision and minimum refractive errors before retreatment, the current data indicate that retreatment is necessary because low UDVA and low efficacy diminished subjective patient satisfaction.

Any refractive surgery can be influenced by a variety of factors, including surgical technique, surgeon nomogram, specific Laser function, and criteria for performing retreatments. To exclude differences related to these factors, this study was based on a highly standardized treatment protocol with strictly defined treatment settings, the same surgical protocol was applied, and all surgeons involved were experienced consultants. Nevertheless, our study is limited by a 6-month follow-up after retreatment, which means long-term safety, predictability, and efficacy, although not expected (Frings et al. 2016), could be different. Moreover, the association between retreatment success and further parameters such as room temperature, humidity, or month or season of primary surgery were not part of this analysis (Hiatt et al.2006; Montague and Manche 2006).

Table 13. Preoperative and postoperative refractive data for LASIK and retreatment (Table taken from Frings et al. J Cataract Refract Surg. 2017; 43: 1436–1442; permission to reuse obtained)

| Parameter | Preop | | Postop | | P Value |
|---|---|---|---|---|---|
| | Range | Mean ± SD | Range | Mean ± SD | |
| LASIK | | | | | |
| Keratometry (D) | 38.9, 46.3 | 42.96 ± 1.42 | 40.5, 47.5 | 44.46 ± 1.53 | <.001* |
| Manifest sphere (D) | 1.25, 5.00 | 3.13 ± 0.94 | −0.50, 2.75 | 1.40 ± 0.58 | <.001* |
| Manifest cylinder (D) | −3.75, 0.00 | −0.70 ± 0.79 | −2.50, 0.00 | −0.74 ± 0.46 | .123† |
| Manifest SE (D) | 1.25, 4.63 | 2.78 ± 0.86 | −1.00, 2.25 | 1.03 ± 0.60 | <.001* |
| Cycloplegic sphere (D) | 1.25, 5.75 | 3.39 ± 1.02 | −0.50, 4.25 | 1.71 ± 0.68 | <.001* |
| Cycloplegic SE (D) | 1.25, 4.88 | 3.04 ± 0.92 | −1.00, 3.00 | 1.34 ± 0.67 | <.001* |
| UDVA (logMAR) | — | — | −0.06, 0.70 | 0.19 ± 0.17 | <.001† |
| CDVA (logMAR) | −0.10, 0.30 | −0.01 ± 0.07 | −0.10, 0.28 | 0.02 ± 0.08 | <.001† |
| Retreatment | | | | | |
| Keratometry (D) | 40.5, 47.5 | 44.54 ± 1.51 | 40.8, 48.5 | 45.21 ± 1.69 | <.001† |
| Manifest sphere (D) | −0.50, 2.75 | 1.41 ± 0.59 | −0.50, 2.00 | 0.49 ± 0.54 | <.001* |
| Manifest cylinder (D) | −2.50, 0.00 | −0.75 ± 0.47 | −1.50, 0.00 | −0.44 ± 0.35 | <.001* |
| Manifest SE (D) | −1.00, 2.25 | 1.03 ± 0.62 | −0.50, 1.38 | 0.27 ± 0.47 | <.001* |
| UDVA (logMAR) | — | — | −0.10, 0.30 | 0.04 ± 0.08 | .017* |
| CDVA (logMAR) | −0.10, 0.28 | 0.02 ± 0.07 | −0.10, 0.22 | 0.01 ± 0.06 | .095* |

CDVA = corrected distance visual acuity; logMAR = logarithm of the minimum angle of resolution; SE = spherical equivalent; UDVA = uncorrected distance visual acuity; *Paired-samples t-test; †Wilcoxon matched-pairs signed-rank test

Table 14. Efficacy and safety data between the first treatment and the retreatment (Table taken from Frings et al. J Cataract Refract Surg. 2017; 43: 1436–1442; permission to reuse obtained)

| Parameter | N | Efficacy Index | | | | | Safety Index | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | First Treatment | | Retreatment | | P Value | First Treatment | | Retreatment | | P Value |
| | | Range | Mean ± SD | Range | Mean ± SD | | Range | Mean ± SD | Range | Mean ± SD | |
| All eyes | 113 | 0.17, 1.02 | 0.65 ± 0.22 | 0.60, 1.85 | 0.99 ± 0.21 | <.001* | 0.52, 1.25 | 0.96 ± 0.12 | 0.68, 1.92 | 1.05 ± 0.18 | .004* |
| Eyes with preoperative | | | | | | | | | | | |
| Manifest SE ≤2.50 D | 47 | 0.40, 1.02 | 0.71 ± 0.19 | 0.73, 1.20 | 0.97 ± 0.12 | <.001† | 0.83, 1.20 | 1.00 ± 0.09 | 0.77, 1.20 | 1.03 ± 0.12 | .282† |
| Manifest SE >2.50 D | 46 | 0.17, 1.00 | 0.61 ± 0.24 | 0.60, 1.85 | 1.01 ± 0.26 | <.001* | 0.52, 1.25 | 0.93 ± 0.14 | 0.68, 1.92 | 1.06 ± 0.21 | .005* |
| Manifest cylinder ≤1.00 D | 93 | 0.17, 1.02 | 0.64 ± 0.23 | 0.60, 1.85 | 1.00 ± 0.22 | <.001* | 0.52, 1.20 | 0.95 ± 0.12 | 0.75, 1.92 | 1.05 ± 0.18 | .002* |
| Manifest cylinder >1.00 D | 20 | 0.45, 1.00 | 0.69 ± 0.17 | 0.78, 1.28 | 0.97 ± 0.16 | .004† | 0.72, 1.25 | 0.99 ± 0.13 | 0.68, 1.37 | 1.03 ± 0.20 | .606† |
| K ≤44.00 D | 84 | 0.17, 1.00 | 0.64 ± 0.21 | 0.60, 1.85 | 1.02 ± 0.23 | <.001* | 0.52, 1.25 | 0.96 ± 0.13 | 0.77, 1.92 | 1.07 ± 0.19 | .004* |
| K >44.00 D | 29 | 0.63, 1.14 | 0.91 ± 0.14 | 0.63, 1.14 | 0.91 ± 0.14 | .003† | 0.67, 1.29 | 0.97 ± 0.15 | 0.67, 1.29 | 0.97 ± 0.15 | .507† |

K = keratometry; SE = spherical equivalent; *Wilcoxon matched-pairs signed-rank test; †Paired-samples t-test

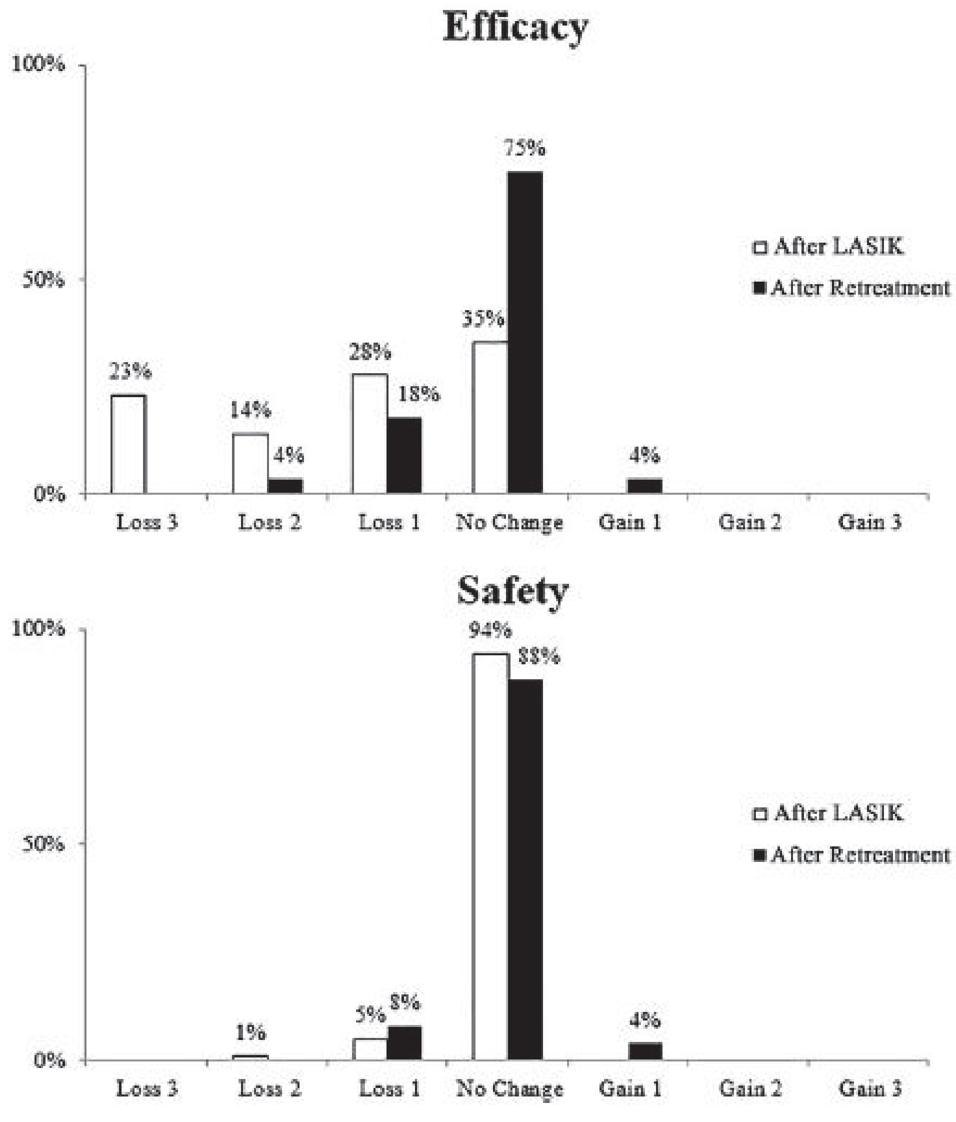
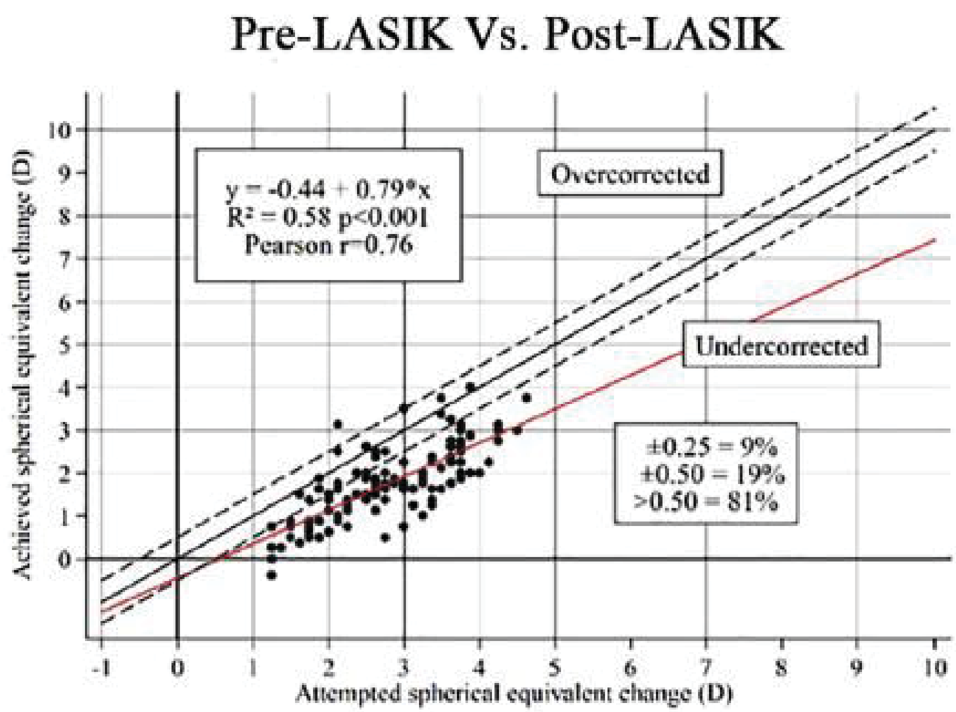
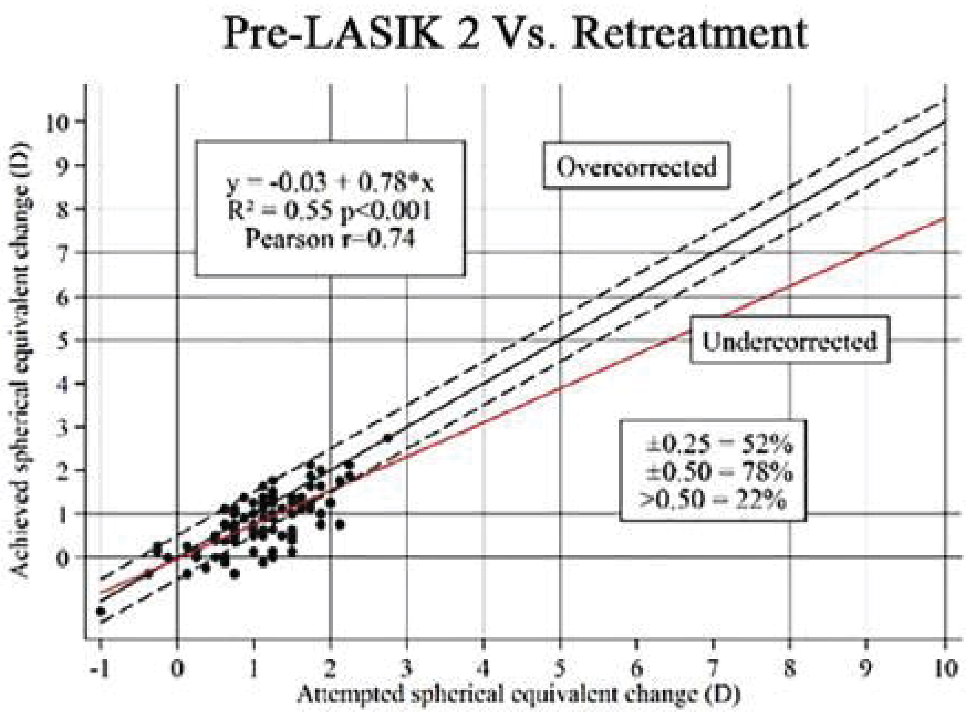



Figure 6. Change in lines of efficacy (mean of ratio of postoperative UDVA to preoperative CDVA) and safety (mean of ratio of postoperative CDVA to preoperative CDVA) (Figure taken from Frings et al. J Cataract Refract Surg. 2017; 43: 1436–1442; permission to reuse obtained)


Pre-LASIK Vs. Post-LASIK
y = -0.44 + 0.79*x
R² = 0.58 p<0.001
Pearson r=0.76
Overcorrected
Undercorrected
±0.25 = 9%
±0.50 = 19%
>0.50 = 81%
Achieved spherical equivalent change (D)
Attempted spherical equivalent change (D)


Pre-LASIK 2 Vs. Retreatment
y = -0.03 + 0.78*x
R² = 0.55 p<0.001
Pearson r=0.74
Overcorrected
Undercorrected
±0.25 = 52%
±0.50 = 78%
>0.50 = 22%
Achieved spherical equivalent change (D)
Attempted spherical equivalent change (D)

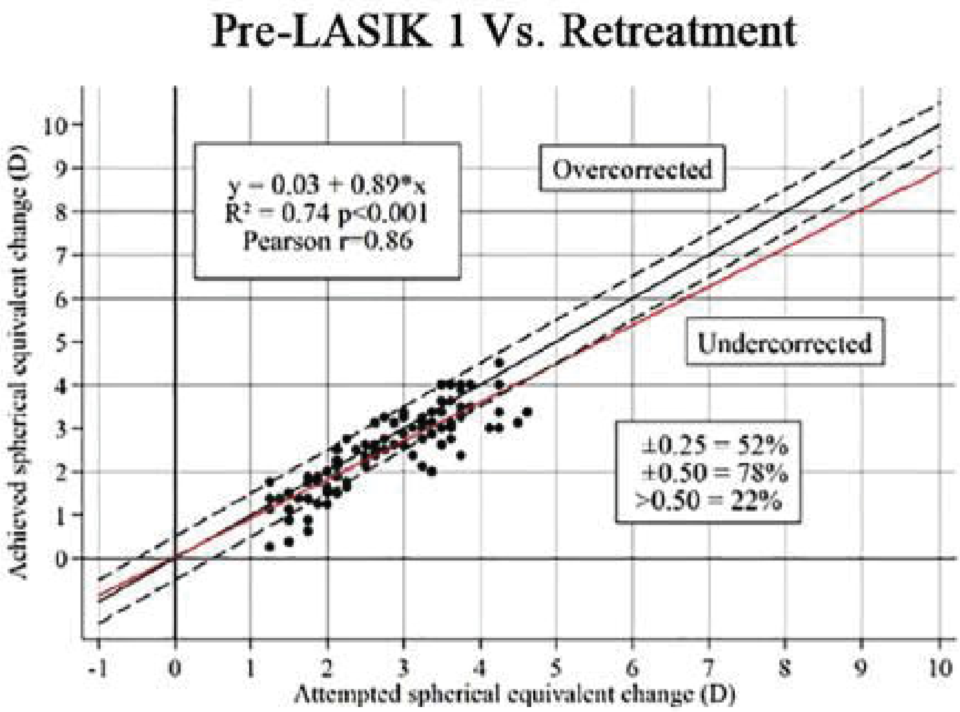



Figure 7. Attempted versus achieved SE correction. The red lines indicate a trend toward undercorrection (Figure taken from Frings et al. J Cataract Refract Surg. 2017; 43: 1436–1442; permission to reuse obtained)

To conclude, retreatment after hyperopic LASIK in eyes with a difference between cycloplegic and manifest refraction of 1.00 D or less prior to the first treatment results in high efficacy, predictability, and safety when the surgery is based on manifest refraction. Efficacy and safety of the retreatment are not influenced by preoperative manifest spherical equivalent of less than 2.50 D, manifest cylinder, keratometry, or optical zone diameter, whereas the treatment predictability was statistically significantly lower in eyes with a preoperative spherical equivalent of 2.50 D or more. Nevertheless, hyperopic LASIK must be held to the same standards as myopic LASIK.

## 7. Summary / Zusammenfassung auf Deutsch

Laser-in-situ-Keratomileusis (LASIK) has become a popular method of surgical vision correction. Minimal discomfort, rapid recovery of visual acuity, high efficacy, and a minimal wound-healing response have been described as major advantages of the technique. As discussed in this thesis, there are some hurdles to be taken when full refractive correction is the goal of treatment. Subgroups of patients with different types of ametropia should be addressed individually and thus, treatment planning is highly demanding. There is no one fits all solution. The following paragraphs summarize the main findings of this thesis which aim at improving safety, efficacy and predictability of Excimer Laser refractive correction in ametropic eyes.

Study I

The contributors to refractive cylinder are the anterior cornea and the ocular residual astigmatism. The latter is defined as the vectorial difference between the corneal topographic astigmatism and the refractive cylinder (Alpins et al. 2012; Alpins and Stamatelatos 2007; Kugler et al. 2010). This difference can be significant and may lead to suboptimal visual outcomes after refractive corneal surgery (Kugler et al. 2010). Results of Study I indicate that subjective sphere ($P = 0.02$) and male sex ($P < 0.001$) were statistically significant negative predictors for the degree of preoperative ocular residual astigmatism, while increasing age and larger mesopic pupil sizes did not indicate an orientation of preoperative ocular residual astigmatism. With-the-rule astigmatism meridian was more likely in eyes with low ocular residual astigmatism while oblique and against-the-rule meridia were common in high ocular residual astigmatism. The current data can help identify patients at high risk for having a significant difference between subjective cylinder and topographic astigmatism thereby improving safety, efficacy and predictability of the Excimer Laser treatment.

Study II

Myopic eyes with preoperatively zero refractive cylinder but low topographic astigmatism and low ocular residual astigmatism are correlated with low postoperative ocular residual astigmatism and better refractive results after LASIK. The results of Study II indicate that a preoperative corneal astigmatism of 0.9 Dioptre and higher could (partially) be treated at the same time even when the subjective refractive cylinder is neutral. This goal can favourably be reached by applying vector analysis according to Alpins (Alpins 1993 and 1997; Alpins and Stamatelatos 2007 and 2008). In such cases, 50% of the preoperative corneal topographic astigmatism should be corrected initially to analyse the effect on the postoperative refractive cylinder to improve safety, efficacy and predictability of the Excimer Laser treatment.

Study III

Previous studies have shown that the creation of the LASIK flap induces significant ocular aberrations (Pallikaris et al. 2002); however, other studies (Porter et al. 2003; Zhou et al. 2011) have reported that most aberrations after LASIK are induced by the ablation and not by the flap creation. The results of Study III of this thesis show that approximately 10% of preoperatively myopic eyes with preoperatively zero refractive cylinder but a topographic astigmatism of less than 1.00 Dioptre tend to be overcorrected in the astigmatic component which can affect safety, efficacy and predictability of the Excimer Laser treatment. Nevertheless, independent of the type of microkeratome, the mean magnitude of refractive cylinder after LASIK was 0.29 Dioptre or less.

Study IV

Study IV shows that a preoperative difference of 1.00 Dioptre or more between the manifest spherical equivalent and cycloplegic spherical equivalent occurs in about 13% of hyperopic eyes. Our results suggest that hyperopic correction should be based on the manifest spherical equivalent in eyes with a preoperative difference of less than 1.00 Dioptre between the manifest and the cycloplegic spherical equivalent to improve safety, efficacy and predictability of the Excimer Laser treatment. If the preoperative difference between the manifest and the cycloplegic spherical equivalent is 1.00 Dioptre or more, treatment may produce manifest undercorrection, and therefore it is advisable that the patient should be warned about lower predictability. In these cases, the arithmetic mean calculated from the preoperative manifest and cycloplegic spheres should be applied for treatment planning.

Study V

Retreatment after hyperopic LASIK in eyes with a difference between cycloplegic and manifest refraction of 1.00 Dioptre or less prior to the first treatment results in high efficacy, predictability, and safety when the surgery is based on manifest refraction. Efficacy and safety of the retreatment are not influenced by preoperative manifest spherical equivalent of less than 2.50 Dioptres, manifest cylinder, keratometry, or optical zone diameter, whereas the treatment predictability was statistically significantly lower in eyes with a preoperative spherical equivalent of 2.50 Dioptres or more.

In general, corneal refractive surgery already offers a safe, efficient and predictable way to correct ametropia. However, there is still room for improvement.

This thesis discussed distinct parameters that have an influence on treatment planning, the surgery itself and thus, refractive results. Among these parameters were the preoperative ocular residual astigmatism and preoperative topographic astigmatism, the method of LASIK flap creation, the difference between manifest and cycloplegic refraction in hyperopic eyes and parameters related to retreatment settings for hyperopia. All of these aforementioned parameters take influence on treatment safety, efficacy and predictability.

Based on the results presented in this thesis, improvement of currently used and inauguration of new treatment approaches will enable us to treat refractive disorders in an even safer, more precise and predictable way.

**Zusammenfassung auf Deutsch**

Die Laser-in-situ-Keratomileusis (LASIK) ist eine populäre Methode zur Korrektur einer Ametropie. Hauptvorteile dieser Technik sind in der Regel geringe subjektive postoperative Beschwerden, eine schnelle Wiederherstellung der Sehschärfe, eine hohe Wirksamkeit und eine minimale Wundheilungsreaktion. Wie in dieser kumulativen Arbeit diskutiert, müssen jedoch einige Hürden genommen werden, um die avisierte refraktive Korrektur das Ergebnis der Behandlung werden zu lassen. Untergruppen von Patienten mit verschiedenen Ausprägungsgraden von Ametropie sollten individuell behandelt werden, und daher kann die Behandlungsplanung sehr anspruchsvoll sein. Es existiert keine „one fits all solution“. Die folgenden Paragraphen fassen die wichtigsten Ergebnisse dieser kumulativen Arbeit zusammen, die darauf abzielt die Sicherheit, Wirksamkeit und Vorhersagbarkeit der Excimer-Laser-Korrektur von Ametropie zu verbessern.

Studie I

Die Hauptquellen des refraktiven Zylinders sind der Hornhautastigmatismus (v.a. der Vorderfläche der Hornhaut) und der okuläre residuale Astigmatismus. Letzterer ist definiert als der vektorielle Unterschied zwischen dem topografischen Hornhautastigmatismus und dem refraktiven Zylinder (Alpins et al. 2012; Alpins and Stamatelatos 2007; Kugler et al. 2010). Dieser Unterschied kann signifikant sein und zu suboptimalen visuellen Ergebnissen nach refraktiver Hornhautchirurgie führen (Kugler et al. 2010). Ergebnisse der Studie I zeigen, dass die Höhe der präoperativen subjektiven Sphäre ($P = 0,02$) und das männliche Geschlecht ($P < 0,001$) statistisch signifikante, negative Prädiktoren für den Grad des präoperativen okulären residualen Astigmatismus waren, während die Parameter höheres Patienten-Alter und ein größerer (mesopischer) Pupillendurchmesser keine Korrelation zeigten. Bei Augen mit geringem okulären residualen Astigmatismus war der steile Meridian häufiger mit der Regel, während bei Augen mit geringem okulären residualen Astigmatismus der steile Meridian häufiger gegen die Regel oder oblique lag. Die Ergebnisse der Studie I können dazu beitragen, Patienten mit einem hohen Risiko für einen signifikanten Unterschied zwischen subjektivem Zylinder und topografischem Astigmatismus zu identifizieren und so die Sicherheit, Wirksamkeit und

Vorhersagbarkeit der Excimer-Laserbehandlung zu verbessern, idem bei der Planung der Excimer-Laserbehandlung auf hohen okulären residualen Astigmatismus Rücksicht genommen werden kann.

Studie II

Myope Augen ohne präoperativen refraktiven Zylinder, aber einem geringen topografischen Astigmatismus und einem geringen okulären residualen Astigmatismus korrelieren mit einem geringen postoperativen okulären residualen Astigmatismus und besseren refraktiven Ergebnissen nach LASIK. Die Ergebnisse der Studie II zeigen, dass ein präoperativer Hornhautastigmatismus von 0,9 Dioptrien und höher (anteilig) behandelt werden könnte, selbst wenn der subjektive refraktive Zylinder neutral ist. Die Behandlungsplanung kann methodisch durch Anwendung der Vektoranalyse nach Alpins durchgeführt werden (Alpins 1993 und 1997; Alpins und Stamatelatos 2007 und 2008). In solchen Fällen sollten zunächst 50% des präoperativen topografischen Hornhautastigmatismus korrigiert werden, um die Auswirkung auf den postoperativen refraktiven Zylinder zu analysieren und die Sicherheit, Wirksamkeit und Vorhersagbarkeit der Excimer-Laserbehandlung zu verbessern.

Studie III

Frühere Studien haben gezeigt, dass der LASIK-Flap signifikante Aberrationen hervorruft (Pallikaris et al. 2002); andere Studien (Porter et al. 2003; Zhou et al. 2011) haben jedoch auch berichtet, dass die meisten Aberrationen nach der LASIK durch die Ablation und nicht durch den Flap hervorgerufen werden. Die Ergebnisse der Studie III dieser Arbeit zeigen, dass ungefähr 10% der präoperativ kurzsichtigen Augen mit einem präoperativ refraktiven Zylinder von null Dioptrien, aber einem topografischen Astigmatismus von weniger als 1,00 Dioptrien dazu neigen, in der astigmatischen Komponente überkorrigiert zu werden, was die Sicherheit, Wirksamkeit und Vorhersagbarkeit der Excimer-Laserbehandlung beeinträchtigen kann. Unabhängig von der Art des Mikrokeratoms war der mittlere Betrag des refraktiven Zylinders nach LASIK 0,29 Dioptrien oder geringer.

Studie IV

Studie IV zeigt, dass ein präoperativer Unterschied von 1,00 Dioptrien oder mehr zwischen dem manifesten sphärischen Äquivalent und dem cycloplegischen sphärischen Äquivalent bei etwa 13% der hyperopen Augen vorliegt. Unsere Ergebnisse legen nahe, dass die Hyperopiekorrektur auf dem manifesten sphärischen Äquivalent in Augen mit einem präoperativen Unterschied von weniger als 1,00 Dioptrien zwischen manifestem und cycloplegischem sphärischen Äquivalent basieren sollte, um Sicherheit, Wirksamkeit und Vorhersagbarkeit der Excimer-Laser-Behandlung zu verbessern. Wenn der präoperative Unterschied zwischen dem manifesten und dem cycloplegischen sphärischen Äquivalent 1,00 Dioptrien oder mehr beträgt, kann die Behandlung nach manifester Refraktion zu einer Unterkorrektur führen. Daher ist es ratsam, die Patienten vor einer geringeren Vorhersagbarkeit des refraktiven Ergebnisses zu warnen. In diesen Fällen sollte das aus den präoperativen manifesten und den cycloplegischen Werten berechnete arithmetische Mittel für die Behandlungsplanung herangezogen werden.

Studie V

Eine Nachbehandlung nach hyperoper LASIK bei Augen mit einem Unterschied zwischen cycloplegischer und manifester Refraktion von initial 1,00 Dioptrien oder weniger führt zu einer hohen Wirksamkeit, Vorhersagbarkeit und Sicherheit, wenn die Nachbehandlung auf der manifesten Refraktion beruht. Wirksamkeit und Sicherheit der Nachbehandlung sind unabhängig vom präoperativen sphärischen Äquivalent bis zu 2,50 Dioptrien, dem manifesten Zylinder, der Keratometrie oder dem Durchmesser der optischen Zone. Bei der Behandlung von Augen mit einem präoperativen sphärischen Äquivalent ab 2,50 Dioptrien ist die refraktive Vorhersagbarkeit statistisch signifikant geringer.

Im Allgemeinen stellt die refraktive Excimer-Laserbehandlung bereits ein sicheres, wirksames und vorhersagbares Verfahren dar. Es gibt jedoch noch Raum für Verbesserungen.

In dieser Arbeit wurden verschiedene Parameter diskutiert, die Einfluss auf die Behandlungsplanung, die Operation selbst und damit auf die Refraktionsergebnisse haben. Zu diesen Parametern gehören der präoperative okuläre residuale Astigmatismus und der präoperative topografische Astigmatismus, die Methode zur Erzeugung des LASIK-Flaps, der Unterschied zwischen manifester und cycloplegischer Refraktion bei hyperopen Augen und Parameter in Bezug auf die Einstellungen für die Nachbehandlung bei Hyperopie. Alle diese vorgenannten Parameter beeinflussen die Sicherheit, Wirksamkeit und Vorhersagbarkeit der Excimer-Laserbehandlung.

Basierend auf den in dieser Arbeit vorgestellten Ergebnissen wird es uns durch die Verbesserung der derzeit verwendeten und die Einführung neuer Behandlungspläne möglich sein, Ametropie noch sicherer, präziser und vorhersagbarer zu behandeln.

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