Surgery of late in-the-bag intraocular lens dislocation

A randomized clinical trial

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ABBREVIATIONS

BCVA   best-corrected visual acuity

CCC   continuous circular capsulorrhexis

CME   cystoid macular edema

D   diopters

DSAEK   Descemet´s Stripping Automated Endothelial Keratoplasty

ECD   endothelial cell density

IOL   intraocular lens

IOP   intraocular pressure

logMAR   logarithms of the minimum angle of resolution

OCT   optical coherence tomography

PEX   pseudoexfoliation syndrome

SIA   surgically induced astigmatism

UCVA   uncorrected visual acuity

UGH   uveitis-glaucoma-hyphema

LIST OF PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. **Olav Kristianslund, Marianne Råen, Atle Einar Østern, Liv Drolsum.**
Late In-the-Bag Intraocular Lens Dislocation: A Randomized Clinical Trial Comparing Lens Repositioning and Lens Exchange.
Ophthalmology 2017;124:151-159

II. **Olav Kristianslund, Atle Einar Østern, Liv Drolsum.**
Astigmatism and Refractive Outcome After Late In-The-Bag Intraocular Lens Dislocation Surgery: A Randomized Clinical Trial
Investigative Ophthalmology & Visual Science 2017; doi:10.1167/iovs.17-22723 (Article in press)

III. **Olav Kristianslund, Marianne Råen, Atle Einar Østern, Liv Drolsum.**
Glaucoma and Intraocular Pressure in Patients Operated for Late In-the-bag Intraocular Lens Dislocation: A Randomized Clinical Trial
American Journal of Ophthalmology 2017;176:219–227

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INTRODUCTION

Cataract surgery

Cataract is a condition with opacities of the eye lens, which in most cases progresses gradually with increasing age. More than 50% of the population is affected at the age of 75.[1] Cataract causes reduced vision and remains a leading cause of blindness globally,[2] even though it can be treated effectively by removal of the biological lens followed by implantation of an artifical intraocular lens (IOL). In many developed countries, this is the most frequently performed surgical procedure in the healthcare system,[3] and in Norway more than 40 000 eyes are operated per year.[4] The demand for surgery is expected to rise further in the years to come, due to increased life expectancy, wider access to affordable surgical care, especially through large global and local health initiatives in less developed countries,[5-8] and changing indications for surgery. The latter includes clear lens extraction for the purpose of refraction change[9] or intraocular pressure (IOP) lowering,[10] both of which appear to be increasing.

History of cataract surgery

Treatment for cataract has been performed since ancient times, as documented in manuscripts from the 7th century BC.[11] At that time, the procedure known as couching was performed with dislocation of the biological lens (phacos) with hypermatur cataract downwards, resulting in a free and transparent visual axis. A more recent historical milestone was the introduction of the first artificial IOL (pseudophakos) by Harold Ridley in the 1940s.[12] In the 1960s, Charles Kelman introduced phacoemulsification[13] although it was not until some years later that the method came into routine use. Another major achievement was the development of IOLs made by foldable materials, such as acrylic and silicone IOLs, in the 1980s.[14] This enabled cataract surgery with small incisions, which was an advantage not least in terms of induced astigmatism.[15] In the same period, the continuous circular capsulorrhexis (CCC) technique for removal of the central anterior lens capsule was introduced.[16] A CCC with implantation of the IOL inside the capsule (in-the-bag) was considered beneficial to achieve a stable, well-centered lens with less iris friction and reduced inflammation. The recent introduction of the femtosecond laser may prove to be another major improvement in modern cataract surgery.

Complications from standard cataract surgery

The risk of complications from today´s standard cataract surgery with clear corneal incisions, a CCC, phacoemulsification of the biological lens, and in-the-bag implantation of a foldable IOL is minor, and the visual outcome is usually excellent unless the patient has other eye diseases.[17] However, adverse events may occur.

In approximately 2% of all cataract operations there is capsule rupture with or without vitreous loss,[18,19] which is considered a serious complication because of the significant risk for adverse visual outcome often as a result of subsequent treatment-resistant cystoid macular edema (CME).[18,20,21] Perioperative zonular dialysis occurs in 0.5% of all operations according to one large study,[18] whereas serious postoperative complications such as endophthalmitis and retinal detachment seem to be rare with modern cataract surgery.[18,22] In a recent study from the Swedish National Cataract Register, the endophthalmitis rate was reported as low as 0.03%.[23] A more common postoperative complication is loosening and dislocation of the IOL, which causes vision loss and requires surgical treatment.[24,25] The frequency of IOL dislocations has not been completely clarified, as will be discussed later.

Intraocular lens dislocation

Intraocular lens dislocation is classified according to the position of the IOL, which can be either partly or totally outside the capsule (*out-of-the-bag*) or inside the capsule (*in-the-bag*), thus rather representing a dislocation of the whole IOL-capsule complex.

Out-of-the-bag IOL dislocation has traditionally occurred in the early postoperative period, often associated with rupture of the posterior capsule leading to asymmetric fixation of the IOL, i.e. one haptic in the capsular bag and the other in the ciliary sulcus.[26] *In-the-bag IOL dislocation* usually occurs at a much later stage after cataract surgery, associated with other factors.[27] It was first reported by Davison in 1993,[28] and has been described as almost non-existent until the advent of CCC.

In-the-bag IOL dislocation is presumed to occur as a result of weakening and loosening of the zonules in the eye (Figure 1), in some cases along with pronounced contraction of the anterior lens capsule.[24,25,28,29] The zonules consist of multiple fibrous strands that are anchored to the ciliary muscle and attached to the lens capsule in a circumferential manner (Figure 2).[29,30] They make up the suspensory ligament of the lens capsule, ensuring a stable position of the

lens or the IOL. Different conditions may predispose for progressive loosening of the zonules, as discussed below.
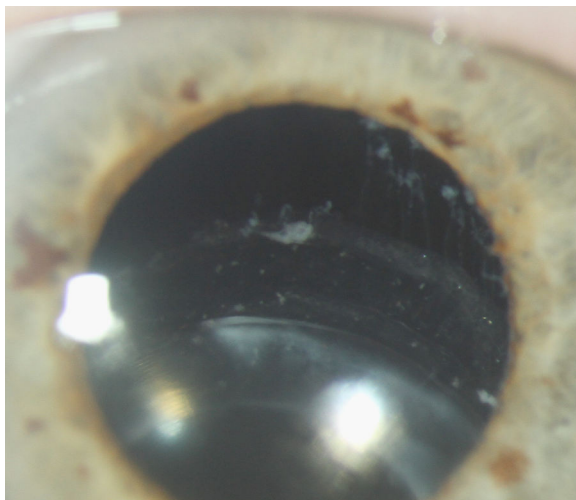

Figure 1 Late in-the-bag intraocular lens dislocation with loosening of the superior zonules. Photo: Oslo University Hospital
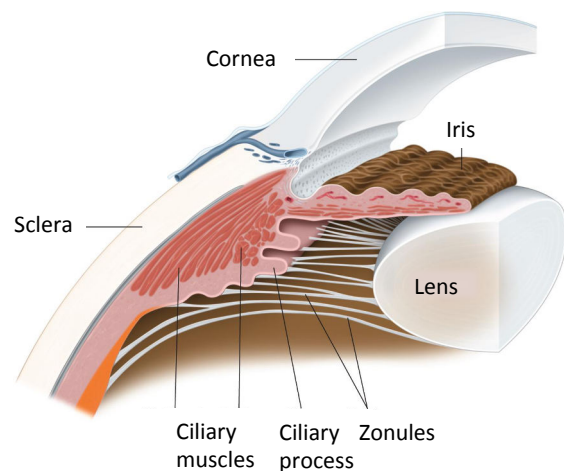
Figure 2 Illustration of the zonules in the anterior segment of the eye. © 2017 American Academy of Ophthalmology

Incidence of intraocular lens dislocation

While the number of early out-of-the-bag IOL dislocations seems to have decreased,[27,31] several articles have showed an increasing trend for in-the-bag IOL dislocation.[27,29,32-34] In a few recent studies, IOL dislocation was reported with an annual incidence of 0.0%-0.05%[32,35] and a cumulative incidence of 0.1%-1.7% over 10-25 years.[31,32,36,37] One of these studies[31] found that an additional 2.1% had moderate or pronounced pseudophakodonesis (movement of the IOL) 10 years after cataract surgery. It has been hypothesized that the variation in incidence is a result of unequal distribution of predisposing conditions across various populations.[36] Furthermore, the calculations in the referred studies differed to some extent, particularly in relation to whether the reported incidence included all dislocations,[37] late dislocations[31,35,36] or only late in-the-bag dislocations,[32] and also whether the incidence was calculated for pseudophakic eyes[32,35,36] or pseudophakic patients.[31,35,37]

The increasing trend for in-the-bag IOL dislocation may possibly reflect an increased incidence or it may simply be a result of more cases due to a larger pseudophakic population.[35,36] Furthermore, it is uncertain whether the trend is caused mainly by demographic changes (e.g. increased life expectancy) or by surgical factors (e.g. change in surgical technique), or possibly both. A population study from Olmsted County, Minnesota[36] found a stable incidence of late IOL dislocation over a 20-year period, and the authors

assumed that the increased number of cases could be explained by more people with an IOL, and thus at risk. This view seems to be supported by similar findings over a much shorter time span in a study from southern Sweden,[35] whereas a population study from western Australia[37] found an increased incidence of IOL dislocation over a period of 22 years.

None of these studies reported numbers for any subgroup of IOL dislocation. However, a cohort study from Värmland, Sweden[32] focusing on late in-the-bag IOL dislocation reported that the incidence of this condition increased over a 20-year period even after adjusting for the growing pseudophakic population. Proposed explanations for this increase was a longer mean duration of pseudophakia in the population, and possibly a lower threshold in recent years to perform surgery on more challenging cases with a higher risk for dislocation. Also others have emphasized surgical indications and techniques as possible explanations for the increase.[29]

The term *late* in-the-bag IOL dislocation is often used in research studies, which by definition excludes the cases occurring a few months after surgery.

Late in-the-bag intraocular lens dislocation

Late in-the-bag IOL dislocation occurs on average 6-9 years after cataract surgery[24,25,29,34,35,38-40] and the mean patient age has in various studies been between 70 and 85 years.[26,29,32,34,35,38-42] Different conditions predispose for late in-the-bag IOL dislocation. Pseudoexfoliation syndrome (PEX) has been established as one of the most important, being present in 44%-70 % of the cases[24-26,29,33,34,39-42] except in a few studies with lower proportions.[38,43,44] Other predisposing conditions are previous vitreoretinal surgery,[29,38,45] myopia/increased axial length,[26,32,38] uveitis,[24,29] retinitis pigmentosa,[26,38] trauma,[24,29,38] and certain connective tissue disorders.[46] It is assumed that these conditions predispose through weakening and loosening of the zonules (Figure 1).[24-26,28,29,47] This process may even start before implantation of an IOL,[32,35,48] as shown in one study in which 38% of the eyes with in-the-bag IOL dislocation had zonular dehiscence already at the time of cataract surgery.[35]

Some studies of late in-the-bag IOL dislocation have reported a preponderance of males,[24,26,31,38,49] and a proposed explanation has been that they have weaker zonules[38] and/or more frequently experience trauma.[31] However, other studies have found a preponderance of females,[34,35,39,41] which have been suggested to reflect their likely higher prevalence of PEX[50-52] and/or the gender difference for pseudophakia with more females having cataract

surgery.[35,53] Based on these contradictory findings, it seems uncertain whether gender is an individual risk factor for late in-the-bag IOL dislocation.

A possible relation to specific IOL designs and materials has also been discussed, although published results are inconsistent.[24-26,29,35,40] In the studies that have shown an association,[24-26,40] it likely reflected the IOL types that were used most frequently some years in advance.[27,40] Nevertheless, it has been stated specifically that plate-haptic silicone IOLs are at an increased risk for anterior capsule opacification with secondary capsule contraction,[54-56] which in turn is assumed to increase the risk for late in-the-bag IOL dislocation.[28]

Posterior capsulotomy with Neodymium:Yttrium-Aluminium-Garnet (Nd:YAG) laser has also been considered as a possible risk factor, however, study findings are ambiguous.[29,34,35] Even if an association is to be found, it might be difficult to conclude whether Nd:YAG laser capsulotomy is a risk factor or rather a consequence of a common factor that leads to both posterior capsule opacification, requiring laser treatment, and anterior capsule contraction, which contributes to progressive loosening of the IOL-capsule complex.

Finally, an association between late in-the-bag IOL dislocation and glaucoma and/or increased IOP has been shown.[34,35,39-42] A clinically important question in this regard is whether the increased IOP is caused by the IOL dislocation, and thus can be expected to resolve by dislocation surgery, or if rather both conditions are results of another causal factor. The association with increased IOP seems especially prominent in studies with a high proportion of PEX, and one study suggested that the IOL dislocation and the simultaneous increased IOP were both linked to advanced-stage PEX.[41] However, others have reported an improvement in the IOP after dislocation surgery and in some patients even discontinuation of glaucoma medication in the postoperative period,[39,40] indicating that the dislocation itself contributed. Two further studies[32,42] had more ambiguous results, hence the definite answer to this question has been uncertain.

Operation methods for intraocular lens dislocation

Late in-the-bag IOL dislocation requires surgical treatment, but there has been no clear consensus on the optimal operation method and the choice has mainly been dependent on the surgeon's preference. A number of treatment-related questions arise when late in-the-bag IOL dislocation is diagnosed, as pointed out in previous publications.[27,57] These questions will be addressed in the following, and further elaborated in the *Discussion* section of this thesis.

Is surgery indicated, and is it urgent?

Late in-the-bag IOL dislocation is part of a continuum from pseudophacodonesis, through subluxation, to total dislocation of the IOL-capsule complex into the vitreous cavity. Common symptoms are visual disturbance such as diplopia, oscillating vision, glare, and halos, as well as visual impairment dependent on the degree of dislocation. The assessment of surgical indication takes into consideration the patient's symptoms, whether there is actually a dislocation of the IOL-capsule complex, and the assumed risk for further loosening. Surgery is usually indicated, and recommended, in cases of in-the-bag IOL dislocation with disturbing symptoms.[27]

The optimal timing of surgery has, however, not been clarified. At least, there are few specific recommendations in the literature. Østern et al[34] observed that while only 4% of late in-the-bag IOL dislocations deteriorated in the first month after referral, the corresponding number was approximately 40% when the operation was delayed between one and six months. If assuming that surgery is easier to perform and has fewer complications when the IOL is not completely dislocated,[27] it seems advantageous to perform the operation within a few weeks after referral.[34]

Surgical access: anterior or pars plana approach?

In cases with complete dislocation of the IOL-capsule complex into the posterior part of the eye, vitreoretinal surgery with a pars plana approach is required. In several eye clinics vitreoretinal surgeons operate all the IOL dislocations, whereas in other clinics anterior segment surgeons manage these cases if surgery can be performed with an anterior access. Potential advantages with the pars plana approach is the opportunity for posterior vitrectomy when indicated, easier management of preexisting or perioperatively occurring retinal pathology (e.g. retinal tears), and retrieval of the IOL if it dislocates posteriorly.[57] Advantages with the anterior approach is less resource demanding surgery, possibly a shorter surgical time, and the avoidance of certain complications associated with pars plana vitrectomy.[27]

A study by Jakobsson et al[39] showed more postoperative events associated with the anterior approach in comparison with pars plana vitrectomy. Otherwise, no clinical studies have to our knowledge compared the efficacy and safety of these two approaches.

Main operation methods: intraocular lens repositioning or exchange?

A dislocated IOL can be either repositioned or exchanged, and various surgical techniques exist. Except for repositioning of one misplaced haptic back into the capsule, the treatment options are principally the same regardless of whether the IOL dislocation is out-of-the-bag or in-the-bag, and several studies have included both conditions in the comparison of operation methods[26,33,39,49,58] with separate reporting of results only to varying degrees. It should be remembered, though, that there are likely differences between the two conditions in terms of treatment outcomes and surgical complications. For exchange surgery, there is a considerable difference between explantation of only the IOL versus the whole IOL-capsule complex. And for IOL repositioning it seems likely that the risk for redislocation is different dependent on whether the scleral sutures are tied only around the haptic or if they also pass through the lens capsule. Therefore, overall results for the treatment of both conditions might not be directly applicable to either one of them.

Furthermore, it is essential to keep in mind that much of the research on IOL types used for exchange surgery has included other conditions than IOL dislocation, such as aphakia after trauma or surgical complications. In this thesis, some of these studies are referred to regarding certain IOL types and surgical techniques. The intention has been to illustrate important aspects related to late in-the-bag IOL dislocation surgery, and not to provide an overview of all IOL surgery.

Intraocular lens repositioning by scleral suturing is mentioned in a number of articles as the recommended operation method for in-the-bag IOL dislocation,[34,35,38,57,59] whereas only a few authors have argued that IOL exchange is favorable.[43] Arguments in favor of IOL repositioning have been that it is less traumatizing, especially for the corneal endothelium, and that hypotony during surgery is easier to avoid with the smaller incisions, thus reducing the risk for serious complications such as choroidal expulsive hemorrhage.[24,35,38,57,59] Small incisions have also been considered beneficial in terms of surgically induced astigmatism (SIA).[27] In favor of IOL exchange surgery, some authors have claimed that it results in a better centration and possibly a better stability of the IOL, and that fundus visualization is improved after removal of the capsule.[43] In addition, iris-claw IOLs avoid the risk for suture breakage or suture slippage, although it remains unclear whether this outweigh their risk for disenclavation. Finally, IOL exchange is the only option in some cases, related to for example

IOL designs that cannot be sutured, damage to the IOL, or requirements for refraction change.[38,42]

Several previous studies on late in-the-bag IOL dislocation surgery[24,26,33-35,38-40,42,44,49] have described and to some extent compared different operation methods and placements of the IOL, although many have applied a retrospective research design and/or included few patients. Results have indicated that IOL repositioning and IOL exchange yield similar visual outcome,[34,40,44] whereas in terms of complications, the findings have been more ambiguous.

What are the options for intraocular lens exchange?

If exchange surgery with removal of the dislocated IOL-capsule complex is the chosen operation method, there are a number of IOL types that can be considered for implantation. Alternatives include open-loop anterior chamber IOLs, scleral-sutured IOLs or iris-sutured IOLs. Wagoner et al[60] conducted a review of secondary IOL implantation in eyes without adequate capsular support for various reasons (thus, also other surgical indications than IOL dislocation) and concluded that there is no clear evidence that any of these IOLs are superior to the others. However, the review did not consider iris-claw IOLs or sutureless scleral fixation techniques, both of which appear to be used increasingly with good results.[34,40,61-71]

The iris-claw IOL was developed and certified as a *phakic* IOL for refractive purposes. Later, it has become available also as an *aphakic* IOL (without approved indications), branded either as the Verisyse aphakic IOL (VRSA54; Abbott Laboratories Inc., Abbott Park, USA) or as the Artisan aphakic IOL (Ophtec BV, Groningen, The Netherlands), which according to the manufacturers are identical lenses (personal correspondence). In a large study of 128 aphakic eyes, Guell et al[63] showed that implantation of the iris-claw IOL was an effective and safe technique with excellent refractive outcomes and a low rate of complications. Also studies of IOL dislocation surgery have reported promising results with this lens.[34,40,61,62,64] It has varied whether the iris-claw IOL has been enclavated to the anterior or the posterior surface of the iris. No large clinical trial has to our knowledge compared these two positions.

In recent years, different techniques for sutureless scleral fixation of the IOL have emerged as treatment options in aphakic eyes, with fixation of the IOL haptics by the use of fibrin-glue and scleral tunnels alone or in combination,[65-69] or by the use of needle-guided scleral fixation with cauterization of the haptic end to make a flange.[70] These techniques may possibly be suitable also for IOL exchange surgery.

Pseudoexfoliation syndrome

Pseudoexfoliation syndrome is one of the most common predisposing conditions for late in-the-bag IOL dislocation. It can be recognized as deposits of fibrillar material on the anterior surface of the lens capsule (Figure 3), as first described by Lindberg in 1917.[72] Later research has shown that the material is deposited throughout the anterior segment of the eye, and it has also been observed in other parts of the body.[73-76] In pseudophakic eyes, PEX can typically be identified by pseudoexfoliative material on the pupillary edge.

The condition has been given various terms and abbreviations, including pseudoexfoliation syndrome (PEX, PXF, PES), exfoliation syndrome (XFS, ES), and fibrillopathy. In this thesis, pseudoexfoliation syndrome (PEX) is used. A thorough description of the condition can be found in numerous articles and reviews,[75,77-79] and only a brief overview is presented here.
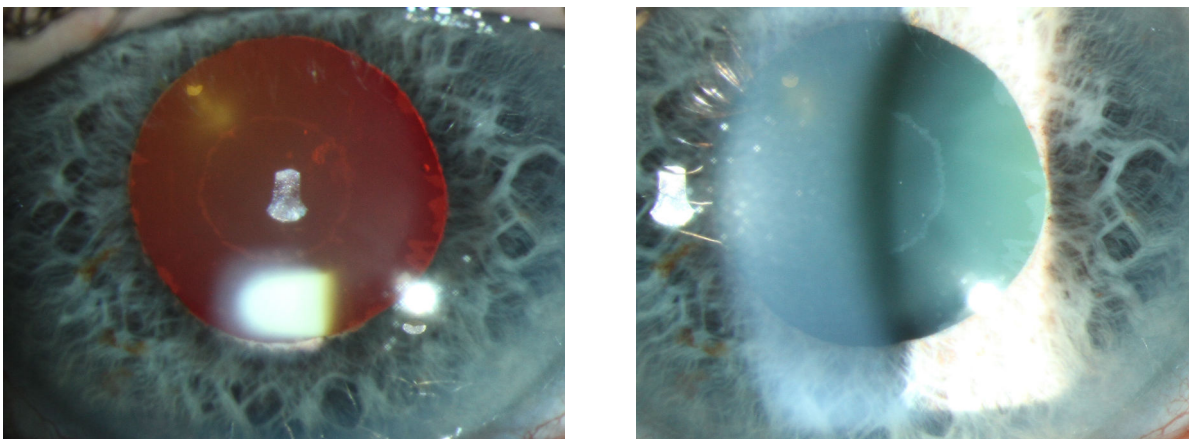
Figure 3 Pseudoexfoliative material on the anterior lens surface. Photos: Oslo University Hospital

The prevalence of PEX increases with age.[80] Furthermore, it varies geographically, being especially prevalent in the Scandinavian countries.[80-82] While a US population study[52] found PEX in 0.5% of patients above the age of 60, a Norwegian population study[83] reported a prevalence of 10%-21% in the same age group, and a Swedish population study[50] reported a prevalence of 23% and 61% at the age of 66 and 87, respectively. In previous studies from our department, PEX was registered in 11%-17% of the patients referred for cataract surgery.[84-86] Several explanations for the geographical variation have been proposed including variable attention to the signs of PEX during eye examination.[87] A genetic association has also been suspected and in 2007, Thorleifsson et al[88] showed that PEX and especially PEX glaucoma is associated with the LOXL1 genetic locus. This finding has been confirmed by

others,[89] including in a study by Aung et al in 2015,[90] where they also demonstrated an association with the CACNA1A genetic locus.

Patophysiologically, PEX has been associated with iris atrophy, poor pupillary dilation, weak zonules, and a fragile lens capsule,[91,92] and PEX eyes are also more prone to develop contraction of the anterior capsule.[25,28,29,47,93] Traditionally, it has also been claimed that patients with PEX suffer from an increased risk of complications from cataract surgery. The increased risk perioperatively has been explained mainly by more frequent capsule/zonule rupture and vitreous loss in PEX eyes.[84,85,92,94-97] However, a few more recent studies on phacoemulsification cataract surgery were not able to identify a significant difference in the rate of perioperative complications between patients with and without PEX.[98-100] In terms of postoperative complications, it has been stated that PEX eyes suffer from an increased risk of posterior capsular opacification and endothelial cell loss,[101,102] however, recent studies have questioned also these findings.[103,104]

Nevertheless, it seems to be agreed that patients with PEX suffer from an increased risk of late in-the-bag IOL dislocation, even following cataract surgery with modern techniques. A clinical study[105] showed that IOLs were positioned significantly lower in PEX eyes compared with control eyes several years after phacoemulsification cataract surgery. This finding is consistent with a study on autopsy eyes[47] and indicates that late in-the-bag IOL dislocation is usually a gradual process in patients with PEX. The dislocation process is thought to occur because pseudoexfoliative material attaches to and weakens the zonules and impairs the anchoring both to the lens capsule and the bulbus.[78,91] Pseudoexfoliation syndrome also seems to increase the risk for pronounced contraction of the anterior capsule.[28] These factors, alone or in combination, may ultimately result in loosening and dislocation of the IOL-capsule complex.[25,28,29,47]

Pseudoexfoliation glaucoma

Pseudoexfoliation syndrome is further associated with increased IOP,[106] and these eyes suffer from a higher risk of progression to glaucoma compared to non-PEX eyes with ocular hypertension.[107,108] Pseudoexfoliative material has been shown to deposit in the trabecular meshwork, Schlemm's canal and the collector channels.[109,110] This likely increases the outflow resistance and hence explains the elevated IOP that may be seen in these eyes.

An association between PEX and glaucoma has been known for decades,[87,111-113] and PEX has eventually been recognized as the most common risk factor for open-angle glaucoma.[109] It further seems that the glaucomatous outcome is on average more pronounced and serious for PEX glaucoma compared with primary open-angle glaucoma.[107,114-117]

Intraocular pressure and glaucoma after cataract surgery

A number of studies have shown that cataract surgery lowers the IOP, both in patients with and without PEX,[95,118-121] and some have even found a more pronounced postoperative IOP decrease in patients with PEX. [95,118,121] However, it has also been shown that PEX eyes are at increased risk of having an IOP spike shortly after cataract surgery.[92,100,122]

In an article not included in this thesis (Kristianslund et al 2016),[86] we compared the IOP change and the glaucoma development in patients with and without PEX 6-7 years after cataract surgery. Both patient groups experienced a significant IOP decrease in this postoperative period, with a tendency for a more pronounced decrease in the PEX group. With these results, our study confirmed that the IOP reducing effect of cataract surgery may persist even several years after the operation. In the same study, we calculated the annual glaucoma incidence in both groups postoperatively. This incidence was lower than expected, especially in the PEX group, when compared to population studies of approximately the same age group but with mainly non-pseudophakic patients. Hence, it seemed that the IOP lowering effect of cataract surgery was particularly beneficial for patients with PEX and that it possibly reduced the risk for glaucoma or at least delayed the development.

Possible explanations may be that cataract surgery removes a certain amount of pseudoexfoliative material and pigment from the eye, and that the release of pseudoexfoliative material postoperatively is reduced due to less rubbing and iris friction after removal of the thick biological lens and the central anterior capsule. These factors may have resulted in less clogging of the trabecular meshwork in PEX patients postoperatively. Although speculative, this theory is partly supported by a pathological study that showed a correlation between the amount of pseudoexfoliative material in the trabecular meshwork and glaucoma.[110]

Based on this possible reduced glaucoma risk, we speculated if there should be a rather low threshold for cataract surgery in patients with PEX.[86] Our results were, however, uncertain, and the study had several limitations, hence more research is needed before certain clinical

recommendations can be given. It also seems important to consider whether such a change in surgical indication is expected to affect the rate of IOL dislocations. In accordance with the findings in a previous study[32] it seems likely that a longer duration of pseudophakia will be associated with a higher risk for IOL dislocation. However, on the contrary, one may speculate that early lens extraction in patients with PEX, before pronounced zonular dehiscence has occurred, can be beneficial and reduce the risk for IOL dislocation. A previous study showed that a lower age at cataract surgery was correlated with a longer time to IOL dislocation.[35] It still remains uncertain what the overall consequences of a changed indication with earlier lens extractions would be, and this question was also not the focus of this thesis.

Basis for this research project

Despite an increasing number of cases with late in-the-bag IOL dislocation and a growing interest in this research field, the choice of surgical technique in the treatment still depends mostly on the surgeon's preference. Previous studies have described, and to some extent compared, different operation methods for late in-the-bag IOL dislocation surgery. However, these have mainly been retrospective and often with few patients included, and the question of whether one of the operation methods is superior to others has not been completely clarified.

Being a treatment efficacy question, the most ideal research design would be a randomized clinical trial. This design is advantageous also to monitor and compare adverse events (safety) in a standardized manner. To the best of our knowledge, no such trial on surgery of late in-the-bag IOL dislocation had been conducted previously, and this lack of knowledge formed the basis for our research project.

AIMS OF THE THESIS

The main aim of this thesis was to study the surgical management of late in-the-bag IOL dislocation by comparing the two operation methods IOL repositioning versus IOL exchange in a randomized clinical trial. This thesis investigated the 6-month follow-up data.

The specific research aims were as follows:

1. Compare the efficacy, in terms of visual outcome, and the safety, in terms of complications, between the two operation methods.
2. Compare the SIA and the refractive outcomes between the two operation methods.
3. Identify whether there is an association between late in-the-bag IOL dislocation and high IOP and, if so, to evaluate possible reasons for this association. Essential to such an evaluation is to determine whether IOL dislocation surgery has an IOP-lowering effect and compare this possible effect between the operation methods.
4. Identify patient characteristics and predisposing factors for late in-the-bag IOL dislocation, and in particular to determine, in a standardized prospective study, the proportion of patients with PEX.

MATERIAL AND METHODS

This section gives a brief overview of material and methods used in this thesis. More detailed descriptions can be found in Paper I-III, and a discussion of the study design, the surgical techniques to be compared, SIA analysis methods, and some other aspects of material and methods has been provided later under the heading *Methodological considerations*.

Study population

Our research project was conducted at the Department of Ophthalmology at Oslo University Hospital, which is both a local hospital department and a specialized tertiary referral clinic. The hospital is part of the South-Eastern Norway Regional Health Authority, which is responsible for a population of approximately 2.9 million inhabitants, or more than 50% of the total Norwegian population. A large proportion of all late in-the-bag IOL dislocations occurring within this area are being operated at our department, since these cases are often considered in need of special expertise. Patients referred with this condition during the 3-year inclusion period, beginning January 2013, were evaluated at the Anterior Segment Section and when an anterior surgical approach was considered technically possible, the patients were consecutively assessed for eligibility.

Research design and intervention groups

We conducted a randomized parallel-group clinical trial with comparison of two different operation methods. Briefly described, the intervention groups were managed as follows:

1. **Intraocular lens repositioning:** The ab externo scleral fixation method was used, and the operation was performed by fixating the dislocated IOL-capsule complex to the scleral wall with a suture loop through the capsule and around the haptic, using a 10-0 Prolene suture (Ethicon, Somerville, USA). One suture loop was made for each of the haptics and the knots were placed under scleral triangular flaps.
2. **Intraocular lens exchange:** The dislocated IOL-capsule complex was explanted through a 5.5-mm scleral pocket frown incision, followed by implantation of an iris-claw IOL fixated retropupillary. The scleral incision was closed with one cross-suture.

All patients were operated by the same surgeon, Professor Liv Drolsum.

Sample size

The sample size calculation for this trial was performed with postoperative best-corrected visual acuity (BCVA) as the efficacy variable, converted to logarithms of the minimum angle of resolution (logMAR) for statistical purposes. A difference of 0.15 logMAR between the operation groups was considered clinically relevant. With an anticipated standard deviation of 0.2 logMAR, a test power of 80% and a 5% significance level, it was calculated that a minimum of 28 eyes were required in each group. Some loss to follow-up throughout the study period was expected, in particular due to the high mean age in the patient population and thus some expected serious comorbidity. Hence, we aimed for a sample size above this minimum.

Enrollment, randomization and masking
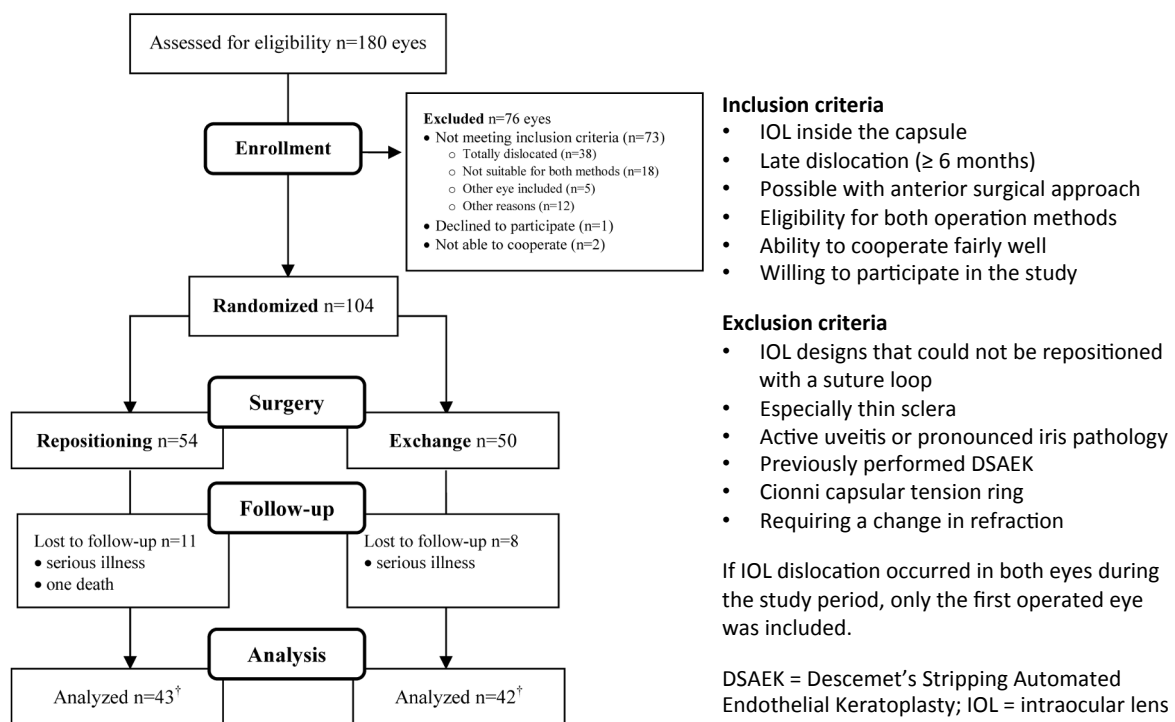
Figure 4 Study flowchart from Paper I and inclusion and exclusion criteria

Patients were evaluated for eligibility according to the inclusion and exclusion criteria listed in Figure 4. Over a period of 3 years, 175 patients (180 eyes) with in-the-bag IOL dislocation were evaluated and 104 patients (104 eyes) were enrolled. Reasons for exclusion are listed in the flowchart (Figure 4). The most frequent cause was total dislocation of the IOL-capule complex, requiring pars plana surgery.

The randomization was performed by a computer program that provided random permuted blocks and enrolled patients were assigned to intervention groups using an allocation ratio of 1:1. Masking (blinding) for group affiliation was only performed during image analyses.

Statistical analysis

Statistical analysis was conducted with the computer program SPSS (IBM Corp., Armonk, USA), and data in the two operation groups were compared with an independent-samples t-test (continuous variables) or a chi-square test (categorical variables). For analysis of change over time within each operation group, a paired-samples t-test was used (continuous vaiables). In a few cases with uncertain normal distribution of the data, the analysis was performed with a non-parametric test (Mann-Whitney U test). Results have been presented as mean ± standard deviation or number (%), unless otherwise stated. The trial is reported in accordance with the international CONSORT statement,[123] with no p values for the group comparison of preoperative data and with standardized and thorough descriptions of the research design and study findings. This enables an interpretation of the results that takes study limitations into consideration, which is beneficial to determine the external validity and clinical applicability of the findings.

Ethics

Based on previous studies on surgery of late in-the-bag IOL dislocation, there was no clear indication in advance that one of the compared operation methods was superior to the other. It was therefore considered ethical to randomize patients to intervention groups. A disadvantage for the patients participating in this trial was possibly a few additional postoperative examinations, and for some patients a longer travel distance compared to ordinary clinical practice. Otherwise, there were no obvious additional risks or disadvantages. A benefit from the thorough study examinations was the opportunity to discover late postoperative complications or other eye conditions requiring further examinations and in some cases interventions.

The research study was approved by the Data Protection Office at Oslo University Hospital and the Regional Committee for Medical and Health Research Ethics, South-East Norway (project code: 2012/1981), and the study has been registered at ClinicalTrials.gov (identifier NCT01784926). Written informed consent was obtained from all study patients, and the research has been performed in accordance with the Helsinki declaration.

SUMMARY OF RESULTS

Paper I – Late In-the-Bag Intraocular Lens Dislocation: A Randomized Clinical Trial Comparing Lens Repositioning and Lens Exchange

Paper I was the first report from our randomized clinical trial on late in-the-bag IOL dislocation surgery. In this paper, we compared the safety and efficacy measures between the two operation groups and presented baseline characteristics and operation parameters. The main outcome measure, BCVA six months after surgery, was 0.24 ± 0.29 logMAR in the repositioning group and 0.35 ± 0.54 logMAR in the exchange group ($P = 0.23$). Perioperatively, IOL repositioning had a non-significant tendency for more intraocular hemorrhage, whereas IOL exchange had significantly more iris injuries. Cystoid macular edema and IOP increase were the most frequent postoperative complications, with no significant differences between the groups. However, the endothelial cell density (ECD) loss after surgery was significantly more pronounced in the exchange group. Altogether, the operation groups had similar efficacy in terms of visual outcome, and both had fairly low proportions of serious perioperative and postoperative complications. Mean surgical time was significantly longer for IOL repositioning compared to IOL exchange. Pseudoexfoliation syndrome was present in 83% of the study patients, which made it by far the most frequent predisposing condition.

Paper II – Astigmatism and refractive outcome after late in-the-bag intraocular lens dislocation surgery in a randomized clinical trial

Paper II reports the SIA and the refractive outcomes in the two operation groups. The SIA, calculated by vector analysis, was modest in both groups, albeit with a tendency of being more pronounced after IOL exchange compared to IOL repositioning. There was further a tendency towards inducing against-the-rule astigmatism, especially for exchange surgery. The mean postoperative spherical equivalent was -1.6 ± 1.6 diopters (D) after IOL repositioning and -0.5 ± 1.0 D after IOL exchange ($P < 0.001$). The repositioning group experienced a myopic shift from before the IOL dislocation to six months after the surgery, and only 57% of the patients had a refractive outcome within ±1 D of this pre-dislocation refraction, which in the paper was defined as target refraction for this group. In the exchange group, 83% of the patients had a refractive outcome within ±1 D of target refraction determined by preoperative

biometry. Based on optimization calculations, the paper suggested an optical biometry A-constant of 117.3 (SRK/T formula) for retropupillar implantation of an iris-claw IOL in eyes with late in-the-bag IOL dislocation.

Paper III – Glaucoma and Intraocular Pressure in Patients Operated for Late In-the-bag Intraocular Lens Dislocation: A Randomized Clinical Trial

In Paper III, we reported the glaucoma status, IOP changes and the IOP-lowering treatment requirements in the two operation groups. The main outcome measure in this paper, 6-month postoperative IOP change, was -1.2 ± 5.8 mmHg after IOL repositioning and -3.8 ± 6.4 mmHg after IOL exchange. The difference in IOP change between the two operation groups was borderline significant ($P = 0.05$). Out of 104 study patients with late in-the-bag IOL dislocation, 39 (38%) of the patients had preexisting glaucoma and 23 (22%) had a high IOP (≥ 22 mmHg) before surgery without known glaucoma (*suspected glaucomas*). Several patients required IOP-lowering treatment before and/or after IOL dislocation surgery. Of the suspected glaucomas, only three of the patients did not require any IOP-lowering treatment six months after surgery. The remaining patients with associated high IOP were presumed to have underlying glaucoma, in almost all cases PEX glaucoma.

Table 1 Baseline characteristics for the 104 enrolled patients

Age (years)	81.7 ± 8.0 (56 – 95)
Gender (male/female)	41 (39%) / 63 (61%)
Time since cataract surgery (years)	10.3 ± 4.3 (1 – 20)
Predisposing conditions[1]	
Pseudoexfoliation syndrome	86 (83%)
Myopia	17 (16%)
Vitreoretinal surgery	13 (13%)
Trauma	10 (10%)
Chronic uveitis	4 (4%)
Unknown	3 (3%)
Previously diagnosed glaucoma[2]	39 (38%)
Suspected glaucoma[3]	23 (22%)

Results are mean ± SD (range, mininmum – maximum) or n (%)
[1] Some patients had more than one predisposing condition
[2] Known glaucoma before the IOL dislocation. Of these patients, 17 (44%) had high IOP (≥ 22 mmHg) measured in the period from dislocation diagnosis until the preoperative visit
[3] High IOP ≥ 22 mmHg measured in the period from dislocation diagnosis until the preoperative visit but no previously known glaucoma

Table 2 Operation parameters and 6-month postoperative outcomes in the two operation groups: repositioning versus exchange

	Repositioning	Exchange	*P*
Operation parameters			
Surgical time (minutes)	24 ± 6	14 ± 3	<0.001
Anterior vitrectomy (manual or vitrector)	7%	70%	<0.001
Intraocular hemorrhage	7%	0%	0.12
Iris injury	0%	18%	0.001
Postoperative complications (6 months)			
Cystoid macular edema (at 6-month visit)	7%	10%	0.71
IOP increase after surgery	28%	21%	0.62
ECD change (% of preoperative value)	−3%	−10%	0.04
6-month postoperative outcome			
Visual outcome			
BCVA (logMAR)	0.24 ± 0.29	0.35 ± 0.54	0.23
BCVA ≥ 20/40 (Snellen)	61%	62%	0.99
BCVA worse after surgery	21%	26%	
Refractive outcome and SIA			
Spherical equivalent (D)	−1.6 ± 1.6	−0.5 ± 1.0	<0.001
Spherical equivalent ±1D from target refraction[1]	57%	83%	0.01
Prediction error (D)[2]	−0.7 ± 1.0	−0.3 ± 0.9	<0.001
SIA (D @ °)	0.24 @ 8	0.65 @ 171	
Mean SIA magnitude (D)	0.6 ± 0.5	1.1 ± 0.9	0.004
IOP and glaucoma			
IOP (mmHg)	16.5 ± 5.2	14.9 ± 4.2	0.13
IOP change (mmHg)	−1.2 ± 5.8	−3.8 ± 6.4	0.05
Glaucoma treatment increase after surgery	28%	21%	0.62
Initiation (+) or	+ 2 patients	+ 0 patients	
discontinuation (-)	- 0 patients	- 3 patients	
of IOP-lowering treatment after surgery			

BCVA = best-corrected visual acuity; D = diopter; ECD = endothelial cell density; IOL = intraocular lens; IOP = intraocular pressure; SIA = surgically induced astigmatism. Results are mean ± SD or n (%)
[1] Target refraction defined for the repositioning group as the subjective refraction measured before dislocation of the IOL, and for the exchange group as calculated from the preoperative biometry.
[2] Difference between the postoperative spherical equivalent and the target refraction
More details / explanations presented in Paper I-III

DISCUSSION

Methodological considerations

Research design – randomized clinical trial

The findings presented in this thesis were obtained in a *prospective randomized parallel-group single-center single-surgeon clinical trial*. To our knowledge, it is the first and so far only randomized trial on IOL dislocation surgery. With pre-defined eligibility criteria, randomized allocation to treatment groups, and a comprehensive and standardized assessment of both efficacy and safety measures, we believe our study provides a valid and reliable comparison of two widely used operation methods.

Most previous studies on late in-the-bag IOL dislocation have been retrospective. Several of them have further been descriptive without statistical comparison of operation methods. A retrospective research design allows for a long mean follow-up and an acceptable sample size even for rare diseases. However, such studies are associated with a number of biases, in particular selection bias.[124] This can occur if the choice of operation method is related to the experience of the surgeon or to the severity of the condition, and may consequently affect group comparison and lead to erroneous estimates of treatment effects and complication rates. In addition, data used in retrospective studies have often been registered and obtained in a non-standardized manner, which can lead to inaccuracies in the evaluation of for example adverse events. Prospective studies are to some extent opposite in terms of advantages and disadvantages. Combining results from retrospective and prospective studies may therefore be beneficial in reaching strong clinical recommendations.

A randomized research design is usually considered the gold standard for comparison of treatment effects.[123,125] This design avoids selection bias by distributing known and unknown confounders randomly between the intervention groups, thereby ideally creating equal groups prior to the intervention. The differences in outcomes observed can then, apart from random error, be attributed to the examined interventions.[124,126] However, there is a risk for unequal groups after randomization if the sample size is small. Specific methods for randomization try to overcome this issue,[125] and in our trial, restricted randomization with random permuted blocks was applied to achieve similar group sizes. The intervention groups were also similar

in terms of important baseline characteristics such as age, gender, and predisposing conditions. However, there were group differences at baseline with regard to BCVA, grading of IOL dislocation, and ECD. One may therefore question whether stratified randomization[123] could have been beneficial in our trial.

Masking (blinding) is a possible advantage of the randomized research design, in that it may improve the internal validity of a study.[126] However, masking is not always possible to implement, for instance if group affiliation is obvious during patient examination, such as in our study. Masking of our patients was not performed either, since they of ethical and practical reasons were informed about the operation method used, and in particular whether a new IOL was implanted or not. Nevertheless, the possible disadvantages with non-masking of clinical examiners and patients were not a great concern in this thesis. The study examinations were conducted in a standardized manner, and we had no clear hypothesis in advance that favored either of the operation methods. Further, no patient-reported outcome measures were included in the papers, and we believe the placebo effect of this type of surgical treatment is small.

Single-center, single-surgeon
Our study was conducted at one hospital department and the same surgeon performed all the operations. This was feasible because the department has an experienced eye surgeon highly capable of performing both IOL repositioning and IOL exchange (Dr. Drolsum). A major advantage of the *single-center, single-surgeon* approach is that it minimizes the variation related to other factors than the operation methods, such as the skills of the surgeon or methods used to measure outcomes. Hence, it becomes more likely that discovered group differences in outcomes are actually related to the interventions. It should be mentioned, though, that one surgeon is not necessarily equally experienced with each operation method that are being compared in an intervention study, such as in our case where the surgeon had slightly less experience with IOL exchange prior to the initiation of the trial. This may have introduced a bias in the results, although we have no particular reason to suspect that, especially since the complication rates in both groups were satisfactory compared with previous studies (Paper I).

However, a single-center, single-surgeon approach may affect the external validity, and it has been indicated that a multicenter trial have greater clinical applicability at least for some conditions.[127] Also other centers within our health region perform IOL dislocation surgery

and possibly to an increasing extent. The experience of the surgeons as well as the severity of the operated IOL dislocation cases likely differs between departments. Thus, the surgical outcomes from our trial may not be directly comparable to all clinical centers treating these patients. But all things considered, we believe the single-surgeon, single-center approach with its standardized research design was beneficial in achieving the main aims of our trial.

Operation methods

In this randomized clinical trial, we aimed to compare two widely used surgical techniques that each represented the main operation methods IOL repositioning or IOL exchange.

Scleral suturing is the most common surgical technique for IOL repositioning, and was the chosen technique in this intervention group. Suturing of a dislocated complex to iris[128] appears to be rarely used in clinical practice,[27] whereas sutureless scleral fixation techniques[65-70] seem to apply only for fixation of an IOL (implanted or removed from the capsule) and not for repositioning of the whole IOL-capsule complex.

A number of surgical techniques and IOL types are available for exchange surgery, as described in the *Introduction* of this thesis, and the choice in clinical practice usually depends on the surgeon´s experience and preference. According to the literature, iris-claw IOLs constitute a popular and promising alternative,[129] and was already in use at our department prior to the initiation of the present trial. Implantation of this IOL type was therefore the chosen technique in the IOL exchange group.

Intraocular lens repositioning by scleral suturing – surgical aspects to consider
Not all dislocated IOLs have a design that allows for repositioning by scleral suturing, e.g. plate-haptic IOLs without peripheral holes, and these cases were excluded from our trial. Furthermore, some surgeons have advocated that one-piece acrylic IOLs with thick haptics (n = 29 in our study) should neither be repositioned, due to the risk for iris chafing and development of the uveitis-glaucoma-hyphema (UGH) syndrome.[130,131] This seems sensible if a dislocated IOL is outside the lens capsule (out-of-the-bag).[132] However, in our clinical experience, the risk of UGH syndrome seems to be minor when the dislocated IOL remains inside the capsule (in-the-bag). Hence, dislocated one-piece IOLs were found eligible for both operation methods and included in our trial. This view finds support in the literature, although there are to some extent varying opinions on the matter.[130,131,133]

Suture erosions and suture breakage have occurred with the 10-0 polypropylene suture that is often used for scleral fixation. A few studies have reported rates as high as 18%-28% in the longer term,[134,135] and some surgeons have thus recommended to rather use the 9-0 polypropylene suture or a gore-tex suture.[59,136] However, these unusually high rates were in studies on scleral suturing of only the IOL (not the capsule), and in addition, other studies on the same type of surgery have not confirmed the findings.[137] Suture breakage further seems to occur particularly in younger patients.[134,136] This view corresponds with clinical experience from our clinic, as we have experienced several cases of suture breakage in secondary implantation of sutured posterior chamber IOLs or Cionni ring implantations, while we have barely seen this complication following scleral suturing of a dislocated in-the-bag IOL, which have been performed for more than 10 years in our clinic. We therefore hypothesize that the risk for suture breakage is low when the whole IOL-capsule complex is sutured to the sclera in elderly patients. A possible explanation is that the capsule to a certain extent prevents direct fricton between the suture and the (sharp) haptic edge.

In the present study, the 10-0 polypropylene suture was used and as of today, the 9-0 polypropylene suture and the gore-tex suture is not available in Norway.

The sutures for scleral fixation have been positioned at a distance of 1.0-2.0 mm posterior to the limbus in various studies.[26,33,49,59,138] The ciliary sulcus is often the recommended position for out-of-the-bag IOLs and it seems that some surgeons reposition dislocated in-the-bag IOLs to the sulcus as well.[79] Results from an anatomical study by Duffey et al[139] indicated that an exit point for the scleral sutures of less than 1 mm posterior to the limbus is required for sulcus positioning. This result finds support in a few more recent studies,[140,141] whereas an anatomical study by Pavlin et al[142] suggested that a suture distance of approximately 2 mm posterior to the limbus is often required.

Repositioning of a dislocated IOL-capsule complex to the sulcus is expected to provide a myopic shift, since it leads to a more anterior position of the IOL than the physiological capsular bag position.[143] In our study, we intended to reposition the IOL-capsule complex close to the previous physiological position, and the scleral sutures were placed at an attempted distance of 1.5-2 mm posterior to the limbus. The relationship between the position of the scleral sutures and the refractive outcome has not been a main focus in previous studies on IOL dislocation surgery. A discussion of this aspect was provided in Paper II, however,

detailed analyses could not be conducted in this thesis as we did not measure the suture position for each individual patient.

Intraocular lens exchange with an iris-claw lens – retropupillar fixation

Although the originally recommended placement of the iris-claw IOL is in the anterior chamber, a number of studies have enclavated this IOL to the posterior surface of the iris (retropupillary).[62,71] No large clinical trial has to our knowledge compared these two positions. While some have argued in favor of an anterior chamber position due to its simplicity and allegedly better control of the centration and orientation of the IOL,[63] others have advocated that a retropupillar fixation represents a more natural positioning of an eye lens and that it may also be protective and beneficial for the corneal endothelium.[71,144] The latter assumption finds some support in a case series of 27 patients that included both positions.[145]

A retropupillar fixation was applied in our trial (Figure 5). By placing the iris-claw IOL in the posterior chamber we achieved a quite similar position of the IOL in the two operation groups.
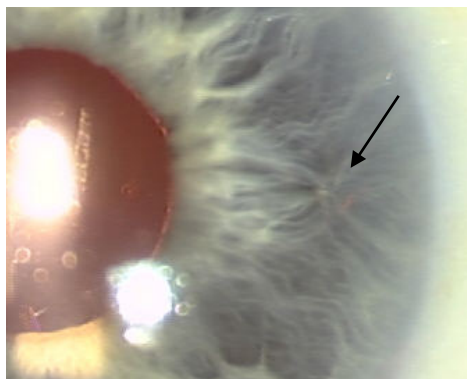
Figure 5 Retropupillar fixation of an iris-claw intraocular lens, with the iris enclavation shown (arrow). Photo: Oslo University Hospital

Sample size

Despite the increasing trend of late in-the-bag IOL dislocation in recent decades, the condition is still rather uncommon. Hence, it can be challenging to enroll a sufficient number of such patients in a prospective clinical study. Furthermore, this patient group has a high mean age, at least in our country, and thus some risk for loss to follow-up due to serious disease or even death throughout the follow-up period. These aspects had to be taken into consideration in the design of our study.

Not having high age as an exclusion criterion enabled the enrollment of more patients and also resulted in a more representative study population, which we believe strengthened the external validity of our trial. Altogether 104 patients were included, which is well in accordance with the sample size calculation and satisfactory compared with previous non-

randomized studies.[24,33-35,40,49] Such a large sample size was made possible by patient referrals from a large geographical area surrounding our hospital. In addition, the elderly population in this region has a quite high prevalence of PEX,[86] which is likely associated with a correspondingly high incidence of late in-the-bag IOL dislocation.

Follow-up and dropout

Six months follow-up was not sufficient to fully compare important outcomes in the two operation groups, especially relating long-term complications. However, this period was chosen for the analysis of the first study results as a compromise between duration and expected dropout. The dropout rates after six months was 16%-20% in the two groups, which we consider acceptable given the high mean age of the study patients in particular. Nevertheless, it is still a limitation of the study.

In order to evaluate whether there were any bias related to the patients that were lost to follow-up, we strived to collect additional postoperative data from all study patients including the 19 dropout patients. A comparison of available BCVA measurements from either our clinic or the patients' private ophthalmologist one month after surgery revealed no significant difference between the dropout patients (0.36 logMAR; n = 9) and the other study patients (0.30 logMAR; n = 61) ($P = 0.59$). At least some clinical information was available from most of the 19 dropout patients, and from this information it appeared that their IOLs were well positioned with no registered cases of retinal detachment, endophthalmitis, vitreous hemorrhage or reoperations. Hence, there were no clear indications that these patients differed considerably from the other study patients. However, these patient data were uncertain and too limited to finally conclude in this matter.

In all the papers we have used the *completer analysis approach* (or available case analysis),[123] which means that in each analysis only patients with a recorded outcome measure at that time point were included. Hence, missing data were excluded from the data analysis.

Image analysis of the corneal endothelium

The corneal endothelium was examined and analyzed with a non-contact confocal microscope (ConfoScan4, Nidek, Padova, Italy) as described in Paper I. Contact and non-contact confocal microscopy have previously been found interchangeable.[146] However, concerns have been raised that the fully automatic ECD analysis available with several instruments may yield inaccurate measurements compared with manual or semi-manual counting methods.[147-151]

With these latter methods, it has been recommended that at least 75 cells per endothelium are counted to reach an acceptable intersubject variance,[152] although some previous cataract studies have aimed for 50-60 cells counted per endothelium at minimum.[153-156] To further deal with intersubject variance, many studies have analyzed either three different images from each patient, or three or five different positions on the same image.[103,153-158]

In our study, the ECD was measured both in fully automatic mode and in semi-manual mode. Prior to the analysis, we tested the reliability for semi-manual counting between two independent examiners in a methodological pilot study of approximately 15 cases, and we found satisfactory inter-observer reliability (within ± 5%). Nevertheless, it was decided that one examiner (O.K.), masked to each patient's group affiliation, performed all the image analyses. A pre-defined frame size was used, and more than 75 cells per image were counted, except in a few cases with especially low ECDs.

In corneas with high ECDs, there was acceptable agreement between the automatic and the semi-manual counting. However, at lower ECDs we encountered pronounced differences. The automatic method considerably overestimated the ECD in numerous cases (Figure 6), which is consistent with the findings by others.[147-151] It may be argued that such inaccuracies will be evenly distributed between the study groups. However, in our study, the preoperative ECD was lower in the exchange group, and the larger discrepancy between the analysis methods at lower ECDs could therefore have biased the results if we had used the automatic ECD count.
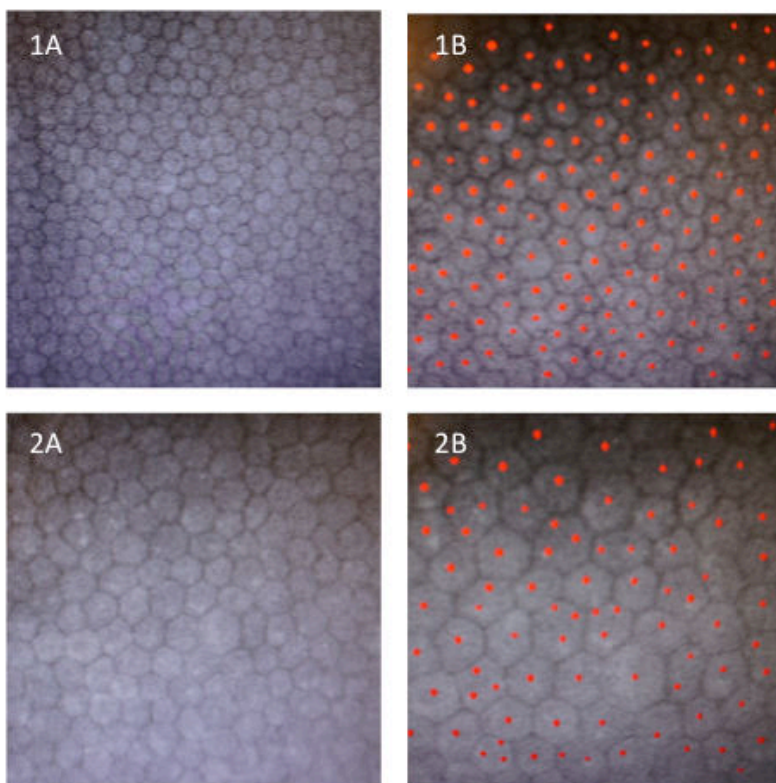

Figure 6 Confocal microscopy images of the corneal endothelium in two cases. Automatic counting with red dots (B). 1A and 1B shows an ECD of about 2300 cells/mm^2 with good agreement between automatic and manual counting. 2A and 2B shows an ECD of about 1000 cells/mm^2 by semi-manual counting, with overestimation of the ECD by automatic counting. ECD = endothelial cell density

A considerable number of patients had missing or unsatisfactory ECD recordings (preoperatively n = 23, postoperatively n = 15). Reasons were, as listed in Paper I, technical failure, challenges in patient cooperation, and images that were not clear enough for analysis. Due to the high mean age of the patients, we expected some lack of cooperation with the confocal microscopy examination. However, the final number of images available for analysis was lower than expected and limits the applicability of the ECD results.

Vector analysis for surgically induced astigmatism

Ocular astigmatism is characterized by a magnitude, measured in diopters (D), and a direction, measured in degrees. Different methods have been used for analysis of the astigmatism induced by surgery, especially in relation to cataract surgery, and the methods have only to a varying degree taken the direction of the astigmatism into account.

Analysis methods for surgically induced astigmatism
Comprehensive descriptions of analysis methods can be found in the literature.[159-161] The *simple subtraction method* evaluates SIA by comparing the preoperative and the postoperative magnitudes of astigmatism (i.e. mean cylinder) without considering the axes.[160,162] Despite its common use, this method has been considered inadequate both in mathematical and practical terms.[159,163] *Astigmatic decomposition* is based on the division of every cylinder into two cross cylinders at 0 degree and 45 degrees, and doubling of the axis. This enables calculation of means, however, the formulas described has not been considered adequate to analyze SIA for aggregate data.[160]

With *vector analysis,* the axis of astigmatism is taken into account. The method by Alpins[162] calculates and describes the total astigmatic change of a surgical intervention characterized by both astigmatic magnitude and direction. The polar value method, as described by Næser,[160,164,165] reports the SIA as flattening or steepening in preselected directions. With this method the plane of the main surgical incision is often chosen as reference meridian, in which the power of the SIA is calculated, whereas the torsional force twisting the astigmatic direction in a clockwise or counter-clockwise direction is calculated in a plane inclined 45 degrees to this meridian. With the method described by Holladay,[163,166] cylinder data are converted to Cartesian coordinates (*x* and *y* coordinates) with doubling of the axes so that 0 degree and 180 degrees become equivalent. Once the data with these two methods have been converted to polar values[164] or *x* and *y* coordinates,[166] the converted values are orthogonal and standard descriptive statistics can be applied, e.g. calculation of means. In this way, aggregate

data can also be analyzed. With both methods, standard formulas are used for reconversion of the aggregate data back to the standard notation for astigmatism.[163,165] The Alpins, Næser and Holladay methods have been claimed to yield consistent results, both for individual data and for analysis of aggregate data.[159]

Many studies have, by the use of various vector analysis methods, correctly calculated magnitude and direction of the astigmatism for individual study patients but not performed reconversion on aggregate level.[160] Instead, they have simply averaged the astigmatic magnitude of each patient. This method, sometimes called *astigmatic magnitude not considering axis* or *mean SIA magnitude*, has been claimed to yield inconsistent results and systematic errors.[159,160,163]

Analysis methods used in this thesis

Alpins method is often recommended for SIA analysis of refractive surgery,[167] which often has reduction of astigmatism as a main purpose of the treatment. Alpins method can describe the SIA fully in various surgical meridians, and thus enables a comparison with the target induced astigmatism to evaluate the treatment result.[162] In our study, the surgical treatment was not specifically targeted to reduce astigmatism. Further, the surgical meridian was not exactly defined in every case. Supported by the literature[159,168] we considered the Næser and Holladay methods for SIA analysis as adequate for our purpose. Since the *mean SIA magnitude* has been widely reported in the literature, we also included such results in Paper II.

Management of intraocular pressure lowering treatment

At the time of IOL dislocation diagnosis, 38% of our study patients had preexisting glaucoma. This proportion is not surprising in such a patient population considering the high mean age and the frequent occurrence of PEX (83%). In a previous study,[86] we found a glaucoma proportion of 33% in a comparable group of patients with a mean age of 82 years, PEX, and pseudophakia, examined 6-7 years after cataract surgery. None of those patients had IOL dislocation, at that time or before, and none had an IOP above 21 mmHg. In the present trial, however, we found that 22% of the patients had high IOP ($\geq$ 22 mmHg) but no previously known glaucoma. Also 44% of the patients with preexisting glaucoma had a high IOP.

A question has been raised whether the associated high IOP is directly related to the IOL dislocation and can be resolved by dislocation surgery, or if it is a result of other underlying pathology and consequently requires additional IOP-lowering treatment.[39-42] We decided to

treat the patients with recently identified high IOP without preexisting glaucoma as one subgroup at baseline, termed *glaucoma suspects*, although they had quite considerable differences. While some had an IOP above 30 mmHg, PEX and a pronounced excavation of the optic disc, others had more unclear findings with a moderately increased IOP and an apparently normal optic disc, and in several patients the dislocated IOL-capsule complex disturbed the evaluation of the optic disc. A more certain glaucoma status in these patients was determined after six months of follow-up.

Most study patients were diagnosed with late in-the-bag IOL dislocation outside our department; by a private ophthalmologist or at another hospital department. Since there has been no clinical consensus on how to treat associated high IOP in these patients, this was managed differently. Some patients had their high IOP treated before referral, in one case even with filtering surgery, whereas other patients were referred immediately for urgent dislocation surgery without initiation of any IOP-lowering treatment. This resulted in a considerable variation in the IOP measured at the preoperative study examination, which was not necessarily representative for the IOP at IOL dislocation diagnosis. Therefore, we gathered and registered data from the examinations before referral as well. This provided a more complete overview of the IOP development, not least in relation to IOP-lowering treatment given preoperatively, as illustrated in Figure 7.
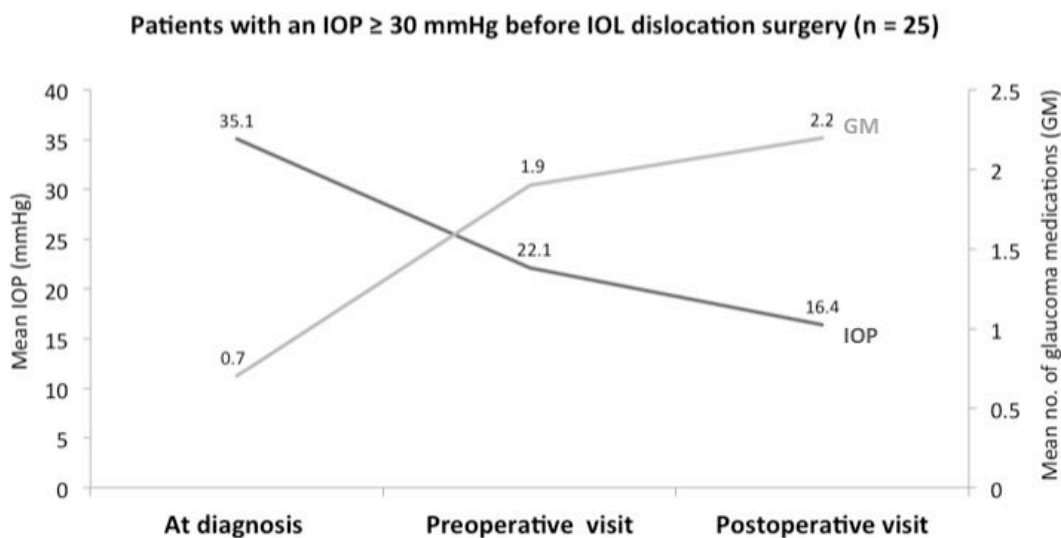

Figure 7. Changes in intraocular pressure (IOP) and mean number of glaucoma medications (GM) for the 25 patients with an IOP of 30 mmHg or higher before surgery. Some patients were also treated with IOP-lowering surgery and/or laser.

We relied mainly on the patients' own ophthalmologists for relevant glaucoma diagnostics and evaluation of IOP-lowering treatment requirements postoperatively. In particular, this meant that the decision whether or not to discontinue glaucoma medication was often taken regardless of the study setting. Furthermore, the postoperative study examination did not include standardized glaucoma diagnostics, such as visual field analysis. This lack of standardization limits the ability to draw certain conclusions from our findings. However, it reflects a realistic clinical setting, and we still consider the results to be highly relevant.

The 6-month postoperative IOP change was the main outcome measure in Paper III. Methodologically, one may question the robustness of the data this analysis is based upon. The IOP was measured at only one time point before and after surgery and by only one examiner at each study visit. This leaves some obvious uncertainties in the results. However, there is no particular reason to suspect a group bias in the IOP measurement and we still consider our prospective standardized research design as favorable to retrospective studies. Our study further included a high number of patients with associated high IOP compared to other studies, which improve the ability to draw conclusions and discuss possible clinical implications.

External validity

External validity is the extent to which study results form a correct basis for generalization to other circumstances.[126] We believe our study results are highly relevant for the majority of patients with late in-the-bag IOL dislocation treated at our department, since we recruited patients from the entire area that constitutes our large health region and all referred patients with the condition were considered for inclusion. The eligibility criteria were quite broad, with no upper age limit. We also succeeded in the inclusion of patients within a reasonable time frame, and the dropout rate after six months follow-up was acceptable. There are, however, a few limitations in the external validity in relation to the various exclusion criteria as listed in Figure 4.

The two operation methods that were compared in the present trial are widely recognized nationally and internationally, and the research was conducted as part of ordinary clinical practice except for the more comprehensive study examination. Hence, important study findings should be feasible to implement in clinical practice both at our department and at other ophthalmology centers. However, the applicability of our results to other settings might be affected by the single-centre, single-surgeon approach, as previously discussed. The

experience of the surgeons and/or the severity of the operated dislocation cases may differ between centers. In addition, we excluded totally dislocated IOLs that required pars plana surgery. In many centers, this is the main surgical approach in the treatment of these patients, even when the IOL is not totally dislocated.[24] It should further be mentioned that we excluded out-of-the-bag IOL dislocations. Although these are sometimes operated with the same surgical techniques as in-the-bag dislocations, patient characteristics may differ and our study results may not be directly applicable to this patient group.

The study patients had a frequent occurrence of PEX, as expected in our geographical area. This probably affected the IOP and glaucoma results, which may be different in populations with a lower prevalence of PEX. In terms of ethnicity, all except two of the study patients were Caucasians, which can be relevant to take into consideration especially in the interpretation of refractive outcomes and glaucoma results.

A concern in surgical studies lasting for several years (long inclusion period and/or a long follow-up) is that clinicians adapt new surgical techniques before the study results are published. Whether the operation methods we compared are more or less relevant today than prior to the initiation of our trial remains uncertain. To date, IOL repositioning by scleral suturing seems to be widely used. In terms of IOL exchange, some new fixation methods have emerged in recent years, and no aphakic iris-claw IOL have been FDA-approved yet. However, implantation of an aphakic iris-claw IOL seems to be a popular option in Europe and some other parts of the world both for IOL dislocation and in aphakic eyes.

Overall, we believe our study results are of relevance to a wide range of clinicians treating patients with late in-the-bag IOL dislocation. By reporting the methods and the results in a standardized manner[123] we have enabled others to evaluate the applicability of the study findings to their setting. The results might also be relevant for other types of IOL surgery, such as treatment of out-of-the-bag IOL dislocation or aphakia. In addition, some of the study results, in particular regarding glaucoma and IOP, may be of relevance to an even wider range of clinical and research settings.

Main strengths and limitations of the trial

Strengths and limitations of our trial are discussed throughout this thesis. In this section, a summary is presented:

Strengths

- Prospective randomized research design
  (first randomized trial on IOL dislocation surgery to our knowledge)
- Comparison of two relevant operation methods
- Large sample size
- Rather broad inclusion criteria, which improve the external validity
- All patients operated by the same surgeon
- Standardized study examinations, all performed at one center
- Comprehensive evaluation of both visual outcome (efficacy) and surgical complications (safety) for both operation methods in the same clinical trial
- Surgically induced astigmatism assessed by vector analysis
- Refractive outcome for IOL repositioning compared with *pre-dislocation* refraction
- Comprehensive evaluation of the association between high IOP and IOL dislocation

Limitations

- Considerable loss to follow-up (18%)
- Missing data for other reasons, in particular for corneal endothelial measurements
- Rather short follow-up in this thesis (six months)
- Lack of masking (blinding) in other aspects than image analysis
- Inadequate statistical power for small group differences and subgroup analyses
- Placement of the scleral suture not routinely measured during repositioning surgery
- Surgical meridian not used as reference meridian for SIA calculation in all patients
- Lack of standardization in glaucoma diagnostics
- No early postoperative routine follow-up regarding IOP-lowering
- External validity (generalizability) may be limited by:
  - Exclusion criteria, in particular totally dislocated IOLs
  - Unusually high prevalence of PEX
  - Homogenous ethnic group
  - Performed in a specialized university clinic with only one surgeon
  - Not all clinics have aphakic iris-claw IOLs as a treatment option (e.g. in the US)

Discussion of results

Late in-the-bag IOL dislocation has increased in recent years.[27,29,32-34] It is therefore of great importance to determine the best treatment option for this condition with serious visual impairment. Maintaining an acceptable visual function is essential for the ability of elderly people to perform daily life activities and possess a good quality of life. Although a few retrospective studies have indicated that the operation methods IOL repositioning and IOL exchange provide similar visual outcomes,[33,34,40,42,44] it has been unclear whether their surgical complications differ. Furthermore, some of these studies included both in-the-bag and out-of-the-bag IOL dislocations, and their abilities to reach certain clinical recommendations have been limited by research design and sample size.

Addressing this lack of knowledge, we conducted the present randomized clinical trial with comparison of IOL repositioning by scleral suturing and IOL exchange with an iris-claw IOL. A main conclusion in Paper I was that the two operation methods had similar efficacy in terms of visual outcome. In the following, visual outcomes and some other selected aspects of study results from Papers I-III will be discussed.

Visual outcome

The mean 6-month postoperative BCVA was 0.3 logMAR for all study patients. This is favorable to the mean of 0.4-0.5 logMAR that most other studies on IOL dislocation surgery have reported.[33,38-40,42,44] The group comparison in our study showed no statistically significant difference between IOL repositioning and IOL exchange, which is in accordance with the previously referred retrospective studies.[33,34,40,42,44] To our knowledge, no articles comparing visual outcome for these two operation methods has been published after Paper I. With the randomized research design and the quite large sample size, we believe our trial provided a robust basis for comparison of visual outcome. It should be mentioned, though, that the sample size calculation was performed with an anticipated between-group difference of at least 0.15 logMAR. Our study may therefore have lacked the statistical power to detect minor between-group differences in BCVA. In this regard, a large prospective multicenter trial or a future metaanalysis may be advantageous to reveal more certain conclusions.

Unlike some previous IOL dislocation studies that have emphasized the BCVA improvement following surgery (i.e. change),[26,38,40,42] we had postoperative BCVA as the main outcome measure. A main reason was that a pronounced BCVA improvement was not expected in

several of these patients when we compared the preoperative and the postoperative study examination results. The standardized preoperative examination included an attempted correction with a high plus lens in eyes with a considerably dislocated IOL, being practically aphakic (Figure 8). In several of these patients the plus correction resulted in a large difference between the greatly deteriorated uncorrected visual acuity (UCVA) and the rather acceptable preoperative BCVA. Also other study patients had a quite pronounced difference between the UCVA and the BCVA preoperatively. The same aspect was appearent in a study by Hayashi et al[26] that found a statistically significant improvement in the UCVA but not the BCVA after IOL dislocation surgery.

It may possibly be the case that not all IOL dislocation studies have performed the preoperative measurement of the visual acuity in the same manner as we did. This could potentially overestimate the postoperative BCVA change in some studies, and thus, complicate the comparability between studies.
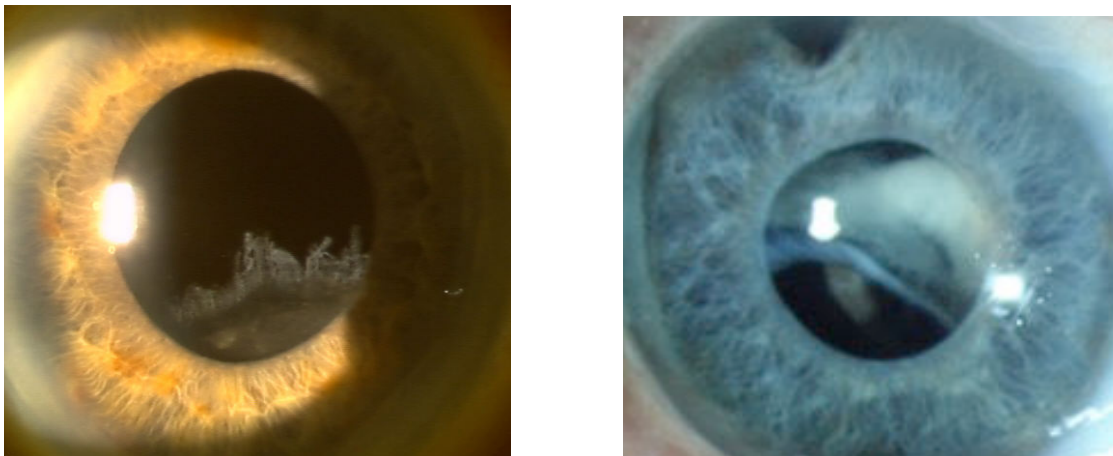
Figure 8 Late in-the-bag IOL dislocation, with the dislocated complex below the optical axis (left) or disturbing the optical axis (right). Photos: Oslo University Hospital.

In the analysis of our results, we also calculated the postoperative BCVA improvement and the group comparison showed a tendency towards a greater improvement after IOL exchange. However, the interpretation of these results were complicated by unequal study groups at baseline, with a worse preoperative BCVA in the exchange group compared with the repositioning group. By carefully considering our data we recognized that the preoperative group difference was to a large extent explained by a few patients (n = 7) with seriously impaired BCVA ($\geq$ 2 logMAR), of whom all except one had been randomized to the IOL exchange group. The main reason for their serious visual impairment was optical disturbance

from the haptic and/or superior part of the lens capsule (Figure 8), which is expected to resolve by surgery followed by a pronounced postoperative BCVA improvement. To illustrate this unequal distribution, we included preoperative BCVA measures for each IOL dislocation grade (1 to 3) in the presentation of baseline characteristics in Paper I.

Surgical complications

After six months follow-up, both operation methods appeared to be safe with few serious complications (Paper I). Nevertheless, the two operation methods differed to some extent in their complication profiles, especially in terms of perioperative complications. The repositioning group had a non-significant tendency of more intraocular hemorrhage, as well as the only two cases of presumed fluid misdirection syndrome. The exchange group, on the other hand, had more vitreous loss to the anterior chamber and more iris injuries, as well as the only two cases of choroidal effusion postoperatively.

Two previous retrospective studies on surgery of late in-the-bag IOL dislocation have indicated that IOL exchange is associated with more surgical complications overall[42] or at least perioperatively[34] compared with IOL repositioning. Otherwise, there seems to be a lack of such comparisons for these operation methods in the literature. Although our trial provided a comprehensive evaluation of surgical complications, it should be emphasized that the sample size was too small for an adequate group comparison of rare complications. The results may still show possible differences between the treatments that can be relevant to take into consideration in clinical practice.

The overall surgical complication rates in our study, without considering operation methods specifically, showed quite favorable results as compared with other studies. Of special note, we had no cases of endophthalmitis or retinal detachment after six months follow-up, and only one case of redislocation, which was a temporal disenclavation of an iris-claw IOL that was successfully re-enclavated. However, it can be inferred from our results that both operation methods were associated with more complications than previously reported for routine cataract surgery.[18] Although as expected, this can be useful information for both patients and surgeons to take into consideration in the treatment decision when late in-the-bag IOL dislocation has been diagnosed.

Cystoid macular edema

In our registration of CME we included all cases with macular cysts postoperatively, which were three cases (7%) in the repositioning group and four cases (10%) in the exchange group ($P = 0.71$). However, by taking into consideration that two cases in the repositioning group had a few macular cysts present before surgery, there seemed to be a tendency towards more CME after IOL exchange, although these numbers are too small to conclude.

Cystoid macular edema was defined in our study as macular cysts detected by OCT at the 6-month postoperative visit. This is not the peak interval for the postoperative occurrence of CME after IOL surgery,[169] however, since our trial had visual outcome as the main focus we wanted to register the number of cases that could be long-term vision threatening. This may have limited the comparability with other IOL dislocation studies. However, this postoperative complication does not seem to have been registered in a consistent manner previously either. Studies have reported CME in 0%-24% of the patients following surgery of IOL dislocation.[24,33,34,40,44,49] Although this wide variation is probably partly reated to surgical techniques, it likely also reflects the different time points for postoperative examination(s), the considerable variation in follow-up intervals, differences in sample size, weak study designs (often retrospective), and other surgical indications than late in-the-bag IOL dislocation in some of the patients. In addition, most studies relied upon clinical examination for detection of CME without any routine image analysis.

Redislocations and long-term complications

There were no redislocations after IOL repositioning surgery in this study. This supports our hypothesis that the risk for suture breakage is minor after scleral fixation of a dislocated IOL-capsule complex, even after using the 10-0 polypropylene suture. Suture slippage, with loosening of the sutures from the haptic, also seems less likely when the suture passes through the lens capsule.[136]

Nevertheless, it is important to emphasize that this thesis only presents the results after six months follow-up, which is short in terms of these complications. A longer follow-up is needed to detect the rate of suture breakage, as well as other possible long-term complications such as considerable ECD loss with corneal decompensation or pronounced iris atrophy.

Endothelial cell density loss

As shown in Paper I, there was a significantly more pronounced ECD loss after IOL exchange (10%) compared with IOL repositioning (3%) ($P = 0.04$). However, as previously discussed

in this thesis, there were methodological issues related to the analysis of the corneal endothelium in our trial. The ECDs in the two groups 6 months after surgery were not suitable for direct comparison because the groups differed in this parameter also before surgery, with a lower preoperative ECD in the exchange group. In addition, the comparison of the postoperative ECD loss (change) was considerably limited by missing data and this was slightly more prominent in the exchange group. It may have been the case that corneas with low ECDs more often had unclear confocal microscopy images not suitable for analysis, thus possibly creating a group bias. Since these factors limited the ECD evaluation, we were cautious to draw conclusions from the ECD data and excluded this parameter from the clinical implications mentioned in Paper I.

Nevertheless, the results indicated a difference between the two operation methods that may be of relevance to clinicians. There are several factors that theoretically can lead to a quite pronounced ECD loss after IOL exchange with an iris-claw lens. This includes the large corneal wound (if a corneal incision is chosen), surgical manipulation near the corneal endothelium especially when the IOL-capsule complex is removed, frequent need for anterior vitrectomy, and increased inflammation following explantation of the dislocated complex through the pupil and/or in relation to iris fixation of the IOL. We had no measurement of the corneal endothelium shortly after surgery, thus, we cannot conclude whether perioperative or postoperative factors contribute the most to the encountered ECD loss.

Only a few studies have evaluated the corneal endothelium after surgery of IOL dislocation, and none of them are directly comparable to our study. Kim and Kim[49] found an ECD loss of 11% and 13% after scleral and iris fixation, respectively. However, only 43% of the patients had in-the-bag IOL dislocation and iris fixation was performed with sutures. Labeille et al[64] found a median ECD loss of 21% in the first three months after pars plana vitrectomy and implantation of an iris-claw IOL. However, this study included dislocation of both biological lenses and IOLs, and 75% of the cases were caused by trauma (intraoperative or contusive).

The largest published patient materials on iris-claw IOLs are from aphakia surgery. In a study that included 128 eyes with an iris-claw IOL positioned in the anterior chamber, Güell et al[63] found a significant postoperative ECD loss of approximately 12% over a period of 5 years, with an even more pronounced cell loss after 3 years. In a study of 320 eyes with a retropupillar iris-claw IOL, Forlini et al[144] observed no significant postoperative change in the ECD after a mean follow-up of approximately 5 years. However, these studies had other

surgical indications than late in-the-bag IOL dislocation and the patients had a mean age of only 55 and 60 years, respectively. One may speculate whether the main reason for the difference in ECD loss between our study and that of Forlini et al,[144] is that we explanted the whole IOL-capsule complex, which represents a considerable surgical trauma. Nevertheless, to reach more certain conclusions regarding ECD loss after IOL dislocation surgery, more prospective studies and longer follow-up are needed.

Surgically induced astigmatism and refractive outcome

The SIAs of the two operation methods have been discussed thoroughly in Paper II as well as previously in this thesis, and will not be further elaborated here. As for the refractive outcome, we concluded in Paper II that the refractive predictability was satisfactory for IOL exchange, whereas IOL repositioning resulted in a mean myopic shift. This indicates that the IOL-capsule complex in the repositioning group was, on average, positioned more anterior after surgery compared to before the IOL dislocation.[143] It further shows that with the usual suture position applied for scleral suturing, a myopic shift must be expected, and thus the risk for anisometropia should be considered before an operation method is chosen. An advantage of our study was that we managed to gather information about the refraction before the IOL dislocation for most of the patients in the repositioning group, consequently avoiding the uncertainties in the refraction at the preoperative examination related to dislocation and possible tilt of the IOL. We believe the inclusion of the pre-dislocation refraction in the analysis enabled a more valid and clinically relevant evaluation of the refraction change induced by repositioning surgery.

Based on our findings, it seems reasonable to suggest that the scleral sutures should be positioned more posterior to the limbus than in our trial, to achieve an IOL position more in accordance with the previous physiological position. However, it is not unlikely that such a position can lead to an unstable IOL-capsule complex due to lack of support from the iris and/or ciliary process, with an increased risk for IOL tilt and/or pseudophakodonesis. Following IOL repositioning by scleral suturing, an IOL tilt may otherwise occur if the two sutures are not positioned at the same distance behind the limbus, if one of the suture loops encloses the distal and not the middle part of the haptic, or if one of the sutures loosens.[59,170] An IOL tilt is more unlikely after exchange surgery with an iris-claw IOL, although it may occur if one or both of the enclavations are not properly fixated. Evaluation of IOL tilt was not a main aim of our study and no objective parameter was measured, although our clinical

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impression was that IOL tilt was not frequent. Further, we did not routinely measure the suture position perioperatively for each patient in the repositioning group, and thus we were not able to correlate this surgical factor with the postoperative IOL position, the refractive outcome, and the possible presence of IOL tilt.

The iris-claw IOL was originally developed for an anterior chamber position, and the manufacturer recommends an optical biometry A constant of 115.7 (SRK/T formula).[171] As commented in Paper II, studies have applied different A constants for retropupillar fixation of this IOL, and a recognized website that collects information from research studies and clinicians has suggested an A constant of 116.9 (SRK/T formula).[171,172] This is the value we used. The refractive outcome in our trial showed a mean hyperopic prediction error for IOL exchange surgery. Additional analyses suggested that an A constant of 117.3 would have been better. However, larger patient materials and more studies are needed to finally determine the optimal A constant for this type of surgery.

Intraocular pressure and glaucoma

The 6-month postoperative IOP change was the main outcome measure in Paper III, and the results showed a borderline significant group difference in favor of IOL exchange. In Paper III, we hypothesized that the tendency for a difference in postoperative IOP change between the operation groups might be related to removal of pseudoexfoliative material in relation to IOL exchange surgery. This is in accordance with the explanation we suggested for the quite pronounced IOP decrease experienced by the PEX group in our previously mentioned cataract study (Kristianslund et al[86]). However, this IOP-lowering mechanism remains speculative. Longer follow-up and confirmative studies are needed before we can finally conclude that IOL exchange has a more pronounced IOP-lowering effect compared to IOL repositioning in eyes with late in-the-bag IOL dislocation.

At the time of IOL dislocation diagnosis, 22% of our study patients had high IOP but no previously known glaucoma, and high IOP was further seen in 44% of the glaucoma patients. A number of reasons for this association with high IOP can be hypothesized, as discussed in Paper III and and in other articles[39-42] to varying degrees. Our results seem to be most consistent with Leung et al,[41] which conclude that late in-the-bag IOL dislocation is likely associated with advanced stage PEX with (severe) glaucoma. However, while they found a postoperative IOP decrease only when IOL dislocation surgery was combined with glaucoma surgery, we found a postoperative IOP decrease after dislocation surgery alone, at least for

IOL exchange. This latter finding is partly consistent with others[39,40,42] that have reported some improvement of the associated high IOP after dislocation surgery.

A clinical aspect that was barely addressed in Paper III is the relevance and timing of IOP lowering surgery in eyes with late in-the-bag IOL dislocation and considerably increased IOP. In our study, one patient underwent trabeculectomy between the time of diagnosis and IOL dislocation surgery, whereas three patients underwent trabeculectomy after IOL dislocation surgery. In the literature there seems to be different approaches to whether IOP-lowering surgery, when indicated, is performed before, after, or as a combined procedure with IOL dislocation surgery,[39,41,42,173] and no clear consensus seems to have emerged.

Baseline characteristics

Pseudoexfoliation syndrome was the most common predisposing condition in our trial, being present in 83% of the study patients, as compared with 44%-70 % in several other late in-the-bag IOL dislocation studies.[24-26,29,33,34,39-42] A few studies have even found much lower PEX proportions.[38,43,44] It should be mentioned, though, that not all patients in each of these studies had in-the-bag IOL dislocation. Varying proportions of PEX may further be related to differences in patient age, although also some other studies than ours reported a mean age of about 80 years,[34,39-42] and it could possibly be a result of geographical variation and/or related to the registration of the condition.[87] Signs of PEX can be difficult to detect, especially in pseudophakic patients, and special attention must be paid to the presence of pseudoexfoliative material on the pupillary edge. Information from the patient medical record about the presence of PEX before cataract surgery can be helpful, as was the case for several patients in our study. Otherwise, we believe the prospective research design and the standardized implementation of our study promoted a rather accurate detection of predisposing conditions, and in particular PEX. A previous pathological study[46] found that while 33% of the patients with in-the-bag IOL dislocation were registered clinically with PEX, the proportion increased to 65% when the same complexes were examined microscopically after explantation. This indicates a clinical underdiagnosis of PEX, at least in pseudophakic patients.

Clinical implications

The typical late in-the-bag IOL dislocation patient is an 82-year-old woman at her 10th year after cataract surgery presenting with PEX, glaucoma, and a corrected visual acuity of 0.3 (Snellen). Both IOL repositioning by scleral suturing and IOL exchange with implantation of an iris-claw IOL will be acceptable treatments of her dislocated IOL, and she can expect a postoperative corrected visual acuity of at least 0.5 (Snellen).

This description, based on average results from our trial, is obviously a simplification of the reality given the considerable variation in baseline characteristics and surgical outcomes between late in-the-bag IOL dislocation patients. Nevertheless, it illustrates, to some extent, what kind of patients we have been studying in this thesis.
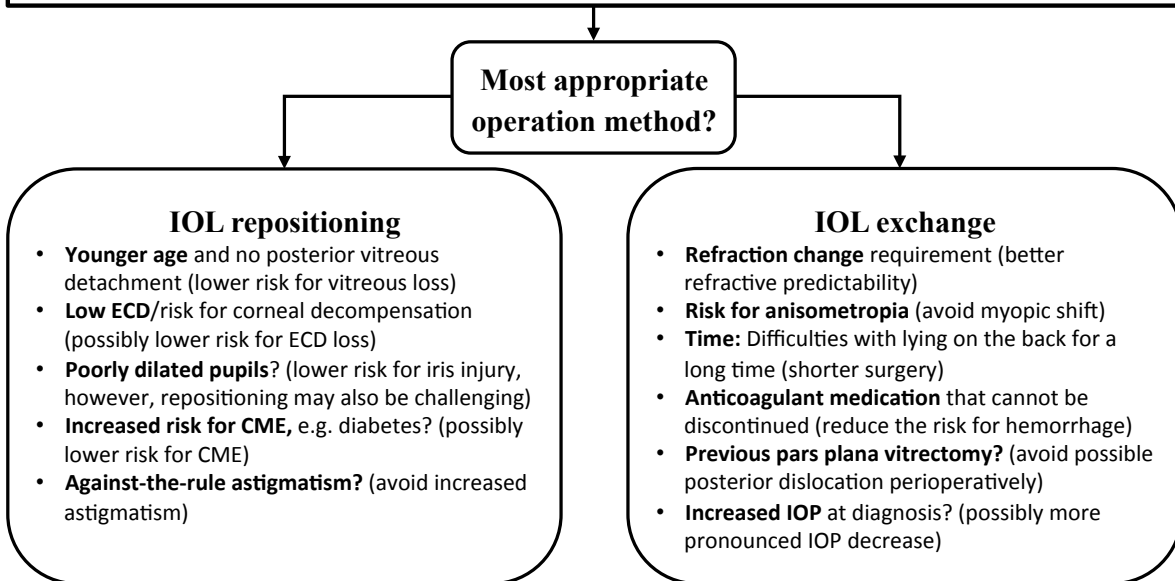
The basis for our research project was the lack of a clear consensus on the optimal surgical treatment of late in-the-bag IOL dislocation. With a growing pseudophakic population and an increasing number of patients with this condition, we believe our study provide important new knowledge. Six months follow-up in our trial could not present convincing results that either IOL repositioning by scleral suturing or IOL exchange with an iris-claw IOL was in all aspects superior to the other, and thus, the best choice for all patients with late in-the-bag IOL dislocation. However, the study provided a number of interesting findings that may have clinical implications and should be taken into consideration in the choice of operation method.

Our main conclusion was that the two studied operation methods had similar efficacy in terms of visual outcome, and both treatments seemed to be safe with few serious surgical complications. A main clinical implication from the results is that for many patients with late in-the-bag IOL dislocation, both IOL repositioning by scleral suturing and IOL exchange with a retropupillar iris-claw IOL are acceptable treatment methods. Nevertheless, the trial revealed some differences between the operation methods that may have other, more specific clinical implications, especially related to differences in complication profiles, refractive predictability and postoperative IOP change. These aspects should be taken into consideration in the choice of operation method in each individual case. For late in-the-bag IOL dislocation, there seems to be a need for diverse treatment recommendations, possibly with treatment algorithms that allow for individual risk evaluation. However, more comprehensive knowledge is required before certain recommendations can be given.

Possible clinical implications from our research have been discussed in the Papers I-III, as well as throughout this thesis, and are summarized in the following overview. These listed implications should be interpreted in light of the various limitations of the results.

Clinical implications from the study results

- Both IOL repositioning by scleral suturing and IOL exchange with a retropupillar iris-claw IOL seem to be highly acceptable treatment choices in many patients with late in-the-bag IOL dislocation
- With both methods there seems to be a more than 60% likelihood of achieving a BCVA of 20/40 or better
- For retropupillar implantation of an iris-claw IOL, an optimized A-constant of 117.3 is suggested
- If repositioning of a dislocated complex back to the previous physiological position is intended, scleral sutures should be placed more than 2 mm posterior to the limbus, however, this may possibly induce IOL tilt
- For IOL exchange, a 5.5 mm scleral pocket incision usually does not result in a problematically large SIA
- In patients with late in-the-bag IOL dislocation, PEX and recently discovered high IOP there is a high likelihood of undiagnosed PEX-glaucoma
- Associated high IOP should be treated in parallel with IOL dislocation surgery
- Patients should be informed that the complication frequency of IOL dislocation surgery is higher than with routine cataract surgery
- In some cases, only one of the operation methods are applicable, as commented in our exclusion criteria.
- Otherwise, the difference in complication profiles should be taken into consideration in the choice of operation methods, as shown below (in parenthesis is why the given operation method should be considered in specific patients, based on the available study results as of now with the previously discussed limitations)

Most appropriate operation method?

IOL repositioning

- **Younger age** and no posterior vitreous detachment (lower risk for vitreous loss)
- **Low ECD**/risk for corneal decompensation (possibly lower risk for ECD loss)
- **Poorly dilated pupils**? (lower risk for iris injury, however, repositioning may also be challenging)
- **Increased risk for CME,** e.g. diabetes? (possibly lower risk for CME)
- **Against-the-rule astigmatism?** (avoid increased astigmatism)

IOL exchange

- **Refraction change** requirement (better refractive predictability)
- **Risk for anisometropia** (avoid myopic shift)
- **Time:** Difficulties with lying on the back for a long time (shorter surgery)
- **Anticoagulant medication** that cannot be discontinued (reduce the risk for hemorrhage)
- **Previous pars plana vitrectomy?** (avoid possible posterior dislocation perioperatively)
- **Increased IOP** at diagnosis? (possibly more pronounced IOP decrease)

CONCLUSION AND FUTURE PERSPECTIVES

After six months follow-up in this first randomized clinical trial on surgery of late in-the-bag IOL dislocation, the following specific conclusions can be drawn:

1. **Safety and efficacy:** The two operation methods, IOL repositioning by scleral suturing and IOL exchange with implantation of a retropupillar iris-claw lens, seemed to have similar efficacy in terms of visual outcome and both operation methods had acceptable safety in terms of perioperative and postoperative complications. However, there were differences in the complication profiles, which should be taken into consideration in the choice of operation method for individual patients. A longer follow-up is required to compare the long-term efficacy and safety.

2. **SIA and refractive outcome:** The SIA was modest in both operation groups, albeit with a tendency for being more pronounced after IOL exchange, seemingly in the direction of against-the-rule astigmatism. Our trial further showed, as expected, that the refractive predictability was better for IOL exchange compared with IOL repositioning. Repositioning surgery led to a myopic shift, indicating that the dislocated IOL-capsule complex was sutured on average more anterior than the physiological lens position. The optimal suture position for this surgical technique remains unclear.

3. **High intraocular pressure:** A considerable proportion of the study patients had a high IOP, and there was a common association with underlying PEX glaucoma, which was likely the explanatory factor for the high IOP in many cases. However, as we did not thoroughly investigate other possible reasons, the conclusion is uncertain. There was an overall IOP decrease after surgery, with a borderline significantly more pronounced IOP decrease for IOL exchange. However, in most cases the high IOP was not fully resolved by dislocation surgery alone, and it therefore seems that a parallel focus on IOP-lowering treatment and IOL dislocation surgery should be recommended in these patients.

4. **Predisposing factors:** A possible predisposing condition was identified in nearly all patients in this trial, and 83% of the enrolled patients had PEX. This proportion is higher than in previous studies, which is likely related to the high occurrence of PEX in our area, and it may also reflect that PEX is often clinically underdiagnosed in patients with late in-the-bag IOL dislocation.

Future perspectives

This thesis presents the 6-month follow-up results from our trial. In the near future we hope that our study data can be further expanded, especially to determine the long-term safety and efficacy of the operation methods. A follow-up of two years is about to be carried out.

Through the work of this thesis, some new research questions have emerged. In Paper I, we found that 24% of those attending the postoperative visit experienced worsening of the BCVA after surgery, consistent with another study.[39] Cystoid macular edema and serious glaucoma were two of the main causes for decreased vision, and we believe these aspects are important to study in more detail as the intention of dislocation surgery is rather to stabilize or improve the vision. In this trial, we performed OCT scans six months after surgery to detect macular edemas that could be long-term vision threatening. The peak for CME, however, is believed to occur 4-6 weeks after surgery, at least for cataract operations.[169] Thus, earlier postoperative visits would yield more comprehensive information about the occurrence of CME throughout the postoperative period. Such knowledge might be useful in an attempt to optimize the postoperative topical drug regimen for this type of surgical treatment.

Another important parameter in this regard is the inflammatory reaction. It may be hypothesized that IOL exchange with an iris-claw lens is associated with more inflammation than IOL repositioning, both in the short-term due to the surgical trauma and in the long-term due to iris-fixation. However, while postoperative inflammation has been studied in great detail after cataract surgery,[169] such studies seem to be missing for surgery of IOL dislocation.

The refractive outcome is important for the patient´s experience of a satisfactory long-term result, and as discussed in this thesis there is room for improvement especially for repositioning surgery. To reach closer to a clinical recommendation in terms of suture positioning for scleral fixation, a simultaneous evaluation of suture position, refractive outcome, and IOL tilt seems sensible.

As briefly mentioned in the introduction of this thesis, several techniques for sutureless scleral fixation of an IOL have emerged in recent years,[65-70] and these are potential treatment options for IOL exchange. One recent study[174] showed that scleral IOL fixation with or without sutures seemed to provide equally good results. However, this study only included aphakic patients. A similar comparison for IOL dislocation patients would be interesting.

In the present study, we demonstrated a close association between late in-the-bag IOL dislocation and increased IOP and glaucoma. However, we had no postoperative study examinations before the 6-month visit, which limited the ability to study early postoperative changes of IOP and glaucoma treatment requirements. Earlier postoperative visits and more standardized management of these cases could possibly have enhanced the knowledge of this important clinical aspect. A better understanding of the association between glaucoma and late in-the-bag IOL dislocation may also expand the understanding of the pathological process that precedes the ultimate loosening of the complex.

Finally, a comprehensive comparison of treatment methods should also include an evaluation of the costs and benefits for society. What type of economic analysis that is most appropriate for comparison of IOL repositioning versus IOL exchange is highly dependent on whether these operation methods are considered to provide equal benefit to the patients or not.[175] The answer to this question is not obvious, as illustrated throughout this thesis.

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The number of pseudopakic people is expected to grow further in the years to come, due to an increased access to affordable surgical care in less developed countries, an increasing life expectancy, and new indications for IOL implanation. It is therefore reason to believe that the number of late in-the-bag IOL dislocations will continue to increase as well. In this perspective, it appears important to continue with more research on both treatment options and other basic and clinical aspects of this potentially vision threatening condition.

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