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MALPOSITIONED AND DISLOCATED INTRAOCULAR LENSES: MANAGEMENT, COMPLICATIONS AND SURGICAL REPOSITIONING

Laura Armonaite

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MALPOSITIONED AND DISLOCATED INTRAOCULAR LENSES: MANAGEMENT, COMPLICATIONS AND SURGICAL REPOSITIONING

Thesis for Doctoral Degree (Ph.D.)

By

Laura Armonaite

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Principal Supervisor:
Professor Anders Behndig
Umeå University
Department of Clinical Sciences
Division of Ophthalmology

Co-supervisor(s):
Professor Anders Kvanta
Karolinska Institutet
Department of Clinical Neuroscience
Division of Eye and Vision

Opponent:
Associate Professor Björn Johansson
Linköping University
Department of Biomedical and Clinical Sciences
Division of Sensory Organs and Communication

Examination Board:
Associate Professor Karin Svedberg
University of Gothenburg
Department of Neuroscience and Physiology
Division of Clinical Neuroscience

Associate Professor Rafi Sheikh
Lund University
Department of Clinical Sciences
Division of Ophthalmology

Associate Professor Gauti Jóhannesson
Umeå University
Department of Clinical Sciences
Division of Ophthalmology

Popular science summary of the thesis

Cataract surgery is the replacement of an opaque lens with an artificial intraocular lens (IOL) in the capsular bag in the eye. One complication is IOL dislocation (IOL is not in the center of the pupil). IOL dislocations are divided into two groups. In-the-bag dislocation is IOL dislocation within the capsular bag, whereas out-of-the-bag dislocation is IOL without surrounding capsular tissue. Both groups are addressed in the three studies that comprise this thesis.

Out-of-the-bag dislocations can be managed surgically in several ways. Suturing of a preexisting dislocated IOL to the iris is a promising but unusual method. Study I showed that iris suture fixation of out-of-the-bag dislocated IOL is an effective and safe surgical method.

In-the-bag dislocations are usually sutured to the sclera by looping the suture through capsule and around the supportive part of IOL, the so called "traditional" method. A modification of the traditional method was created to achieve better IOL position especially in patients with transparent capsular bag. Study II showed that both methods resulted in good IOL position although slightly different from that in normal eyes. Many patients became more near-sighted after operations, which is reported in other studies as well, but IOL induced astigmatism was very low. As there were too few patients with transparent capsular bag in the study, a new study with more such patients would answer whether the modified method is better than the traditional method in these cases. The new imaging device was useful in measuring 3-dimensional IOL position, which can be used in future studies of IOL surgery.

IOL contact with the uveal tissue may cause uveitis-glaucoma-hyphema syndrome (UGH), which manifests as intraocular bleeding and/or inflammation. This condition impairs vision, may increase pressure in the eye, and may cause glaucoma, which sometimes can lead to blindness. Study III showed that surgical treatment cannot always stop UGH syndrome, but it often decreases eye pressure and improves vision. Every second patient needed eye pressure lowering treatment despite the resolution of UGH. IOL instability may cause UGH syndrome. Blood thinners generally are not a risk factor for UGH syndrome, however, Waran® (warfarin) use should be investigated further. Presence of iris defects is not specific to UGH syndrome unless their shape resembles parts of the IOL.

There are currently few papers on surgery of out-of-the-bag dislocated IOL, on UGH syndrome, and on methods to improve in-the-bag dislocated IOL surgery. All these were included as outcomes in this thesis.

Abstract

Cataract surgery (exchange of the non-transparent crystalline lens with an IOL) is the most frequent surgery in Sweden, accounting for more than 130000 surgeries per year. Therefore, complications associated with cataract surgery affect a significant number of patients. One of the complications is IOL dislocation, meaning that the IOL is not located at the central part of the optical zone, which often causes visual impairment. The overall aim of this thesis was to deepen knowledge about dislocated IOLs, especially surgery of out-of-the-bag and in-the-bag dislocated IOLs and management of uveitis-glaucoma-hyphema (UGH) syndrome.

Study I had a retrospective case-control design with a total of 32 patients, and included out-of-the-bag dislocated IOL. The aim was to evaluate the efficacy and safety of 3-piece IOL suturing to the iris. The case group (n=14; Iris group) underwent dislocated out-of-the-bag 3-piece IOL suturing to the iris. The control group (n=18; Exchange group) underwent IOL exchange with a new IOL sutured to the sclera. The groups were followed in the median of 13.5 (interquartile range (IQR) 10–20) and 12.5 (IQR 10–14) months, respectively. Best corrected visual acuity (BCVA) improved significantly in each group with no significant difference in either final BCVA or final intraocular pressure (IOP) between the groups. Complication frequency was similar in the groups. Surgically induced corneal astigmatism (SIA) and number of postoperative visits were significantly lower in the Iris group.

Study II, a prospective randomized clinical trial with a cross-sectional part, included in-the-bag dislocated IOL. A total of 177 patients were analyzed in this study. The aim was to evaluate three-dimensional (3-D) IOL position, refractive change, and IOL-induced astigmatism (IIA), also importance of capsular fibrosis on postoperative IOL position after IOL suturing to the sclera (2.5 mm behind the limbus) using 2 surgical methods: Ab Externo Scleral Suture Loop Fixation (Group A) and a modification, Embracing the Continuous Curvilinear Capsulorhexis (CCC), a technique created by L.A. (Group B). Additionally, the study evaluated the usefulness of swept-source anterior segment optical coherence tomography (SS–AS-OCT) for measuring 3-D IOL position. A total of 117 patients (117 eyes) with in-the-bag dislocated IOL were randomized into Group A (n=61) or Group B (n=56). The control group consisted of patients with ordinary pseudophakia (n=60). The median IOL tilt did not significantly differ between Group A (7.8°, IQR 5.9°–12.0°) and Group B (8.3°, IQR 6.4°–10.8°) but each group was significantly different from the ordinary pseudophakia (5.4°, IQR 3.9°–7.1°) by the mean of 3.75° (CI (confidence interval) 2.54°–4.95°). The direction of IOL tilt was inferotemporal in 87%–87.5% of patients in each of the three groups, and a mirror symmetry was observed between the left and right eyes. IOL surgery resulted in significant myopic shift. In eyes without capsular fibrosis, the median IOL tilt was 15.5° (IQR 7.8°–21.7°) in Group A (n=7)

and 7.0° (IQR 6.6°–11.4°) in Group B (n=5) although without a statistically significant difference. IIA was 0.075 D for each degree of IOL tilt, which was statistically significant. Five patients (three in Group A and two in Group B, of which one IOL was dislocated by intraocular gas) were re-operated after their one-month follow-up visit. IOL position could be measured with SS–AS-OCT in all cases if the IOL could be seen in the pupil. It was also possible to measure and quantify the capsular bag thickness.

Study III focused on UGH syndrome, and had a retrospective case-control design with a cross-sectional part and a descriptive part. A total of 213 patients were included. The study comprised both out-of-the-bag and in-the-bag dislocations as well as other types of IOL malpositions; however, all causing UGH syndrome. The study aimed to evaluate the effect of UGH treatment, a need for IOP-lowering treatment, clinical manifestation (including iris-IOL contact signs) and usage of blood thinners (anticoagulants and antiaggregants), also, which examination–clinical, AS-OCT, or ultrasound biomicroscopy (UBM)–was the most effective tool to diagnose UGH syndrome. Three groups of patients were compared: UGH syndrome (n=71), dislocated IOL without UGH (n=71) and uncomplicated pseudophakia (n=71). Surgical treatment was effective in approximately 77% of cases. IOP and BCVA improved significantly in the operated patients but not in the non-operated patients. In total, 51% of all patients (57% of operated patients) needed IOP-lowering therapy after UGH resolution, and IOP≥22 mmHg at the first (1st) hemorrhage was the only significant predictor identified for this. Pseudophacodonesis (IOL-donesis) was seen in 22.5% of patients at the beginning of UGH syndrome, and was significantly more frequent than in the Pseudophakic group. Transilluminating iris defects (TID) in the UGH group were not more frequent than in the Dislocated group at the beginning of UGH. However, the shape of TIDs differed significantly: haptic or optic edge formed TIDs were seen more frequently in the UGH group. Patients with UGH syndrome did not use blood thinners more frequently than patients in Dislocated group, except Warfarin (Waran®). Examination on a slit-lamp, AS-OCT, and UBM showed iris-IOL contact in 97%, 19%, and 21% of patients, respectively.

Conclusions: Suturing out-of-the-bag dislocated 3-piece IOL to the iris is a safe and effective surgical treatment with less SIA and fewer postoperative visits to an ophthalmologist than IOL exchange.

Suturing in-the-bag dislocated IOL to the sclera results in good IOL position with both surgical methods, although the position differs from the normal pseudophakia by approximately 3.75° which has little clinical significance as IOL-tilt induced astigmatism is low. However, IOL suturing to the sclera induces myopic shift in cases when the IOL is sutured 2.5 mm behind the limbus. A new study with more patients without capsular fibrosis would show whether IOL position is better with the modified method than with the traditional one in this subgroup. SS–AS-OCT is useful for 3-D IOL position quantification after IOL repositioning.

Surgical treatment does not guarantee resolution of UGH syndrome, though BCVA results are better than with conservative treatment. IOL-donesis is a risk factor for UGH syndrome. The impact of Warfarin (Waran®) on UGH development should be investigated further, although other blood thinners probably do not increase the risk for UGH syndrome. TIDs are not specific to UGH syndrome unless they are formed like the haptic or optic edge. Every second patient may need IOP-lowering therapy; IOP≥22 mmHg at the first hemorrhage predicts the need for IOP-lowering treatment in a long run (after UGH resolution). Follow up time should be long after UGH resolution. Clinical examination was more useful for detecting iris-IOL contact than AS-OCT or UBM in study III.

List of scientific papers

I. Armonaite L, Lofgren S, Behndig A. Iris suture fixation of out-of-the-bag dislocated three-piece intraocular lenses. Acta Ophthalmol 2019; 97: 583-588

II. Armonaite L, Behndig A. Repositioning of In-the-Bag Dislocated Intraocular Lenses. A Randomized Clinical Trial Comparing Two Surgical Methods. Accepted for publication. Ophthalmic Res. 2023 01 27.

III. Armonaite L, Behndig A. Seventy-one cases of uveitis-glaucoma-hyphaema syndrome. Acta Ophthalmol 2021; 99: 69-74

Contents

List of abbreviations and terms

AC	Anterior chamber
AS-OCT	Anterior segment optical coherence tomography
AUC	Area under the curve
BCVA	Best corrected visual acuity
Blood thinners	Antiaggregants and anticoagulants
CCC	Continuous curvilinear capsulorhexis
CI	Confidence interval
Ciliary sulcus	Sulcus
ECCE	Extracapsular cataract extraction
IIA	IOL-induced astigmatism
INR	The internationalized normalized ratio
HOA	Higher order aberrations
IOL	Artificial intraocular lens
IOL-donesis	Pseudophacodonesis
IOP	Intraocular pressure
IQR	Interquartile ranges
logMAR	Logarithm of the minimum angle of resolution
OCT	Optical coherence tomography
OHT	Ocular hypertension
PMMA	Polymethylmethacrylate
PPV	Pars plana vitrectomy
PEX	Pseudoexfoliations
ROC	Receiver Operator Characteristic curve
SIA	Surgically induced astigmatism (corneal)
SD	Standard deviation
SE	Spherical equivalent
S ring	Soemmering's ring

SS–AS-OCT	Swept-source anterior segment optical coherence tomography
TID	Transilluminating iris defects
UGH	Uveitis-glaucoma-hyphema syndrome
UBM	Ultrasound biomicroscopy
3-D	Three-dimensional
2-D	Two-dimensional
VA	Visual acuity

1 Introduction

Cataract surgery is the replacement of the opaque lens with an IOL. The predominating type of surgery today is phacoemulsification, where an incision is made in the limbal region, a round opening is created in the anterior lens capsule, the lens is hydrodissected, then fragmented by ultrasonic vibration (i.e., phacoemulsification), and aspirated. Thereafter, the IOL is implanted in the emptied lens capsule bag. IOL consists of an optic part and haptics, and can be divided into different types depending on whether the optic and haptics are made from the same plastic material. In multipiece IOL (usually 3-piece IOL), the optic part and haptics are made from two different materials, whereas a 1-piece IOL is produced in a single step from one material.

One of the more troublesome complications of cataract surgery is IOL dislocation – IOL is not at the central part of the optical zone, which often causes visual impairment. There are 2 types of dislocations based on the presence/absence of the capsular bag. In-the-bag IOL dislocation (Fig.1) is a dislocation within the capsular bag, usually because of progressive zonular weakness. In out-of-the-bag dislocation (Fig.1), the dislocated IOL has no capsular tissue around it. This dislocation occurs mostly in eyes with previously complicated cataract surgery when IOL is implanted in the ciliary sulcus (sulcus) in the presence of zonular weakness (preexisting or later developed); also, the IOL may luxate through the rupture in the posterior capsule into the vitreous cavity. In-the-bag dislocation is more common (87.9%) than out-of-the-bag dislocation.[1] IOL dislocation usually develops approximately 6–12 years after cataract surgery, and main risk factors are pseudoexfoliations (PEX), myopia, and vitreo-retinal surgery.[2] IOL dislocations are divided into “early” and “late”; late IOL dislocation develops ≥3, ≥6 or ≥12 months after the cataract procedure.[2]

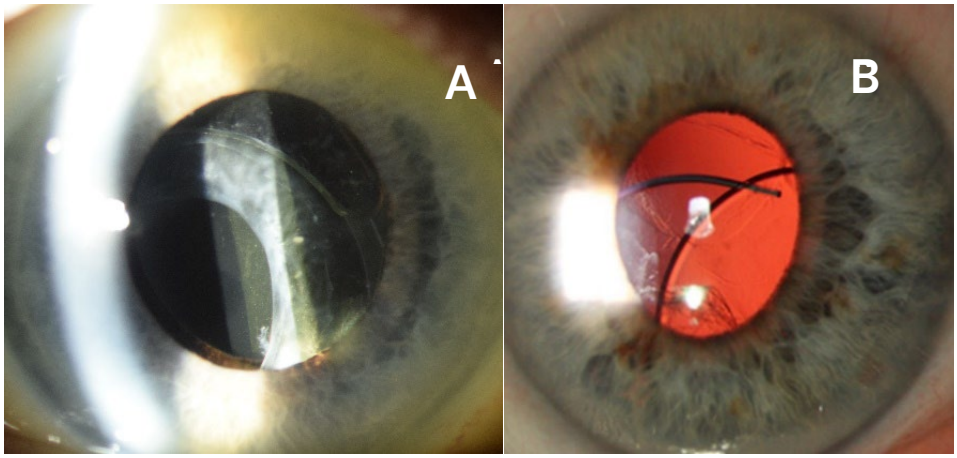


Figure 1. In-the-bag (A) and out-of-the-bag (B) IOL dislocation. Photo: Laura Armonaite

The overall annual incidence of a dislocated IOL (all types) was 0.0%–0.05% and a cumulative incidence was 0.1%–3% over 10 to 25 years according to a recent literature review.[2] In Sweden, the incidence of dislocated IOL surgery was 0.052%–0.6% in pseudophakic population.[3–5] The cumulative incidence for dislocated IOL surgery over 10 and 20 years after cataract surgery was 1% and 1.2% in northern Sweden,[4, 6] and 0.55% and 1% in Värmland county.[5] For the patients with PEX, the cumulative incidence of IOL dislocation surgery over 20 years was 6% (3% in the entire patient group) in northern Sweden.[6]

There are few studies on IOL dislocation frequency outside Scandinavia. In one study from the USA, the cumulative risk of IOL dislocation (all types, >3 months) was 0.1% and 0.7% at 10 and 20 years, respectively, but it did not change significantly over 25 years.[7]

A significant increase in the incidence of dislocated IOL has been noted over the decades, both in Sweden (in-the-bag dislocations over 20 years in one county),[5] Norway (in-the-bag),[8] and Australia (all types of dislocations after all types of cataract surgeries over 22 years),[9] but other studies claim that the increase is not significant, for example, in another county in Sweden over 3 years (all types) and in one state in the USA over 25 years.[3,7]

The common belief is that frequency of IOL dislocations increases after the start of phacoemulsification era. However, IOL dislocations were as frequent even before phacoemulsification was introduced, although the type of dislocation differs as it has shifted from out-of-the-bag to in-the-bag today. An American study reported no association between the method of cataract surgery (phacoemulsification vs. extracapsular cataract extraction, ECCE) and the risk of developing IOL dislocation.[7] Another study has reported IOL dislocation more often after ECCE than after phacoemulsification, although dislocation type was not specified.[9] Indeed, frequency of rigid IOL dislocations reached 2% in the ECCE and ICCE period; even Sir Harold Ridley observed 13% of IOL dislocations with one particular type of rigid IOL.[10] The majority of these dislocations should have been the out-of-the-bag type. Late in-the-bag dislocation was first described in early 1990s. The rise of in-the-bag IOL dislocations during the past years is associated with CCC implementing in phacoemulsification as CCC may contribute to capsular shrinkage and therefore to IOL dislocation, unlike can-opener capsulotomy in ECCE surgery. However, there are more factors predisposing IOL dislocation.[11] Although the overall incidence of IOL dislocation is low, a significant number of people may be affected considering the large number of cataract operations and the growing ageing population.

There are 2 fundamentally different types of IOL surgery: IOL exchange and repositioning/fixation of the pre-existing IOL. None of these surgical methods is superior according to a 2021 literature review.[2] This finding also matches the results of a

randomized study with a two-year follow-up, which compares sutureless IOL exchange and the pre-existing IOL suturing to the sclera.[12] Fixation of the pre-existing IOL has been the traditional surgery at the anterior segment surgery department at St. Erik Eye Hospital. In published literature, the type of IOL dislocation (out-of-the-bag or in-the-bag) does not often play a decisive role in surgical management; usually all types of dislocation are operated the same way. My own attitude is different: I manage dislocated IOLs surgically depending on the type of dislocation, therefore, respect to the type of IOL dislocation permeates all studies in this thesis.

In this thesis, I address a knowledge gap in the field of dislocated IOLs, which required using different designs and included different groups of patients for each study. Out-of-the-bag dislocations are rarely investigated as a separate group, and the few studies that have evaluated IOL suturing to the iris have not strict inclusion criteria. Out-of-the-bag dislocated IOL suturing to the iris was evaluated in **Study I**, which had a retrospective case-control design and included 32 patients.

In-the-bag dislocated IOLs are managed by many surgical methods; however, no agreement has been reached yet on superiority of any of those methods.[2,11] As only one randomized study has been performed,[13] more studies with high level of evidence are needed.[2] In this thesis, surgery of in-the-bag dislocated IOLs was evaluated in **Study II**, which had randomized prospective design and included 177 patients.

UGH syndrome is even less investigated, and only small case-series or case reports have been published. **Study III** included those IOL malpositions (in-the-bag, out-of-the-bag, and other) that caused UGH syndrome. It was a retrospective case-control study with a cross-sectional part and included 213 patients (71 with UGH syndrome).

2 Literature review

2.1 Out-of-the-bag dislocated IOL suturing to the iris vs. IOL exchange with a new IOL fixated to the sclera

Out-of-the-bag dislocated IOL can be fixated either to the sclera or to the iris. Both approaches have advantages and disadvantages. Suturing of iris defects was first described by McCannel in 1976, and IOL suturing to the iris using this modified technique was evaluated in few studies.[14–22] In these studies, case selection was not stringent and different surgical methods were mixed, complicating the interpretation of the surgical success rate. For example, these studies included both in- and out-of-the bag dislocations[15, 18, 23] or only in-the-bag dislocated IOL[21] or cases with simultaneous pars plana vitrectomy (PPV) and IOL suturing to the iris[14,16,18, 23,24] or suturing of a rigid polymethylmethacrylate (PMMA) type IOL[15,19] or a mix of pre-existing IOL or a new IOL[24] or mixing patients with cataract surgery, aphakia, and dislocated IOL into the same group.[25] Furthermore, only one of these studies was comparative, and no randomization was performed; both out-of-the-bag and in-the-bag dislocated IOL were sutured to the iris with worse outcomes than patients with the IOL sutured to the sclera: higher astigmatism, earlier IOL re-dislocation, and less stable refraction.[15] One may wonder whether the results had been the same if out-of-the-bag and in-the-bag dislocated IOL would have been evaluated separately.

Only one paper published in English specifically addresses out-of-the-bag IOL dislocations.[26] However, all the patients in this study underwent IOL exchange, and no other surgical method was evaluated for superiority.

As mentioned, out-of-the-bag dislocated IOL may be sutured to the iris[20] or the sclera[27] or IOL may be exchanged with a new IOL fixated to the sclera. Looping the suture around the haptics of IOL without capsular tissue risks suture slippage and subsequent IOL re-dislocation, but the authors of one study not only sutured in-the-bag but also out-of-the-bag dislocated IOL (40% of the study's patients) to the sclera using the Ab externo scleral suture loop fixation method.[27] IOL was reported as well-positioned in all cases, however, results were not quantified and not compared between the dislocation types. It was thought, also reported in older studies, that IOL suturing to the sclera risks retinal detachment[10,15,28–30], sutures may erode and bother patients[31] or cause endophthalmitis,[32,33] but these complications are not seen with IOL suturing to the iris. Today, however, endophthalmitis or retinal detachment are almost never seen with IOL suturing to the sclera, and complications mainly are vitreous hemorrhage, macular edema, and transient IOP increase.[13,27,34] Other complications are IOL tilting or pupillary capture in cases with PMMA or 3-piece IOL (without capsular bag) sutured to the sclera[28,31,34,35] or 3-piece IOL fixated intrasclerally[34]–notably, pupillary capture can develop after IOL fixating to the iris as well.[14] It was also thought that fixating IOL to the

iris should result in more complications from the contact between the IOL and iris: macula edema, pigment dispersion, or complete UGH syndrome. However, macular edema is also seen in IOL fixation to the sclera[10,12,13,27,30,34] as well as UGH syndrome[36,37] and pigment dispersion.[38]

The common belief is that compared to pre-existing IOL fixation, IOL exchange surgery has increased risk of endothelial cell loss, vitreous loss, and larger SIA.[27,30] Indeed, IOL exchange requires more anterior vitrectomies[8,13] and causes significantly more endothelial cell loss at 6 months (10%±14%) than IOL repositioning (3%±10%).[13] However, no significant difference between the groups was noted over 2 years (17.3% and 15.3%, respectively); notably, incision was scleral pocket, not corneal, in the exchange group.[39] Another study also reported no difference in endothelial cell loss comparing IOL exchange with a new sclera-fixated IOL and pre-existing IOL suturing to the sclera.[40] Compared with iris-sutured IOL (n=11), the mean endothelium loss was 4±1.7% at 16 months postoperatively.[21]

Furthermore, IOL exchange is thought to cause more astigmatism as IOL is usually exchanged through a large corneal incision, whereas suturing of pre-existing IOL is done through a small incision. Indeed, corneal astigmatism increased significantly in IOL exchange with corneal incision, calculated without polar vector analysis[28,41] or with polar vector method in a studies that compared IOL exchange with the pre-existing IOL fixation[40] but not in cases with scleral pocket incision in a randomized study.[42] In the latter study, SIA was 0.65 D at 171°, with no significant difference in vector components between the groups but significantly higher mean SIA (net astigmatism) in the exchange group, calculated with power vector method.[42] Regarding sutureless IOL exchange with a new iris-claw IOL, SIA was calculated in very few studies,[42–45] and only two studies used power vector methods. The mean SIA was large, 2.49 D, with corneal incisions;[45] however, with scleral incisions, SIA was rather small (0.73 D) and significantly lower than with corneal incisions.[45]

Studies that focused on IOL suturing to the iris disclosed good IOL stability (theoretically 9 years[46]), and very few complications.[14,16,18,20,21,23,24,47,48] These non-comparative observational studies included between 11 and 58 cases and reported the following numbers of complications: 1–3 chronic iritis; 1–6 intraocular hemorrhage; 0–2 macular edema; 1–7 new glaucoma or ocular hypertension cases; 0–2 IOL re-dislocations; 0–2 retinal detachments; and 0–2 choroidal effusions. As mentioned above, only one study had a comparative design; it reported worse outcomes in the iris group than in the sclera group.[15] Other studies were conducted in the early 1990s.[49–51] Many patients in these earlier studies underwent penetrating keratoplasty at the same time as IOL fixation to the iris, which confounds evaluation of IOL surgery. Therefore, the worse results reported in one of these studies (n=13)–less BCVA increase and more complications–are not convincing.[50] However, a randomized trial showed that macula

edema and overall risk for complications were lower in IOL suturing to the iris than to the sclera.[51]

Position of the IOL postoperatively was better when IOL was sutured to the iris than to the sclera, evaluated by UBM.[17,38,52] None of the cases (15) of iris-sutured lenses had angle closure or anterior synechiae and 53.3% of haptics were placed in the ciliary sulcus (sulcus) as intended.[17] When IOL was sutured to the sclera, only 37–38% of haptics were found in sulcus[38,52], 38% of the haptics were located anteriorly to the sulcus and caused some degree of angle closure[52]; another study reported 9%.[38] Furthermore, no vitreous incarceration was found in cases with iris-sutured IOL[17] as opposed to 48% of cases with sclera-sutured IOL.[38] Additionally, optic tilt >10° was recorded in 11.5% of sclera-sutured IOLs in 52 eyes,[53] and no tilt was reported in the iris-sutured IOL group.[17] The UBM analysis showed that the only contact between the iris and the IOL was at the point of haptic suture fixation, which explains absence of pigment dispersion postoperatively.[17] Pigment dispersion was noted in 16% of sclera-fixation cases.[38] In summary, IOL suturing to the sclera appears to be a procedure with less visibility and therefore less precise than IOL suturing to the iris.

Study I of this thesis evaluates the safety and efficacy of out-of-the-bag dislocated IOL suturing to the iris, comparing to IOL exchange with a new IOL sutured to the sclera. The study has more rigorous inclusion criteria: only out-of-the-bag dislocated 3-piece IOL was sutured to the iris without additional surgery. Furthermore, the same surgeon (L.A.) performed all operations.

2.2 In-the-bag dislocated IOL: position and refraction after IOL suturing to the sclera

There are two types of methods to introduce sutures when fixating IOL to the sclera: ab interno[54,55] and ab externo[56] based on whether the sutures are initially passed from the inside or the outside of the eye. IOL position did not differ with these two methods as determined by UBM.[57]

Ab externo scleral suture loop fixation is used in many clinics for in-the-bag dislocated IOL suturing to the sclera. This approach includes looping a prolene suture not only around the haptics but also through the capsular tissue, which does not allow suture slippage from the haptics.[27] The method was evaluated in one randomized prospective study[13] and in many retrospective studies, sometimes comparing the method with other IOL fixation methods.[3,8,10,15,22,27,29,30,58] In these studies, BCVA improved significantly and complications rarely occurred. However, some IOLs were not well positioned even after uneventful fixation surgery; a solution for this issue has not been proposed.

No studies have analyzed the reasons for suboptimal IOL position after fixation surgery, and very few studies have suggested improvements to the fixation technique. In papers presenting modifications of the Ab externo scleral suture loop fixation method, the modifications speeded up surgery or made it simpler but was not aimed primarily to improve IOL position.[59–64]

Gimbel et al. presented a method where the CCC was used to suture IOL to the sclera: the suture perforated the edge of CCC.[64] The authors acknowledged that the main disadvantage with this technique is the need for fibrosis in the CCC; otherwise, the bag can tear by the suture, which may result in IOL re-dislocation. The paper presented one clinical case, and no randomized study was performed. The same author presented one more technique, which also risks for capsular bag tearing.[65]

The postoperative IOL position should be quantified to precisely compare surgical methods. IOL malposition negatively affects visual performance, which was studied between the late 1980s and early 1990s. The studies showed that IOL tilt and/or decentration causes spherical and cylindrical refractive errors,[66–68] quantified this relationship,[66] and concluded that a tilt >5° causes refractive error.[68] Another author reported that IOL position towards or away to the retina affects the spherical refractive component, but the impact on astigmatism is small.[69] There are few recent studies, however. One study used a theoretical mathematical model and reported that 5° of tilt induces 0.08 D of astigmatism.[70] Another study measured ocular residual astigmatism (ORA) in normal pseudophakia in humans, which was 0.48 D.[71] ORA is the difference between total ocular astigmatism and corneal astigmatism. IOL tilt and decentration can cause higher order aberrations (HOA).[72–74] However, HOA induced by IOL malposition is generally small in eyes with small pupils,[73] which is common in patients with late IOL dislocation.[75–78] Moreover, IOL tilt is of least importance for HOA, whereas pupil diameter is the most important.[73]

In most studies IOL position was evaluated only on slit-lamp examination and without objective quantification. The authors presented refraction outcomes (indirect measurement of IOL position): corneal astigmatism and overall refraction,[13,15,28] surgically induced corneal astigmatism,[42] or only change of visual acuity,[10,22,27–30,58,79] which does not disclose how the IOL position impacted refraction and astigmatism. Astigmatism induced specifically by the IOL tilt (IIA) was not evaluated in any of these studies. The tilt angle and decentration of the IOL were measured using a Scheimpflug camera,[53] but this method requires pupil dilation >6 mm. Furthermore, this method was criticized for being inaccurate when using commercially available machines.[80]

As IOL tilt is a three-dimensional (3-D) term, IOL position should be measured in 3-D, ideally automatically with a commercially available machine. However, a two-dimensional (2-D) calculation was made when using older type AS-OCT, IOL Master,

UBM, or Purkinje meter.[71,80–85] Some studies presented IOL position as 3-D after cumbersome mathematical reconstructions of the 2-D measurements because a true 3-D position was not obtained automatically.[71,82,85]

SS–AS-OCT (Casia 2, Tomey, Nagoya, Japan) measures 3-D IOL position automatically using the corneal topographic axis as reference. Kimura et al. was the first group to use Casia 2 to measure the crystalline lens and IOL position in normal eyes.[86] Crystalline lenses and IOLs were tilted on average 5° inferotemporally in normal eyes, measured with IOL Master (which uses visual axis as a reference) and Casia 2.[85–88] IOLs were tilted >7° in 12% of normal eyes[86] and in 8% of myopic eyes with an axial length of ≥26 mm.[89] Mirror symmetry between the left and right eyes was also observed. Pupil diameter does not affect measurements with Casia 2.[86]

3-D IOL position measured with SS–AS-OCT after IOL suturing to the sclera has not been reported, and very few studies during the past years have aimed to establish how IOL position affects refractive errors. However, 3-D IOL position after other types of IOL fixation has recently been identified. For example, the median tilt of the posterior iris-claw IOL was 5° (3.7°–6.2°).[90] Intrasclerally sutureless fixated IOL tilt was 8.4°±6.9° (range 0.6°–35.8°).[91] In that study, IOL tilt (but not decentration) impact on sphero-cylindrical shift was significant although little, and only a tilt >10° induced > -0.46±0.49 D of refractive error; however, IIA was not calculated.[91] In another study, intrasclerally sutureless fixated IOL tilt was 3.52°±3.00°; however, it was measured at the "approximate" position of the scleral tunnel,[92] which might not necessarily correspond to the true meridian of largest IOL tilt. The results of another study are also questionable where IOL tilt was reported in 2-D form although SS–AS-OCT provides 3-D measurements: in the group with intrasclerally fixated IOL, the horizontal and vertical IOL tilt were 3.8° and 4.3°, respectively, and in the group with a 3-piece IOL sutured to the sclera, 4.1° and 5.1°, respectively, without group difference.[34]

Currently, no studies systematically address how patients with dislocated IOL should be managed and followed. This was touched upon lightly in two studies, which reported that IOL should be repositioned within 1 month to avoid deterioration of IOL dislocation,[8] and additional time is needed to manage patients with a dislocated IOL (even before the surgery) as this condition is complex.[62]

Study II of this thesis aimed to evaluate the modification (capsulorhexis ring added to the surgery) of the traditional method to suture in-the-bag dislocated IOL to the sclera, to study IIA and refraction changes, and capsular-bag fibrosis impact on IOL position postoperatively. Finally, **Study II** evaluated the usefulness of the SS–AS-OCT to measure the 3-D IOL position.

2.3 Malpositioned IOL and uveitis-glaucoma-hyphema (UGH) syndrome

The underlying mechanism of UGH is a contact between uveal tissue (iris or ciliary body) and the IOL. This contact results in iritis ± pigment release, intraocular hemorrhage, and increase of IOP.[93] Few published papers have addressed UGH. Over the last 20 years, 43 publications have included uveitis-glaucoma-hyphema syndrome in the search title. In this literature review, I included only studies where UGH was caused by a posterior chamber IOL.

Notably, there is a lack of consensus in terminology, diagnosis, and treatment of UGH syndrome. Classic "complete" UGH syndrome is a triad (uveitis, glaucoma, hyphema), but other variants of UGH are possible. For example, "incomplete UGH" is when only one or two of the triad's elements are present[94–96] and UGH Plus syndrome includes vitreous hemorrhage.[97] The term "incomplete UGH" is sometimes replaced with "unexplained recurrent hyphema or vitreous hemorrhage"[98] or "pigment dispersion and recurrent hyphema".[99] Glaucoma diagnosis requires documented visual field defects. Rather than using glaucoma, some authors use increased IOP as inclusion criterion.[95–97,100] Moreover, cases without an increased IOP have also been classified as "(incomplete) UGH syndrome".[96] However, all variations of UGH syndrome share one common denominator– IOL–iris (or ciliary body) contact.

Since the incidence of UGH is low, previous publications consist of single cases or smaller case series.[37,95,97,100–111] Recently, a study of 30 cases of UGH syndrome was published in French.[112] In summary, each of these studies presented a surgical treatment and whether UGH resolved or not. UGH resolved in all studies, but follow-up time varied greatly. In one case-report, the patient was not operated, but UGH was still resolved.[104] UGH did not resolve in another study.[112] Conservative treatment was also reported in another case report.[113] Endoscopic[100] or transscleral diode laser cyclophotocoagulation[114] or neodymium-doped yttrium aluminum garnet laser iridoplasty[115] are alternatives to IOL surgery. The latter included IOL repositioning, exchange, and smaller surgeries such as haptic amputation, implantation of capsular tension ring etc.[100,105,111,112] Various IOL types and positions, including in-the-bag, were reported to cause UGH syndrome in the above mentioned studies. None of those studies systematically analyzed glaucoma development in UGH syndrome or iris-IOL contact signs, and presented only the value of IOP and findings on slit-lamp examination.

There is also lack of larger studies that investigate whether the use of blood thinners induce intraocular hemorrhage. Case reports and small case series studies have reported that administration of antiplatelets[116] and direct and indirect anticoagulants are associated with intraocular hemorrhage.[116–122] Anticoagulants seldom cause intraocular hemorrhages, but patients with IOL malposition could be at higher risk according to a case report where UGH syndrome resolved after discontinuing of warfarin

administration without surgery of the dislocated IOL.[121] However, hemorrhage occurred not only in eyes with iris-IOL contact[119–121] but also in eyes without anterior segment pathology[116–118,122] even in phacic eyes not operated previously.[116] Schiff estimated that patients with iris-fixated IOL and treated with anticoagulants had hyphema 7 times more often than patients without anticoagulants.[119]

The effect of anticoagulants on blood coagulation system, measured by the internationalized normalized ratio (INR), is probably more important than whether a patient is on anticoagulants or not. An INR range of 2.0–3.0 is a usual therapeutic range for patients taking warfarin. The significance of the INR level for developing hemorrhage has been reported in some case-reports.[118,122] In one case, a supra-therapeutic INR of 5.56 was found.[118] In another case, the INR was only 2.6 although intraocular hemorrhage still developed.[122] Both studies reported no other ocular pathology, which can be interpreted as no iris-IOL contact was seen. In conclusion, whether anticoagulants and antiplatelets increase the risk for intraocular hemorrhage if the IOL has a contact with the iris is to be determined. In addition, it is unknown whether treatment with blood thinners should be adjusted in patients with iris-IOL contact.

Study III of this thesis addresses a knowledge gap regarding UGH clinical manifestation, treatment, a need for IOP-lowering treatment, IOL-iris contact, and risk factors for UGH syndrome.

3 Research aims

Study I To evaluate efficacy and safety of out-of-the-bag dislocated 3-piece IOL suturing to the iris.

Study II By comparing two surgical methods, Ab externo scleral suture loop fixation and a modification, Embracing the CCC, to study suturing of in-the-bag dislocated IOL to the sclera in these aspects: which method results in better 3-D IOL position especially in cases without capsular fibrosis, also, to evaluate refractive change, IOL-induced astigmatism (IIA), and usefulness of SS–AS-OCT in measuring 3-D IOL position.

Study III To study UGH syndrome with focus on results of treatment, a need for IOP-lowering therapy, clinical manifestation (including iris-IOL contact signs), and use of blood thinners. Also, to study which examination–slit-lamp, AS-OCT, or UBM–is the most effective in diagnosing iris-IOL contact.

4 Materials and methods

4.1 Ethical considerations (Studies I, II, III)

All studies in this thesis followed the tenets of the Declaration of Helsinki and were approved by the Regional Ethics Committee in Stockholm. Studies I and III include retrospective medical chart review, which was approved by the ethical committee. In Study III, some data of the pseudophakic patients were used from Study II, which was also approved by the ethical committee.

Study II was additionally registered at ClinicalTrials.gov (identifier, NCT04150263). Patients with a dislocated IOL were referred for the IOL surgery to St. Erik Eye Hospital by other ophthalmologists. Patients with ordinary pseudophakia were identified in the Swedish National Cataract Registry and were recruited as controls in accordance with the ethical permission. Participation in the study was voluntary. All participants in Study II were given written information about the study, and, if they wished to participate, they signed the agreement. They had an opportunity to discuss any questions regarding participation in the study. The patients did not receive any benefits for taking part in the study nor they lost anything for not participating. Also, the patients who initially agreed to participate but later changed their mind and finally declined were free to do so without needing to explain their reasons. In the study, a comparison was made between a well-known IOL surgical fixation method and the same method that was modified in one step. As the modification is of limited extent and showed good results, it was deemed ethical to carry on the study. Recruitment took place between October 2018 and October 2020.

4.2 Participants (Studies I, II, III)

In this thesis, patients with either out-of-the-bag IOL dislocation (Study I), in-the-bag IOL dislocation (Study II) or various types of IOL malposition that caused UGH syndrome (Study III) were treated at St. Erik Eye Hospital between 2010 and 2020. The controls in Studies II and III had ordinary pseudophakia.

4.3 Statistical analyses (Studies I, II, III)

Statistical analyses were performed using the software IBM SPSS versions 25, 26, and 27 (IBM Corp., Armonk, New York, USA), PAST 3.20 (Paleontological statistics software by Øyvind Hammer, Paleontological Museum, University of Oslo, Norway; David A.T. Harper, Geological Museum, University of Copenhagen, Denmark; Paul D. Ryan, department of Geology, National University of Ireland, Galway, Ireland), the statistical program R (R Foundation for Statistical Computing), and Statistica 12 (Tibco Software, Palo Alto, CA, USA). A p-value <0.05 was considered statistically significant in all tests; two-tailed significance testing was applied.

Shapiro-Wilks test and normality curves were used to determine the distribution of quantitative data. All not-normally distributed data are reported as medians and (IQR), and for statistical analyses, non-parametric tests were employed (Mann-Whitney U test for comparison of data between groups and Wilcoxon matched-pairs test for comparison within groups). For normally distributed quantitative data, parametric statistics were used when appropriate (two-samples t-test for comparison between the groups and paired-samples t-test for comparison within the groups). Data are presented as means ± standard deviations (SD). For calculations including categorical data, Chi-square or Fisher's Exact tests were used. Snellen visual acuities were converted to logarithm of the minimal angle of resolution (logMAR) values for the statistical analyses. Study-specific statistical analyses are described separately for each study in the Methods section.

4.4 STUDY I

4.4.1 Study design

This retrospective case-control study compares out-of-the-bag dislocated IOL suturing to the iris vs. IOL exchange with a new IOL sutured to the sclera. Data were collected from medical charts.

4.4.2 Patients

The **case** group included 14 patients with out-of-the bag dislocated 3-piece IOL who underwent the pre-existing IOL suturing to the iris (Iris group). The **control** group consisted of 18 patients with dislocated IOL who underwent IOL exchange with a new IOL (Akreos Adapt AO, 1-piece acrylic IOL, Bausch & Lomb, Rochester, NY) sutured to the sclera (Exchange group). All 32 patients were treated between 2015 and 2016. Patients in the Iris group and in the Exchange group were followed-up 13.5 months (IQR 10–20) and 12.5 months (IQR 10–14), respectively.

Inclusion criterion for the Iris group was out-of-the-bag dislocated 3-piece IOL; for the Exchange group, inclusion criteria were IOL dislocation requiring IOL exchange and a new IOL sutured to the sclera. All patients had to be operated by the same surgeon, L.A. One patient underwent surgery in both eyes: IOL was sutured to the iris in one eye, and the other eye underwent IOL exchange.

Exclusion criteria were recent globe injury, history of iritis or macula edema, iris atrophy, and missing outcome data. One patient in the Iris group was excluded due to several ophthalmological conditions and surgeries, which complicated evaluation of the IOL suturing to the iris. No other patients were excluded in the Iris group.

In the Exchange group, 2 patients were excluded because of missing postoperative follow-up and 6 patients were excluded because they were operated by 2 other surgeons and important data were missing.

In the Exchange group, PPV was performed simultaneously with IOL exchange surgery in 2 patients who had parts of crystalline lens in the vitreous. All patients in the Exchange group had in-the-bag dislocated IOL except four with out-of-the-bag dislocations.

4.4.3 Outcome measures

To evaluate surgery's **efficacy**, the following variables were measured and compared between the groups. (1) **BCVA** difference between the groups at the last visit; BCVA change within each group from pre-operative to the final visit after the surgery; number of patients with final BCVA≥0.5; and speed of visual recovery, which was measured as change from preoperative BCVA to visual acuity VA (uncorrected or corrected with current spectacles) one week after the surgery. (2) number of **postoperative visits** to the eye doctor. Additionally, refraction change was calculated for the Exchange group, as difference between the predicted refraction (from biometry) and spherical equivalent (SE) at the last visit.

To evaluate surgery's **safety**, these variables were measured and compared between the groups. (1) **Complications** during and after the surgery: retinal or choroidal detachment, macular edema, intraocular hemorrhage, UGH syndrome, endophthalmitis, IOL re-dislocation that required re-operation, IOP difference within- and between the groups, also, the number of patients who needed extra IOP-lowering therapy or filtering surgery. Macular edema was determined as fluid build-up in the macular region visible with OCT (TOPCON 3D OCT-2000, Topcon Corporation, Tokyo, Japan). (2) Number of cases that required more than usual **anti-inflammatory treatment** after the surgery. (3) **Aqueous humor protein level** was measured at the last visit with a Laser Flare Meter (Kowa FM 500, Dusseldorf, Germany), in photon counts per millisecond (pc/ms). Seven measurements were performed for each patient, the lowest and highest readings were deleted, and the mean value±SD of the remaining 5 measurements was calculated by default. One patient from the Exchange group was excluded from this analysis because of pronounced corneal edema. (4) To establish whether **SIA** differed between these two surgical methods, SIA was calculated using Naeser polar value method and vector analysis[123–126]: elements of net astigmatism were decomposed into the polar values in 0° (the plane of surgical meridian) and 45°, thereafter averaged separately and, finally, reconverted to net astigmatism in diopters and degrees. Net astigmatism was compared between the Iris and the Exchange groups.

SIA calculations were performed as follows. Keratometry was performed with autorefractometer before the surgery and at the final visit. Keratometric values K1 and K2 in diopters and axis of the steep meridian (α) in degrees were converted to net

astigmatism, M = K2 - K1, expressed as M(diopters)@axis°. Axis or meridian (α) was converted to the mirror equivalent.

Thereafter, net astigmatism was converted to polar values (polar value method) of the surgical meridian of 0° (corneal incision in IOL exchange group was at 0° in right eyes, i.e., located temporally) and torsional meridian of 45°: KP0 = M*cos(2*α) and KP45 = M*sin(2*α). KP0 and KP45 were calculated separately for the pre-operative and post-operative astigmatism.

Next, SIA in polar values was calculated by subtracting pre-operative polar values from the post-operative polar values: SIA KP0 = post-op KP0 - pre-op KP0 and SIA KP45 = post-op KP45 - pre-op KP45. Subsequently, values for SIA KP0 and SIA KP45 were averaged and statistical analysis was performed on the vector components to establish flattening/steepening of the surgical meridian.

To evaluate whether flattening/steepening of the surgical meridian differed between the groups, t-test for the two independent samples was used to compare SIA KP0 between the Iris and the Exchange groups.

Finally, vector analysis method for the reconversion of SIA from the averaged polar values to net astigmatism magnitude (M^1) in diopters was performed using the following formula:

$M^1 = \sqrt{SIA\ KP0^2 + SIA\ KP45^2}$.

Reconversion of the axis from the averaged polar values to net astigmatism direction in degrees was calculated using this formula: α = arctan ((M^1 - KP0)/KP45). After the reconversion, SIA net astigmatism was expressed in cylinder and axis: M^1(diopters)@axis°.

To calculate which of the two surgical methods induces larger SIA, M^1 was statistically compared between the Iris and Exchange groups.

4.4.4 Surgical techniques

Surgical techniques are shown in Fig. 2. All patients received topical (intracameral and sub-tenonal) and/or general anesthesia.

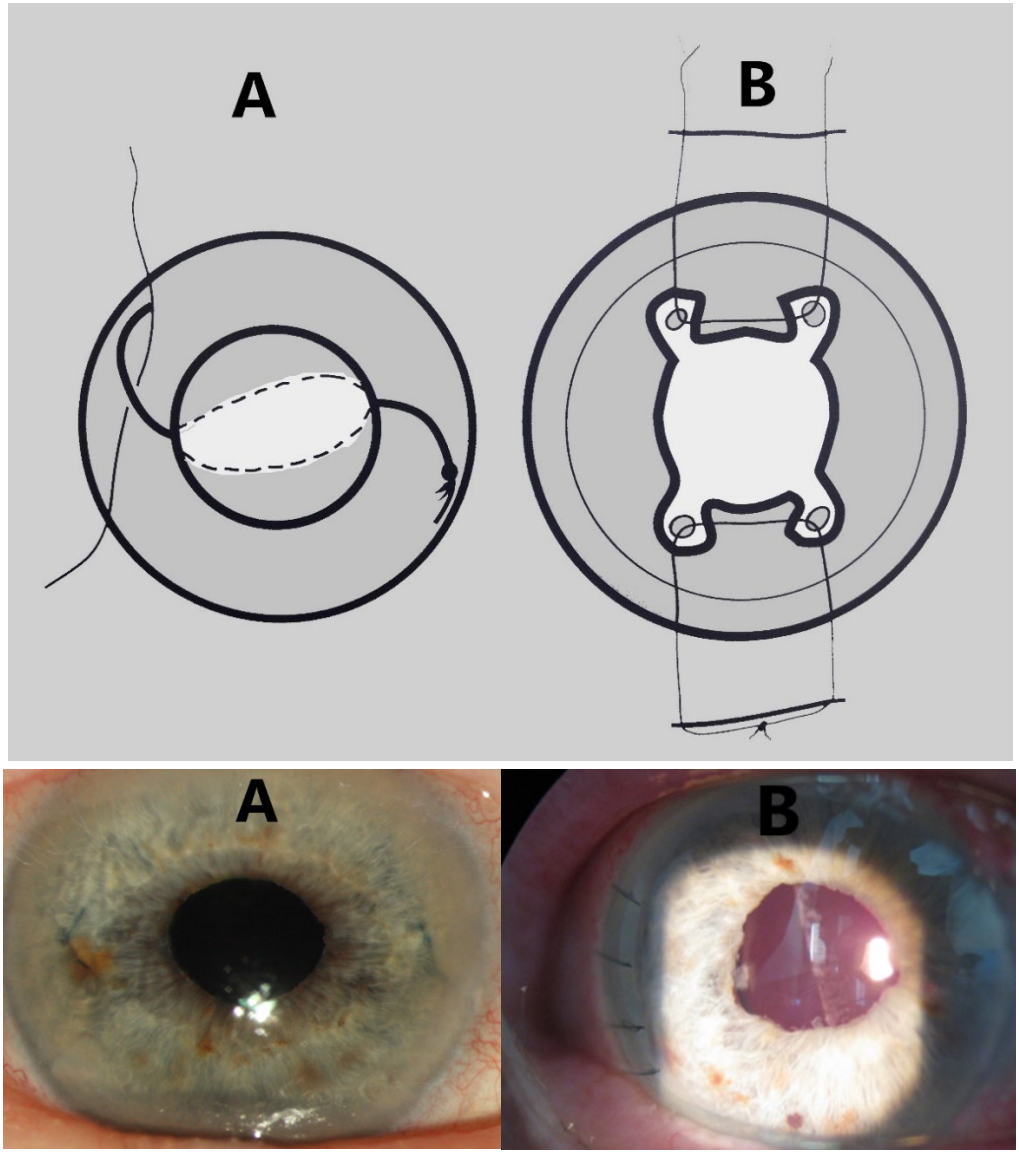


Figure 2. IOL suturing to the iris (A) and IOL exchange with a new IOL sutured to the sclera (B). Picture and photo: Laura Armonaite. Picture adapted from article [127].

3-piece IOL suturing to the iris

A 2-mm corneal incision was fashioned, and sodium hyaluronate was injected into the anterior chamber (AC) (Z-Hyalin plus 15 mg/ml, Carl Zeiss Meditec, Dublin, CA, USA). The optic-part of the dislocated IOL was prolapsed into the AC, and the haptics stayed in the sulcus. Acetylcholine hydrochloride (Miochol-E; Bausch & Lomb, Irvine, CA, USA) was injected into the AC to induce miosis. Four paracenteses were made near the location of the haptics. Siepser sliding-knot technique[20] was used to suture the haptics to the peripheral part of the iris with 10-0 prolene (polypropylene) sutures on long curved

needles (Ethicon, 788G, Tapercut Prolene Non-Absorbable Sutures, Cif-4). After the first knot, the optic was repositioned behind the iris. For oval pupils, the pupil was made round using 2 capsulorhexis forceps. Therafter, prolene was tied completely using the Siepser technique. The ends of the prolene sutures were trimmed, sodium hyaluronate was washed out manually, and intracameral moxifloxacin (Vigamox 1 mg/ml, 0.2 ml) was administered.

IOL exchange

Two conjunctival peritomies and 2 scleral grooves were made at the 6 and 12 o'clock positions 2.5 mm behind the limbus. Sodium hyaluronate was injected into the AC through a 2-mm corneal incision temporally, which later was enlarged by 6 mm and used to explant the dislocated IOL. Thereafter, the incision was sutured with one 10-0 ethilon suture. 10-0 polypropylene sutures (with long straight needles) were pierced through two of four eyelets of the IOL (Akreos Adapt AO, 1-piece acrylic IOL, Bausch & Lomb, Rochester, NY). A 27-gauge needle was introduced through the scleral groove and then out of the eye through the corneal incision. The prolene needle was docked into the 27-gauge needle, and this needle-complex was retracted from the eye through the scleral groove. This procedure was also performed on the other two IOL eyelets. The corneal suture was removed, and the IOL was implanted behind the iris. The prolene sutures were tied in the scleral grooves. The conjunctiva was sutured with 7-0 vicryl. The corneal incision was sutured with 10-0 ethilon. Acetylcholine hydrochloride was injected into the AC, and the vitreous strands were clipped off. Anterior vitrectomy was performed if needed. Sodium hyaluronate was removed manually, and Moxifloxacin was injected into the AC.

Postoperative treatment

Patients administered nepafenac eye drops (nevanac 1 mg/ml) 3 times daily for 4 weeks and dexamethasone (Isopto-Maxidex 1 mg/ml) 4 to 6 times daily tapered over 4–6 weeks. Most patients received acetazolamide 250 mg once or twice a day for 1–7 days.

4.4.5 Statistical analyses

To analyze speed of visual recovery, a Z-test was used for comparison of proportions between two samples. Values of unchanged visual acuity were not included in the analysis. Other analyses are described in section 4.3.

4.5 STUDY II

4.5.1 Study design

Study II, a prospective randomized clinical study with a cross-sectional part, compared two surgical methods in-between–the traditional (the suture perforates the capsular bag) and the modified (the suture embraces the CCC)–and compared to controls with normal pseudophakia.

4.5.2. Patients

Three groups of patients were included: patients with in-the-bag dislocated IOL randomized into two surgical methods and a group with ordinary pseudophakia (the Pseudophakic group). Three postoperative visits–at the 1st, 6th, and 18th month post-surgery–were scheduled. However, the last visit was cancelled due to the Covid-19 pandemic. Like other studies, six months was considered acceptable for the last evaluation of this type of surgery.[10,13,27,79,81]

The Pseudophakic group (n=60) was identified in the Swedish National Cataract Registry. This group served as the controls with normal IOL position. The inclusion criteria were age more than 75 years, uncomplicated phacoemulsification with IOL in-the-bag implantation 7–10 years before the study, and a well-positioned IOL on the examination. Participants with other intraocular surgery were excluded.

The inclusion criteria for the randomized patients with dislocated IOL were in-the-bag IOL dislocation ≥6 months after the cataract procedure, IOL seen in the pupil, intact CCC, and IOL with two open-loop haptics. Even large IOL dislocations with only a bit of the capsular bag visible at the inferior pupillary margin were included in the study. The exclusion criteria were difficulties in cooperating, previously repositioned IOL, and previous ectopia lentis. In bilateral IOL dislocation, only the first operated eye was included.

A flowchart is shown in Fig. 3. During the two-year period, 419 patients were referred with various issues regarding IOL status. Of these, 294 had in-the-bag dislocated IOL that needed surgical treatment, and 117 were randomized either to IOL repositioning by Ab externo scleral suture loop fixation (Group A, n=61) or by the modified method Embracing the CCC (Group B, n=56). Random allocation by the restricted shuffled approach was applied: after identification of the sample size cards were apportioned for each surgery by 1:1, cards were put into opaque sealed envelopes that were mixed and put in a box. Just before the surgery, envelopes were lotted to produce a random assignment without replacement. One surgeon (L.A.) performed all surgeries and could not be masked. Patients were routinely informed about the surgery but they did not know the type of IOL fixation. Outcome assessor was the surgeon who was masked to the type of assigned surgery during data collection: firstly, the data, except the type of surgery were entered into an Excel file, and the type of IOL surgery was included last.

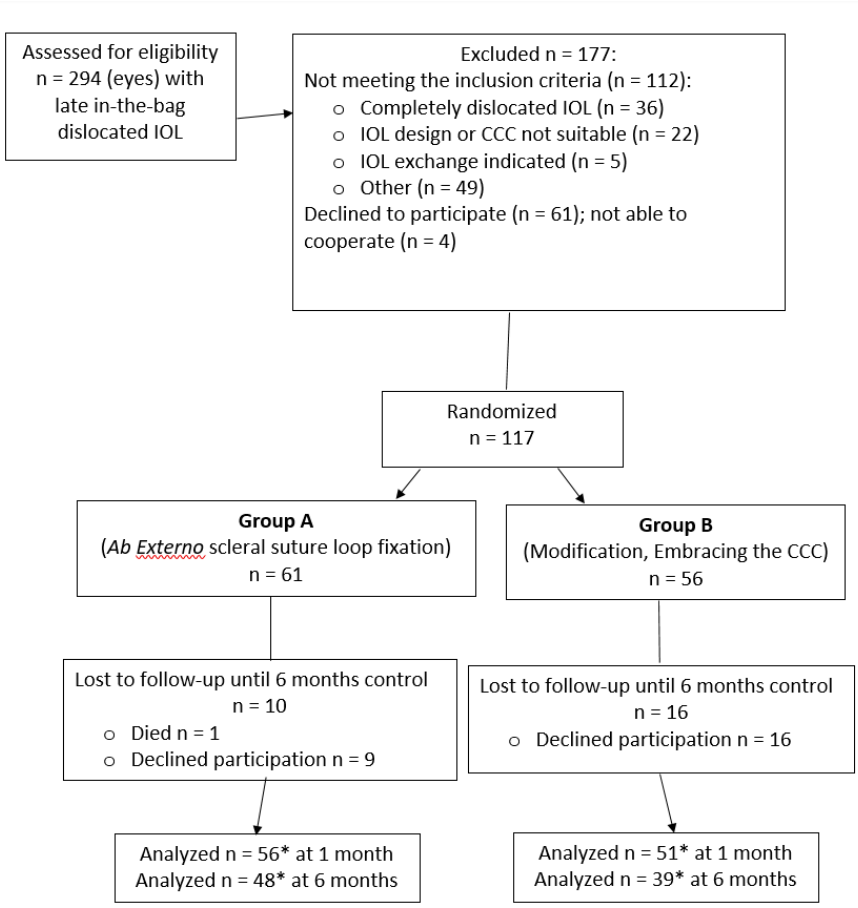


Figure 3. Flowchart presenting follow-up in study II. *Number of cases with available data for IOL tilt (the main outcome). Flowchart was adapted from the manuscript "Repositioning of in-the-bag dislocated intraocular lenses. A randomized clinical trial comparing two surgical methods".

4.5.3 Outcome measures

The main outcome was 3-D **IOL position** in degrees (magnitude and direction of IOL tilt) at six months postoperatively, measured after pupil dilation with SS–AS-OCT (Casia 2, Tomey, Japan) and compared between the three study groups. This SS–AS-OCT produces 2-D and 3-D images of the anterior segment.

To evaluate whether capsular bag fibrosis and Soemmering's ring (S ring) affected the IOL position, IOL tilt was compared between the subgroups with and without fibrosis (and/or S ring), within and between Groups A and B. Fibrosis intensity was categorized as none (the bag was crystal clear), moderate (slightly whitish), and advanced (intensively white) and was evaluated on slit-lamp examination and during the surgery. Presence of S ring was also noted. According to the hypothesis, IOL tilt in patients with no fibrosis was expected to be larger in Group A than in Group B (between-the-groups analysis), and IOL tilt was expected to be larger in patients without fibrosis than with fibrosis in Group A but not in Group B (within-the-group analysis). In addition,

usefulness of SS–AS-OCT for measuring IOL tilt was evaluated using the total number of cases where IOL position could be measured.

Other outcomes were **IIA** in diopters (D) measured after the surgery, change of **refraction** in diopters (D), change of **BCVA**, and **capsular thickness** in millimeters (mm) compared between the groups. Capsular thickness was measured with SS–AS-OCT preoperatively using manual tools, enlarging the picture by 200% 1 mm from the CCC margin at the 12 o'clock position (or other position if the 12 o'clock position was not visible) and compared between all three groups.

Refraction and keratometry were measured with autokeratorefractometer (Auto Ref/Keratometer Nidek Co., ARK-1, Japan). To evaluate whether methods A and B induced different amount of IIA, IIA was calculated using the following formula:

IIA = **Total ocular astigmatism** (by autorefractometry; cylindrical values were used) **– Total corneal astigmatism** (by SS–AS-OCT; posterior corneal astigmatism was also considered).

IIA was calculated using Naeser equations[125] as this method can be used also for IOL-based surgery.[128] Total astigmatism (T) and its angle of cylindrical (not corneal) axis, corneal astigmatism (C) and its angle of corneal steep axis were converted to the astigmatic power vectors KP0 and KP45, separately for (T) and (C): KP0 = T(or C)*cos (2 *axis) and KP45 = T(or C)*sin(2*axis). Thereafter, IIA was calculated in polar values: IIA (KP0) = KP0 (T) - KP0 (C), and IIA (KP45) = KP45 (T) - KP45 (C). Subsequently, IIA in polar values was re-converted to net astigmatism (cylinder) in diopters using the following formula:

$$\sqrt{\mathrm{IIA(KP0)}^2 + \mathrm{IIA(KP45)}^2}.$$

Next, IIA was compared between Groups A and B. However, as the nature of IOL-related astigmatism might be different from corneal astigmatism,[67] IIA was calculated by simple subtraction as well, without using polar vector equations. Finally, linear regression analysis was employed to calculate how much astigmatism is induced by 1°of IOL tilt.

Change of refraction (diopters) was calculated using this formula:

(SE ≥1 year before IOL dislocation) - (SE at 6 months after surgery).

All **complications** were documented during the follow-up time. Macula edema was diagnosed by OCT (TOPCON 3D OCT-2000, Topcon Corporation, Tokyo, Japan). For the re-operated patients, the "last observation carried forward" method was used in analyses of IOL tilt and refraction: their 1-month outcomes were used in 6-month analyses. In the Pseudophakic group**,** IOL position and capsular thickness were

measured with SS–AS-OCT after dilated examination on slit-lamp and compared to Groups A and B.

4.5.4 Surgical techniques

Patients with in-the-bag dislocated IOL underwent randomization between two surgical techniques of IOL suturing to the sclera: either the traditional (the suture perforates the capsular bag) or the modified (the suture embraces the CCC), Fig. 4.

In the traditional method "Ab externo scleral suture loop fixation,[27] a polypropylene (prolene) suture goes around the haptics and perforates the capsular tissue. Postoperative IOL position is usually good, although some of the IOLs are not well centered.[8,15,27,29,30] This might be related to the status of the capsular bag: if the bag is thin and fragile (i.e., not fibrotic), the prolene suture may cut through the bag, especially when pulling and tying the sutures. As the suture loop includes the haptics, the IOL does not dislocate completely. However, even small tears of the capsular bag may result in IOL decentration. Therefore, the traditional method was modified by L.A., where the CCC is embraced by the prolene suture, which goes ***around*** the CCC (Fig. 4). As the CCC provides a tear-resistant opening, tearing of the bag by the suture is unlikely even if the bag is not fibrotic. Gimbel et al suggested IOL suturing ***through*** the CCC[64] (2011); however, this method requires fibrosis of the capsular bag.

Duration of the surgery in Study II was the time between placing and removing the face drape. Topical 1% cyclopentolate and 10% phenylephrine hydrochloride were used to dilate pupils. The modified method (Group B) and the traditional method (Group A) followed the same surgical steps except one, which is highlighted in the text below and shown in Fig. 4. In all cases but one, local anesthesia was applied (topical, subtenonal, or intracameral). Three 2-mm corneal incisions were made and the AC was filled with a viscoelastic device (1% sodium hyaluronate, Z-Hyalin plus 15 mg/ml, Zeiss, Inc.). Next, two conjunctival peritomies and two scleral grooves were created 2.5 mm behind the limbus at the 6 and 12 o'clock positions. If the haptics were not located at the 6 and 12 positions, the IOL was rotated. Thus, IOLs were always sutured at the 6 and 12 positions unless there was a trabeculectomy filtration bleb at 12 o'clock, in that case the IOL had to be sutured at the 3 and 9 o'clock positions (one patient in the study).

In Group B, a 27-gauge needle went through the scleral groove into the eye*,* ***perforated only the posterior layer of the capsular bag*** underneath the haptic, *entered into the bag "cavity," leaving the bag between the IOL optic and the CCC. **In Group A**, however, a 27-gauge needle* ***perforated both layers of the bag*** (Fig 4). Subsequently, the needle was withdrawn from the eye through the corneal incision. A straight needle with 10-0 polypropylene (prolene) suture was docked into the 27-gauge needle. The complex of the needles was retracted from the eye through the scleral groove. Thereafter, this procedure was repeated but with the needles passing through the sulcus without

entering the bag. *Now,* ***the suture has embraced the CCC*** *(including the haptic****) in Group B*** *or* ***perforated the bag and looped around the haptic in Group A***. Thereafter, the same procedure was repeated on the opposite side.

The prolene needles were cut off and the sutures were tied with the knots rotated/hidden into the sclera. The conjunctiva was sutured with 7-0 vicryl (Ethicon, vicryl 7-0, Diegem, Belgium). Acetylcholine hydrochloride (Miochol-E; Bausch & Lomb, Irvine, CA, USA) was injected intracamerally. Vitreous strands were removed with scissors in the AC and at the corneal incision and anterior vitrectomy was performed if needed. Viscoelastic substance was removed manually and moxifloxacin (Vigamox 1 mg/ml 0.2 ml) was injected into the AC.

Patients were given 250 mg acetazolamide once the same day and received dexamethasone eye drops (Isopto-Maxidex 1 mg/ml) 4 times daily, which was tapered off over 4 weeks.

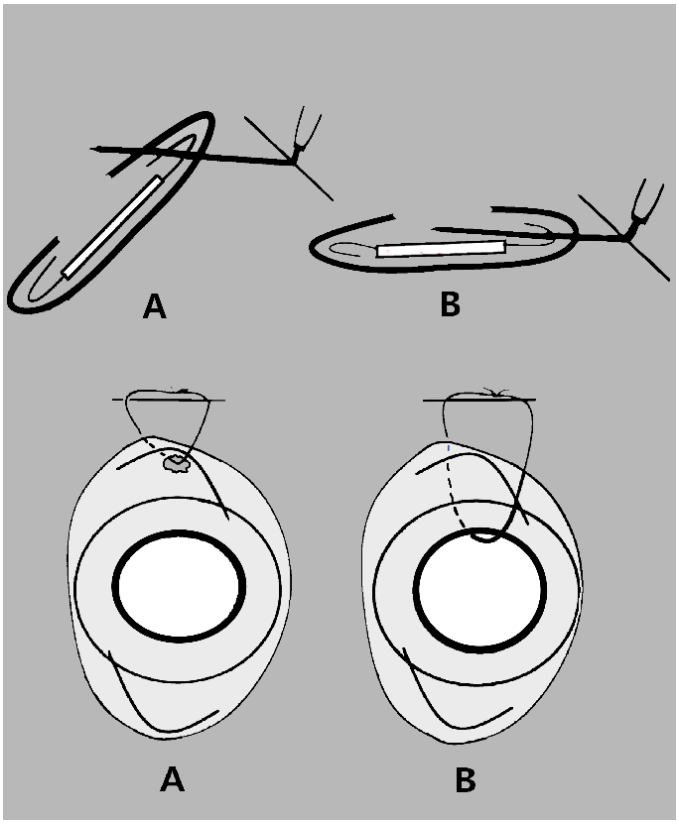


Figure 4. The difference between the traditional method (A) Ab-externo scleral suture loop IOL fixation and the modification (B), Embracing the CCC. Method A: the prolene suture perforates both layers of the capsular bag and does not include CCC. Method B: the suture perforates only the posterior layer of the capsular bag and embraces the CCC. Picture: Laura Armonaite, adapted from the manuscript "Repositioning of in-the-bag dislocated intraocular lenses. A randomized clinical trial comparing two surgical methods."

4.5.5 Statistical analyses

According to power analysis, 27 cases in each group were needed to find a 5˚ difference in IOL tilt between Groups A and B with 95% power, $\alpha = 0.05$, expected standard deviation of 5 and group ratio 1:1. A big number of drop-outs was expected, therefore more patients were recruited for each group.

To compare IOL tilt between the subgroups with/without capsular fibrosis and S ring, statistical analyses for quantitative data were employed as described in section 4.3, also a multivariate regression model was used. A similar model was applied to check whether presence/absence of Soemmering's ring (S ring) impacts IOL tilt in the moderate level fibrosis subgroup.

To find a quantitative relationship between the IIA and IOL tilt, a linear regression model was employed. A 95% CI is reported for BCVA in between-the-groups comparison, and for the IIA in linear regression analysis. Other analyses are described in section 4.3.

4.6. STUDY III

4.6.1 Study design

This retrospective case-control study included a cross-sectional component. Patients with UGH syndrome were compared to two control groups without UGH. Data were collected from medical charts, and the Pseudophakic group was also evaluated cross-sectionally.

4.6.2 Patients

All patients were treated between 2010 and 2018. The study consisted of 3 groups: UGH syndrome (UGH group, n=71), dislocated IOL without UGH (Dislocated group, n=71), and uncomplicated pseudophakia (Pseudophakic group, n=71). Inclusion criteria for **UGH syndrome** were iris-IOL contact that resulted in intraocular hemorrhage and/or uveitis and/or pigment dispersion and/or macular edema.

The **Pseudophakic group** was identified in the Swedish National Cataract Registry and recruited as study II participants whose data was used in this study III. As their uncomplicated cataract surgery was performed between 2010 and 2012, the postoperative time of this group matches the UGH group. Exclusion criterion was other ocular surgery.

Patients in the **Dislocated group** were all patients with dislocated IOL referred to St. Erik Eye Hospital Anterior Segment Surgery Department over seven months. Patients with

dislocated IOL were considered an appropriate control group as this group is very similar to the case group (UGH) in all aspects, except for the outcome–i.e., UGH syndrome. Inclusion criterion was all types of IOL dislocation with the IOL in the pupil plane. The exclusion criteria were history of intraocular hemorrhage, uveitis, and pigment dispersion. Age ≥87 years (30 patients) was also an exclusion criterion as the use of blood thinners (one of study's outcomes) increases with higher age. In the Dislocated group iris-IOL contact signs were allowed, but not uveitis or hemorrhage. Patients with only one episode of uveitis were excluded from the study.

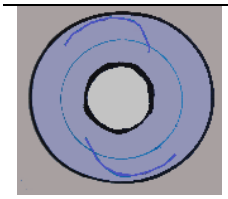
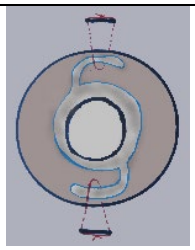
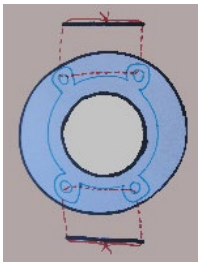
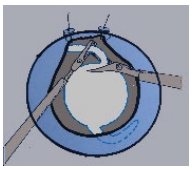
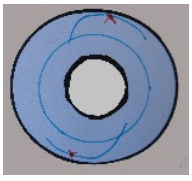
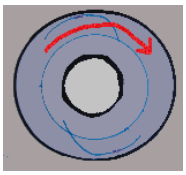
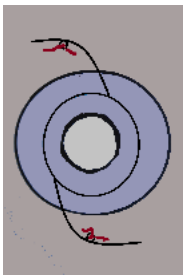
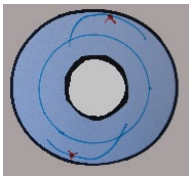
4.6.3 Outcome measures

4.6.3.a Effect of UGH syndrome treatment

Outcome measures were number of patients where UGH syndrome resolved (i.e., treatment was effective), and change in BCVA and IOP. **UGH resolution** was defined as absence of hemorrhage, iritis, pigment dispersion, and macular edema during the postoperative period. The change of **BCVA** and **IOP** was defined as the final BCVA (or IOP) compared to the preoperative BCVA (or IOP) or, if not operated, the BCVA (or IOP) when the decision not to operate was made.

Treatment in this study was either conservative (n=11) or surgical (n=60). A total of 66.6% (40 of 60) surgeries were performed by one surgeon (L.A.); 20 cases were operated by 6 other surgeons. Overall, 11 types of surgery were performed and analyzed as 2 groups: IOL exchange and surgery without IOL exchange. Exchange of IOL comprised 4 types of surgeries (Table 1). Surgery without IOL exchange comprised 7 types of surgeries where the iris-IOL contact was removed with as little intervention as possible, so called "minimally invasive IOL surgery" or surgery of the pre-existing IOL (Table 1). IOL exchange with a new sclera-sutured IOL was performed only when a minimally invasive procedure was not possible. The type of the surgery depended on the type of IOL malposition or dislocation (out-of-the-bag or in-the-bag).

A total of 11 patients were not operated: increased IOP, iritis, or hyphema were treated with IOP-lowering drops or dexamethasone drops (Isopto-Maxidex 1 mg/ml).

Table 1. IOL surgery in patients with UGH syndrome (n=60)			
	IOL exchange n=14	Surgery of the pre-existing IOL/minimally invasive surgery n=46	
	A new 3-piece IOL implantation in the sulcus, n=7	IOL suturing to the sclera using Ab externo suture loop fixation method [27], n=27	
	A new IOL (Akreos Adapt) suturing to the sclera, n=3	IOL haptic amputation, n=8	
	A new 3-piece IOL suturing to the iris, n=2	IOL manipulation or rotation, n=5	
	PPV + a new IOL suturing to the sclera, n=2	IOL suturing to the iris, n=1 *Other surgeries, n=5*[#]	

This table was adapted from article.[129]
[#]PPV (n=1), removal of posterior synechiae (n=2), inspection of IOL position (n=1), other (n=1).

4.6.3.b A need for IOP-lowering treatment after UGH resolution

Outcome measures were number of patients who needed IOP-lowering therapy after UGH resolution. Risk factors are discussed below.

Patients with glaucoma or ocular hypertension (OHT) diagnosed *before* cataract surgery (n=10)–i.e., preexisting conditions–were excluded from the analyses. Many patients with UGH syndrome need IOP-lowering therapy not only during UGH but also after UGH resolution. Patients risk developing glaucoma if they do not receive IOP-lowering

treatment, and they require long follow-up. Therefore, the use of IOP-lowering therapy after UGH syndrome resolution was assessed, and this was considered to be more clinically important than just an IOP increase exceeding 21 mmHg. To ensure UGH syndrome had ceased, IOP value and the therapy was recorded at least 5 months after the patient was UGH free.

Some factors might increase the need for IOP-lowering therapy after UGH resolution, such as IOP at the first hemorrhage (5 cases without hemorrhage were excluded), duration of UGH syndrome (the time from UGH diagnosis to surgery), and whether patients underwent IOL surgery. These factors were analyzed to determine whether they were associated with IOP-lowering therapy after resolution of UGH syndrome.

Additionally, cases of blindness caused by secondary glaucoma (Snellen BCVA <0.05) were registered in the UGH group. Criteria were glaucoma diagnosed after the cataract surgery, with glaucomatous damage to the optic disc and visual field defects.

4.6.3.c Iris-IOL contact signs in the UGH group

Outcome measures were the diversity of iris-IOL contact and which type of contact was specific to UGH syndrome. Iris-IOL contact signs seen on slit-lamp examination were grouped according to the following classification:

• TID;

• highly probable iris-IOL contact: IOL-donesis, one of the haptics in the sulcus, decentered IOL (haptic-optic junction visible in the pupil only after pupil dilation), and dislocated IOL (more pronounced IOL dislocation);

• a mix of signs.

TID form and frequency were compared between all three groups. Additionally, iris-IOL contact change over time in the same patient was described.

4.6.3.d Administration of blood thinners

Administration of blood thinners was compared between the UGH and the Dislocated groups. Five patients without hemorrhage in the UGH group (only iritis, pigment dispersion, macular edema) were excluded from the analysis.

4.6.3.e Usefulness of diagnostic examinations

To establish which examination was the most useful in diagnosing UGH syndrome, cases with visible (or suspected) iris-IOL contact were counted when examined by slit-lamp, UBM, and AS-OCT. UBM was performed with Sonomed VuMax II UBM using a probe with 35 MHz transducer and 22-micrometer resolution (Sonomed Escalon, New York, USA). The patient was placed flat on the back, and in topical anesthesia an eyecup filled with

saline solution was placed between the eyelids. Imaging was performed using the UBM probe immersed in the saline solution.

Two AS-OCT machines were used: AS-OCT (Visante, Carl Zeiss Meditec AG, Berlin, Germany) until April 2018 and SS–AS-OCT (Casia 2, Tomey, Nagoya, Japan) from May 2018. The latter machine was used in Study II as well.

4.6.4 Statistical analyses

Receiver Operator Characteristic curve (ROC) analysis was employed to determine whether IOP at the 1st intraocular hemorrhage predicted the use of glaucoma therapy after resolution of UGH. The cut-off value of IOP was calculated to determine the highest sensitivity and specificity of the test (i.e., the need of glaucoma therapy at the final visit). The area under the curve (AUC) was calculated to establish the predictive capacity of the model. A logistic regression model was used to test whether UGH duration until the IOL operation and whether IOL surgery (patient was operated or not) predicted the need of glaucoma therapy at the final visit. Other statistical tests are presented in section 4.3.

5 Results

5.1 STUDY I

Baseline characteristics of the patients were similar between the groups (Table 2).

Table 2. Baseline characteristics of the Iris group (IOL was sutured to the iris) and Exchange group (IOL was exchanged with a new IOL sutured to the sclera)

	Iris group (n=14)	Exchange group (n=18)
Age (years)	77 (70–86)	81 (69–85)
Gender (female/male)	6/8	10/8
History of trauma that required surgery	2	1
Previous retinal detachment	1	1
Complicated cataract surgery	8	4
Amblyopia	1	1
Corneal edema	0	1
Macula pathologies	3 (one patient had both macula pathology and amblyopia)	3
Glaucoma diagnosis and IOP-lowering treatment before IOL fixation surgery	0	3 (one patient was therapy-free after trabeculectomy)
No glaucoma diagnosis before fixation surgery, but patients were on IOP-lowering therapy, probably because of OHT	2	4
Preoperative BCVA (logMAR)	0.3 (0.17–0.67)	0.61 (0.27–0.89)
Mean preoperative IOP±SD, mmHg	16.2 (±3.8)	16.5 (±5)

This table is adapted from article [127]. Data are median (interquartile range) unless stated otherwise.

5.1.a Efficacy of the surgery

BCVA improved significantly in both groups after the surgery, without between-the-groups difference (Table 3). Speed of visual recovery did not differ significantly between the groups (Table 3). The number of postoperative visits was significantly lower in the Iris group than in the Exchange group (Table 3).

5.1.b Safety of the surgery

The number of complications was similar between the groups, including inflammation measures (Table 3). There was no significant difference in IOP neither within-the-group (preoperative vs. postoperative IOP) nor between the groups at the last visit (Table 3). In

the Exchange group, the median postoperative SE was -0.88 (IQR -2.1 – +0.25), which did not differ significantly from the predicted refraction -0.15 (IQR -1.2 – -0.02), p=0.097, n=17, Wilcoxon matched-pairs test.

Between-the-group analyses showed that flattening of the horizontal meridian and SIA was significantly higher in the Exchange group than in the Iris group (Table 3).

Table 3. Outcomes of IOL suturing the iris and IOL exchange with a new IOL sutured to the sclera.

	Iris group (n=14)	Exchange group (n=18)	p value
Efficacy:			
The median final BCVA (logMAR)[a]	0.19 (0.08–0.2)	0.1 (0.08–0.2)	0.530*
Final BCVA≥0.5 (Snellen chart)	n=12 (86%)	n=16 (89%)	
Final BCVA<0.5	n=2	n=2	
Speed of visual recovery: Better VA[b], n (%) Worse VA[b], n (%)	 6 of 13 (46%) 4 of 13 (31%)	 4 of 13 (31%) 8 of 13 (61%)	0.211**
Postoperative visits, n	2.5 (2–3)	4.5 (3–6)	0.0006*
Safety:			
Complications: retinal detachment choroidal detachment macular edema intraocular hemorrhage UGH syndrome endophthalmitis IOL re-dislocation that required re-operation[d]	 0 0 0 1 0 0 0	 0 2[c] 0 3 0 0[c1] 0	
Additional topical treatment with corticosteroids postoperatively	0	0[e]	
Laser flare, pc/ms	12.6 ± 4.8 (n=13)	11.99 ± 8.9 (n=12)	0.430***
IOP at the last visit, mmHg	15.4 ± 3.9[e1]	15.2 ± 3.1[e1]	0.870***
Number of patients who started or increased IOP-lowering therapy postoperatively	n=2 (14%)[f]	n=2 (11%)[f]	
Power vector SIA KPO[g] Power vector SIA KP45[g] Net astigmatism SIA[g] in diopters @ axis in grades	0.41 ± 0.6 0.12 ± 0.69 0.89 ± 0.44@76°	-0.54 ± 1.3 -0.26 ± 1.0 1.46 ± 0.93@97°	0.011*** 0.225*** 0.03***

Data are presented in mean (±SD) unless otherwise stated. VA=visual acuity, SIA=surgically induced corneal astigmatism.

[a]BCVA improved significantly after the surgery in both groups; p=0.005 in the Iris group and p<0.001 in the Exchange group; Wilcoxon matched-pairs test.

[b]Better or worse visual acuity (VA) was determined as gain or loss of ≥one Snellen line one week after the surgery.

[c]Choroidal effusion and hypotony was caused by leakage through the corneal incision, which was managed by suturing the incision and, in other case, by additionally injecting gas into the vitreous cavity.

[c1]One case of endophthalmitis due to blebitis after trabeculectomy in the Exchange group.

[d]One case of little IOL re-dislocation was observed in both groups, but did not require re-operation.

[e]One patient in the Exchange group received additional therapy with topical corticosteroids because of hyphema.

[e1]The pre-operative and last postoperative IOP did not differ in within-the-groups comparison.

[f]All 4 patients were on IOP-lowering therapy awhile before the IOL surgery. In the Exchange group, two patients underwent IOP-lowering surgery: PPV (n=1) and cyclophotocoagulation of ciliary body (n=1).

[g]Explained in Methods section. SIA KP0 = post-op KP0 - pre-op KP0; SIA KP45 = post-op KP45 - pre-op KP45. Net astigmatism (SIA)= $M^1 = \sqrt{SIA\ KP0^2 + SIA\ KP45^2}$; α = arctan $((M^1 - KP0)/KP45)$.

*Mann-Whitney U test.
** Z-test for independent proportions.
***two-samples t test.

5.2 STUDY II

Baseline characteristics of the participants are as follows. The mean age was 81.4±6.7 years (group A, n=61), 81.4±5.1 (group B, n=56), and 78.8±3.2 (Pseudophakic group, n=60). Gender (female/male) proportions were 56%/44% (Group A), 63%/36% (Group B), and 67%/33% (Pseudophakic group). Right/left eye proportions were 34/27 (Group A), 28/28 (Group B), and 31/29 (Pseudophakic group). Preoperative BCVA and SE are shown in Table 4.

Outcomes of the surgery are disclosed in Table 4. At the six-month follow-up, 87 patients in Groups A and B and 60 patients in the Pseudophakic group were analyzed. The median **IOL tilt** was 7.8° (IQR 5.9°–12.0°) in Group A and 8.3° (IQR 6.3°–10.8°) in Group B (p=0.51). Each group differed from the Pseudophakic group, 5.4° (IQR 3.9°–7.1°; p<0.001); the mean difference was 3.75° (CI=2.54°–4.59°; p<0.001) when compared to the entire (A+B) group. The direction of IOL tilt was inferotemporal (inferotemporal IOL border tilted posteriorly and superonasal IOL border tilted anteriorly) in 87.5%, 87% and 87% of the patients in each group, respectively (Table 4 and Fig. 5).

In patients ***without*** fibrosis and S ring, the IOL tilt did not differ significantly between Group A (15.5°) and Group B (7.0°); notably, the size of the subgroups was very small (Table 4). Presence/absence of S ring did not impact magnitude of IOL tilt (Table 4).

The highest IOL tilt value in the Pseudophakic group was 9.1°. In Groups A and B, 18 patients had IOL tilt ≥15°, 5 were re-operated soon after the one-month follow-up: 3 in Group A and 2 in Group B, where one IOL was twisted by gas after vitreoretinal surgery. Two patients underwent IOL exchange. In 3 other patients, the IOL position was improved by placing an additional prolene suture using Embracing the CCC method; the mean IOL tilt decreased from 18.7° to 9.8°. The other 13 patients were *not* re-operated because they were satisfied with their vision. In these 13 cases, the median IIA was 0.75 D (0.45–2.45).

The **IIA** did not differ significantly between Groups A and B (Table 4).). IIA and IOL tilt were positively correlated (rank-correlation coefficient (r)=0.299, p=0.007, Spearman test). According to the polar vector method and linear regression analysis, IIA increased by 0.075 D with increase of each degree of IOL tilt (95% CI=0.035–0.115; p<0.001). According to simple subtraction method and linear regression model, IIA increased by 0.09 D/1° of tilt, p<0.001.

The median time of surgery was longer in Group B than in Group A. **Complications** are presented in Table 4.

BCVA improved significantly within the groups, without significant difference between the groups (Table 4). At six months (re-operated cases excluded), 71 of 87 patients

(81.3%) in the A+B group had a BCVA of 20/40 or scored a 0.5 on the Snellen chart. A significant myopic shift was seen in group A and B at six months (Table 4). A total of 93% (56 out of 62) of cases had a myopic shift in the entire A+B group, with a median of -0.87 D (IQR -1.62 – -0.40).

It was possible to measure IOL position with SS–AS-OCT in all patients but two in the group A (IOL was behind the iris). Measurement of capsular thickness was also possible in all cases. The CCC margin was significantly thicker in Group A (0.079 mm; IQR 0.059–0.133) and B (0.079 mm; IQR 0.066–0.119) than in the pseudophakic controls (0.064 mm; IQR 0.050–0.080), p=0.003 , Mann-Whitney U test, compared to the entire A+B group.

Table 4. Outcomes of surgery with the traditional method Ab externo Scleral Suture Loop Fixation (Group A) and a modification Embracing the CCC (Group B), and patients with ordinary pseudophakia (Pseudophakic group).

	Time	Group A n=61	Group B n=56	p value and 95% CI
IOL position:				
	6 months post-op[a]	7.8° (5.9°–12.0°; n=48)	8.3° (6.4°–10.8°; n=39)	0.51*
Magnitude of IOL tilt in degrees, °		Pseudophakic group 5.4° (3.9°–7.1°; n=60)		<0.001* (compared to group A) <0.001* (compared to group B)
Inferotemporal IOL tilt, n (see also Fig. 5)	6 months post-op[a]	87.5% (n=48)	87.0% (n=39)	
		Pseudophakic group 87.0% (n=60)		
IOL tilt in subgroups of capsular fibrosis:				
No fibrosis and no S ring	1 month post-op[c]	15.5° (7.8°–21.7°; n=7[#])	7.0° (6.6°–11.4°; n=5)	0.19*
Moderate fibrosis with or without S ring[d]	1 month post-op	8.7° (5.7°–12.5°; n=45[#]) p=0.091* between the subgroups of no and moderate fibrosis	8.6° (6.6°–13.5°; n=38) p=0.91* between the subgroups of no and moderate fibrosis	
Refractive outcomes:				
IOL-induced astigmatism (IIA), diopters, calculated with polar vector method	6 months post-op[a]	1.19 (0.67–1.61) n=46	0.82 (0.44–1.42) n=35	0.139*

Spherical equivalent, diopters	Before IOL dislocation 6 months post-op[a]	-0.25 (-2.25– +0.50; n=33) -1.38 (-2.88– -0.44; n=33) p<0.001****	-0.25 (-1.62– +0.70; n=29) -1.38 (-2.87– -0.19; n=29) p<0.001****	
BCVA, logMAR (mean ± SD)	Preoperative	0.65±0.70; n=61	0.70±0.91; n=56	p=0.65*** CI= 0.23–0.36
	6 months post-op[b]	0.18±0.26; n=48 p<0.001, compared to preoperative values**	0.20±0.28; n=39 p<0.001, compared to preoperative values**	p=0.66*** CI= -0.093– + 0.14
Duration of surgery (minutes) All patients: 22 (20–26, range 13-42)		21 (19–24)	24 (21–27)	0.006*
Complications:				
Vitreous hemorrhage Retinal detachment Chorioidal detachment Macular edema Prolene suture erosion through conjunctiva		4 0 0 1 0	5 1 1 0 0	

Results are presented in medians (interquartile range) unless otherwise stated. Post-op = postoperatively; S ring = Soemmering's ring. Exclusions from analyses were due to missing data (patients lost to follow-up, measurements not performed) or missing documentation of data.
This table is adapted from the manuscript "Repositioning of in-the-bag dislocated intraocular lenses. A randomized clinical trial comparing two surgical methods".

[a] Last Observation Carried Forward (LOCF) method employed for five re-operated patients.

[b] Five re-operated patients excluded.

[c] Subgroup analyses at six-month visit were not possible to perform due to too few patients, and some had missing data; therefore, outcomes from one-month visit are presented. Multivariate analysis showed that the difference of IOL tilt between the groups A and B does not depend on the grade of fibrosis (p=0.066).

[d] A total of 47 patients in Group A and 41 in Group B had moderate fibrosis. According to multivariate regression model, presence/absence of S-ring did not impact IOL tilt neither within nor between Groups A and B (p=0.721). Advanced fibrosis was seen in four (group A) and five (group B) patients.

*Mann-Whitney U test *** Two-samples t test

** Paired-samples t test **** Wilcoxon matched-pairs test.

In 2 patients in Group A (one patient in each subgroup), IOL tilt could not be measured because the IOL was dislocated behind the iris. In these cases, an IOL tilt of 30° was imputed.

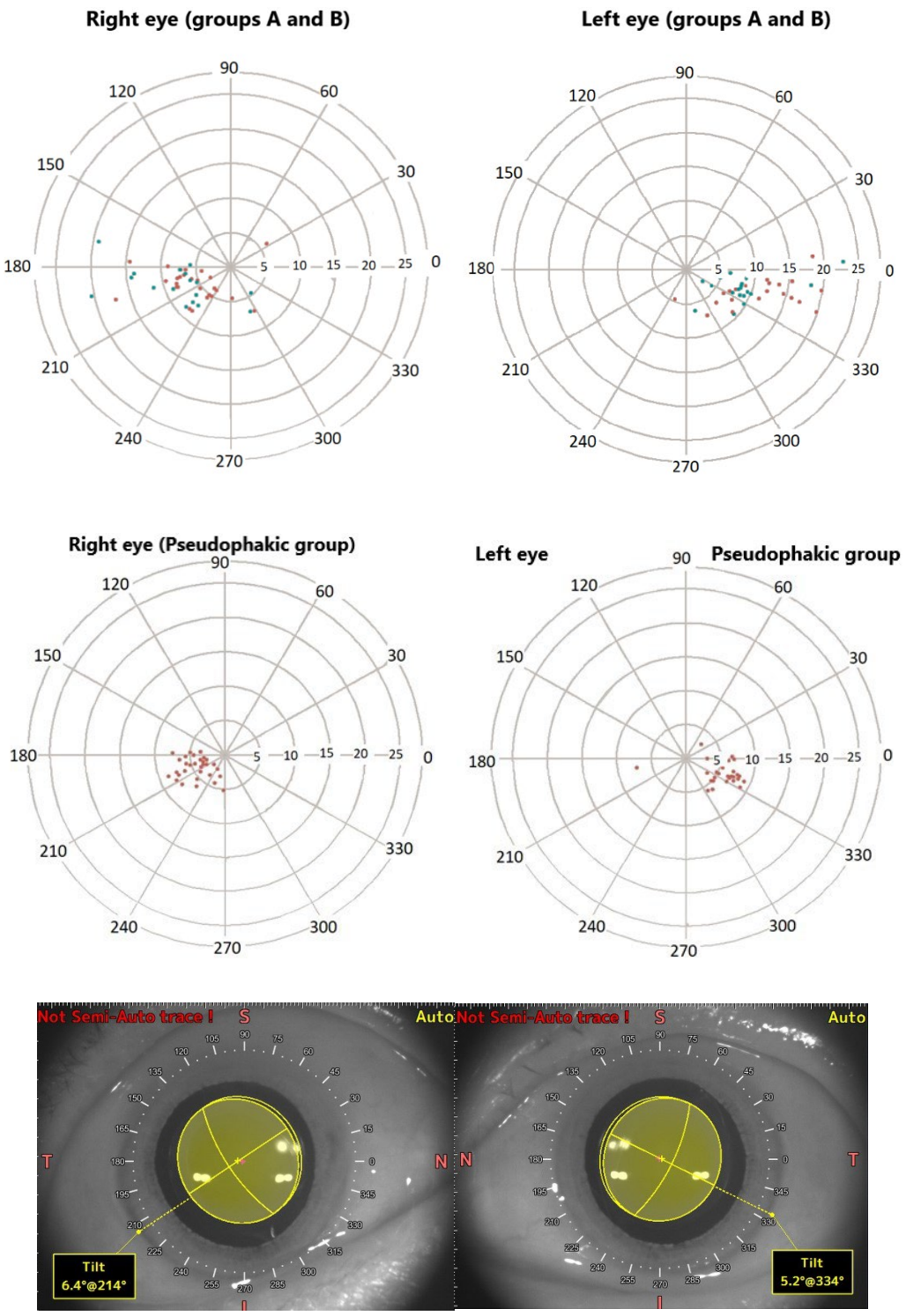


Figure 5. IOL tilt six months after IOL surgery: the cartesian coordinates show the magnitude, and the polar coordinates show the direction. The upper figure shows group A (red dots) and Group B (green-blue dots). The lower figure shows Pseudophakic group with normal pseudophakia, and the photograph shows the normal IOL position measured with SS–AS-OCT. IOLs were mostly tilted inferotemporally (inferotemporal IOL border tilted posteriorly and superonasal IOL border tilted anteriorly) in all groups: 87.5% (42 of 48) in Group A, 87% (34 of 39) in Group B and 87% (52 of 60) in the Pseudophakic group. This figure is adapted from the manuscript "Repositioning of in-the-bag dislocated intraocular lenses. A randomized clinical trial comparing two surgical methods".

5.3 STUDY III

5.3.1 Characterization of the UGH group

A total of 4159 adult patients with intraocular hemorrhage were treated at St. Erik Eye Hospital between 2011 and 2018. IOL was considered to be the reason for the hemorrhage in 66 patients (1.6%), and in 5 other patients IOL was determined to be the reason for the iritis, macular edema or pigment dispersion. Thus, a total of 71 patients were included in the study. The median age of the patients was 76 years (IQR 69–83, range 43–90). Three patients developed UGH in both eyes, but only the first eye was included in the study.

A total of 66 patients had intraocular hemorrhage, and 5 patients had no hemorrhage: 3 had iritis and pigment dispersion, 1 had iritis and macular edema, 1 had iritis, pigment dispersion and macular edema. Three of 71 had cystic macular edema (together with other UGH clinical signs), diagnosed 4–15 years after cataract operation or IOL implantation. In one case, UGH started as isolated macular edema 3 years before the first hemorrhage.

Diabetic retinopathy (n=5) and branch vein occlusion (BVO; n=1) were not the cause of intraocular hemorrhages. Similar rates of diabetic retinopathy and BVO were registered in the Dislocated group (two cases with both pathologies) and in the Pseudophakic group (1 case with diabetic retinopathy and 1 case with BVO).

The median time to develop UGH syndrome after cataract surgery was 6 years (IQR 3–10). Patients were followed 3.3 years (IQR 2.1–5.6). The follow-up time after IOL operation (or after the decision to treat conservatively) was 1.8 years (IQR 0.87–2.8).

The clinical course of UGH syndrome varied greatly and did not follow any regular pattern. Four patients had a long pause (12–33 months) between UGH episodes. UGH masqueraded as herpetic uveitis (n=6), chronic endophthalmitis (n=1), and corneal graft rejection (n=2). In 3 cases, it took several years for iris-IOL contact signs to appear on slit-lamp examination: 12.5 years for IOL dislocation (n=1), 8.1 years for IOL-donesis (n=1), and 7.5 years for TID (n=1).

Description of the controls. The median age of the Dislocated group (78 years (IQR 74–81; range 44–86) was not different from the UGH group, (p=0.116; Mann-Whitney U test). The Pseudophakic group was examined 7.6 (±0.8) years after the cataract operation. The median age of this group was 79 years (IQR 78–82).

5.3.2 Outcomes of UGH syndrome treatment

UGH syndrome resolved in 46 of 60 (76.6%) **operated** patients with a median follow-up of 17.8 months (IQR 8.6–28.5). UGH syndrome ceased in similar proportions in the subgroups with- and without IOL exchange: 10 of 14 (71%) and 34 of 46 (74%), respectively.

UGH did not resolve in 14 operated patients. Seven patients were re-operated with IOL exchange and UGH resolved in these cases. UGH ceased also in 7 not re-operated cases. Thus, UGH resolved finally in all 14 cases, with the mean follow-up of 18.7 months (±3.8). However, macular edema persisted in 2 cases.

The **intraoperative findings** are shown in Table 5. Some findings were observed only in the UGH group, such as the whole 1-piece IOL (or one of the haptics) in a sulcus. Iris-IOL contact was not seen on slit-lamp examination in two cases; however, it was found intraoperatively in one case (haptic of 1-piece IOL in the sulcus). In the other case, the contact was not found intraoperatively, but 7 years lasting UGH syndrome ceased after the surgery.

Table 5. Intraoperative findings

Possible iris-IOL contact found at surgery	UGH group n=60	Dislocated group n=66
Dislocated or unstable IOL because of zonular weakness:	34 (57%)	66 (100%)
· In-the-bag dislocated IOL	29 (48%)	62 (94%)
· Out-of-the-bag dislocated IOL	5 (8%)	4 (6%)
IOL with 1 haptic in the sulcus	19 (32%)*	0
1-piece IOL in the sulcus	4 (7%)	0
No IOL-iris contact found intraoperatively	1#	

This table is adapted from the article [129].
*In 4 cases, the haptic eroded the capsular bag. The IOL was of multipiece type in 3 cases.
7 years lasting UGH syndrome ceased after surgery.

A total of 11 patients were **not operated** for various reasons such as mild UGH syndrome with normal IOP and no visual function in the fellow eye. UGH syndrome did not re-occur for ≥1 year in six cases. Macular edema persisted in one (other) case.

In operated patients, **IOP** decreased from 16 (IQR 13–24) to 15 (IQR 12–18; p=0.002), and **BCVA** (logMAR) improved from 0.37 (IQR 0.10–0.89) to 0.19 (IQR 0.0–0.49; p<0.001, Wilcoxon matched-pairs test). There were no significant changes of IOP and BCVA in non-operated patients.

5.3.3 A need for IOP-lowering treatment after UGH resolution

In the UGH group, 10 of 71 (14.1%) of the patients had *preexisting* glaucoma or OHT *before* cataract operation (in the Dislocated group, 8 of 70, 11.4%), and were excluded from the analyses in this subsection.

During active UGH syndrome (iritis, hemorrhage etc.), IOP increased in 68.8% (42 of 61) of patients without preexisting glaucoma/OHT. In the Dislocated group, the number was 25.8% (16 of 62), p=0.002, Chi-square test. The median IOP was 32 mmHg (IQR 26–42, range 22–57) at the initiation of IOP-lowering therapy (n=27) during ongoing UGH syndrome.

After the resolution of UGH, some patients could finish IOP-lowering therapy, but some patients could not. In total, 31 of 61 (51%) in the entire UGH group ***without*** pre-existing glaucoma or OHT needed IOP-lowering treatment ***after*** UGH syndrome resolved (or did not re-occur). The overall median "UGH-free" period was 17.7 months (IQR 6.7–27.1). In operated cases, 29 of 51 (56.8%) needed IOP-lowering treatment after UGH resolution for a median "UGH free" period of 15.9 months (IQR 6.95–26.2). Three patients underwent glaucoma surgery (plus one other patient with preexisting glaucoma). Three cases (4.2%) of blindness due to secondary glaucoma were caused by UGH syndrome.

The only risk factor for permanent need for IOP-lowering treatment after UGH syndrome resolution was IOP ≥22 mmHg at the 1st hemorrhage (n=38, AUC=0.807; 95% CI 0.666–0.947; p=0.002, ROC analysis). This analysis excluded patients with iritis on IOP-lowering therapy before the first hemorrhage.

The logistic regression analysis revealed that UGH syndrome duration before IOL surgery and the IOL operation did not predict a need for subsequent IOP-lowering therapy. The analysis included 60 patients with all variants of UGH, both operated and not operated.

5.3.4 Iris-IOL contact signs in the UGH group

At the beginning of UGH syndrome, the ***number*** of eyes with TID was 21 in the UGH group and 19 in the Dislocated group (p=0.708; Fisher's Exact test). The *number* of TID in the UGH- and the Pseudophakic groups was 21 and 7, respectively (p=0.005). TID in patients with UGH are presented in Fig. 6. In the Dislocated group, four patients of 19 with TIDs underwent other surgery before the IOL suturing to the sclera, and cataract surgery was complicated in two other patients but no other surgeries were performed.

The TID ***form*** was different between the groups. In the UGH group, the TID shaped as optic edge or haptic was seen in 27 of 42 patients (64%) and in 2 of 19 patients (10%) in the Dislocated group ($p<0.0001$; Fisher's Exact test). In the Pseudophakic group, 7 patients had very small dot-formed unspecific TID. Unspecific TID (although larger) was found in 11 of 71 (15%) patients with UGH syndrome.

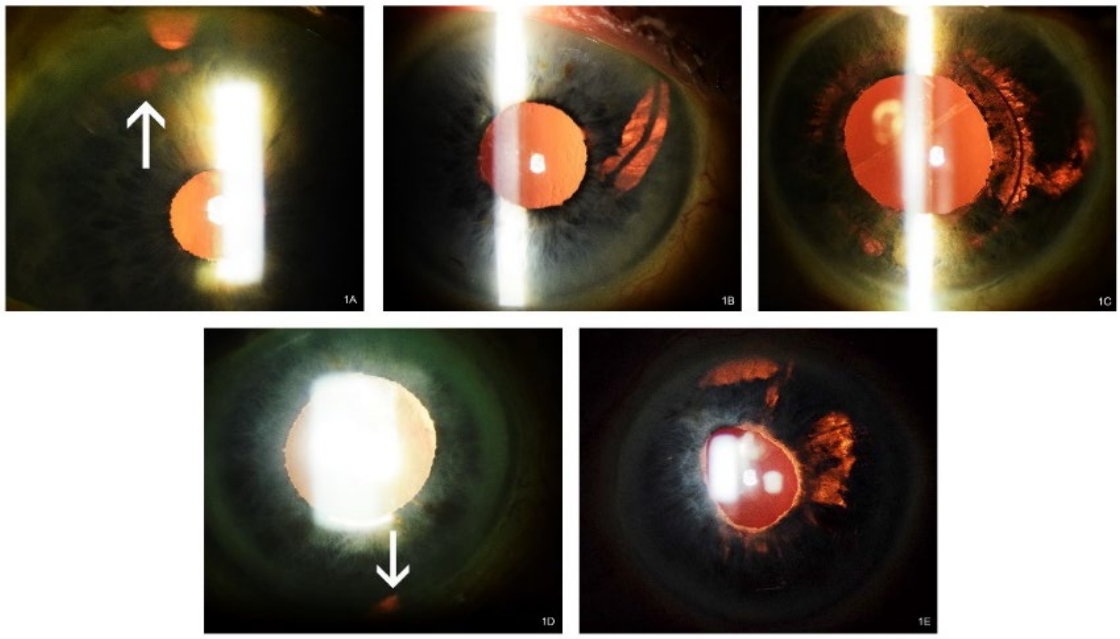


Figure 6. TIDs on slit-lamp examination: A. Formed like the optic edge of the IOL (n=2); B. Formed like the IOL haptic (n=23); C. Combination of (A) and (B), n=2; D. Defect at the iris root (n=4); E. Unspecific form (n=11); not described in detail (n=9). This figure is copied from the article [129]. Photo: Laura Armonaite.

At the beginning of UGH syndrome, many iris-IOL contact signs were isolated: 30% TID (n=21 of 71); 22.5% IOL-donesis (n=16), 4% IOL dislocation (n=3), 11% IOL decentration (n=8), 4% iridodonesis (n=3), 4% IOL partly in sulcus (n=3), and 3% pigment dispersion (n=2). One case of iris-haptic contact was seen only on UBM examination. Two patients (2.8%) did not have any iris-IOL contact signs, and 17% (n=12) patients had a mix of signs.

Iris-IOL contact signs ultimately changed over time in 44 patients, with addition of IOL-donesis, iris defects, and IOL dislocation. Finally, just before the operation (or decision not to operate), 72% (51 of 71) patients had TID, isolated or in combination with other iris-IOL contact signs, 6% (n=4) had IOL-donesis, and 48% (n=34) had mix of signs. UGH syndrome resolved spontaneously in 3 patients with IOL decentration that progressed later to a dislocation, which finally required surgery.

Isolated IOL-donesis had 16 patients in the UGH group and 2 patients in the Pseudophakic group ($p=0.001$, Fisher's Exact test). The time from diagnosis to the surgery was significantly shorter for patients with TID than with IOL-donesis: 7 months

(IQR 2–12) vs. 26 months (IQR 7–61; p=0.018, Mann-Whitney U test). Iris-IOL contact was not seen preoperatively on slit-lamp examination in two cases (see 5.3.2.)

5.3.5 Administration of blood thinners

Patients in the UGH and the Dislocated groups used the following blood thinners: Waran® (warfarin), Trombyl® (acetylsalicylic acid), Eliquis® (apixaban), Plavix® (clopidogrel), Xarelto® (rivaroxaban) and Pradaxa® (dabigatran), with no overall difference between the groups: 30 (42.2%) vs. 23 (32.3%) (p=0.100, Fisher's Exact test). There was a significant difference in Waran® use between the groups: 13 vs. 2, respectively (p=0.027, Fisher's Exact test).

5.3.6 Usefulness of diagnostic examinations

Iris-IOL contact was seen or suspected on slit-lamp examination in 69 of 71 cases (97%), on UBM examination in 3 of 14 cases (21%), AS-OCT Visante in 3 of 16 cases (19%), and SS–AS-OCT in 8 of 8 cases (100%); in the latter case, iris-IOL signs were seen on slit-lamp as well. Of the 14 patients examined with UBM, 7 had IOL or 1 haptic in sulcus; however, UBM examination detected or suspected iris-IOL contact in 3 cases. In patients with a loose IOL, UBM could not detect iris-IOL contact.

6 Discussion

6.1 STUDY I

This study shows that out-of-the-bag dislocated IOL suturing to the iris is a safe and effective surgery, with lower SIA and less post-operative visits than IOL exchange with a new IOL sutured to the sclera. The other safety and efficacy outcomes did not differ significantly from the IOL exchange.

More postoperative visits in the Exchange group than the Iris group can be explained by necessity to remove corneal sutures and complications such as choroidal effusion and intraocular hemorrhage that needed to be followed. Therefore, IOL exchange appeared to be more resource demanding than IOL suturing to the iris (Study I).

Significantly higher SIA in the Exchange group than in the Iris group can be explained by the 6-mm corneal incision in the first group. The polar value method (analysis of decomposed vectors) showed that the surgical meridian at 0° flattened significantly more in the Exchange group than in the Iris group, which is concordant with the temporal location of corneal incision and the larger incision in the Exchange group. Surgery did not induce significant rotation of the astigmatic axis in either group according to the analysis of vector KP45. Another study, which also used vector analysis method according Naeser, also reported significantly higher SIA in IOL Exchange group through 6-mm corneal incision than in pre-existing IOL suturing to the sclera.[40]

Visual outcomes of IOL suturing to the iris were the same or better in Study I than in other studies[14,16,18,47,48] as well as the number of complications.[14,16,18,20,21,23,24,47,48] Complications coming from uveal tissue (e.g., macular edema,[14,18] iritis,[18,47] pigment dispersion[47]) were not observed in Study I, which had a follow-up time of 1 year. Postoperative pupil ovalization is observed in only IOL fixation to the iris (suturing or enclavation) and not in cases with scleral fixated IOLs. In Study I, oval pupil was observed in 1 patient, but other studies have reported this complication in up to 47.7%[48] or in all patients.[21] Pupils can be rounded by pulling the edge of the pupil with 2 forceps simultaneously towards the pupil center.[127] After iris-claw IOLs surgery, oval pupils were observed in up to 32% of cases early postoperatively, which, however, lasted temporary.[43]

Sutureless IOL fixation methods have become popular recently. An alternative method to IOL suturing to the iris might be sutureless IOL fixation methods such as intrascleral fixation of the haptics of the pre-existing IOL or IOL exchange with an iris-claw IOL. However, these methods are not without disadvantages, for example, high SIA in iris-claw IOL fixation if a large (5.5–6.0 mm) corneal incision is made.[45] To diminish SIA, scleral or scleral-pocket incisions should be used;[42, 45] however, higher astigmatism often remains and is statistically significant in some analyses.[42] In contrast, SIA would not be

an issue in intrascleral fixating of a pre-existing IOL because corneal incisions are small with this method; visual results are good and the complication rate is similar to other IOL fixation methods[92], although slightly higher than IOL suturing to the iris in some studies.[92,130]

The complication rate of IOL suturing to the iris in Study I was similar or lower compared to iris-claw IOL implantation.[43,45,131] There were no cases of macular edema in Study I, which was reported in 15% of IOL exchange with iris-claw IOL.[12] Iris-claw IOL fixation has some specific complications, such as iris atrophy at IOL enclavation sites, haptics disenclavation, dull pain and trembling vision (oscillopsia).[43] However, IOL sutured to the iris is expected to dislocate due to prolene suture degradation (no such cases in Study I); theoretical survival time is estimated to be 9 years in previously aphakic eyes.[46] In contrast, iris-claw IOLs are expected to be stable life-long if they do not disenclavate, which, unfortunately, they sometimes do.[12] One more alternative to IOL suturing to the iris is to suture the IOL through the edge of the optic part to the sclera at the 12 o'clock position.

Surgery-induced refraction change was not evaluated in the Iris group in Study I; myopic shift is expected as IOL moves anteriorly after suturing it to the iris. Surprisingly, another study reported hyperopic shift after IOL suturing to the iris,[15] a finding difficult to explain. Postoperative refraction should theoretically be more predictable after IOL exchange than repositioning of the pre-existing IOL. In Study I, the myopic shift of approximately 0.6 D in the Exchange group was not statistically significant. In a randomized study, IOL exchange with an iris-claw IOL had better overall refractive predictability than suturing of pre-existing IOL to the sclera but had a tendency for hyperopic shift of +0.34 D from the intended, and 33% of patients had a refraction between +0.14 and +0.5 postoperatively.[42] From the clinical point of view, myopic shift might not necessarily be a problem if anisometropic complaints are absent. In contrast, hypermetropic shift is not beneficial for any patient.

A limitation of this study is the retrospective design. This, however, was necessary as the incidence of out-of-the-bag dislocations is low. The evaluation of SIA has limitations as well. The surgical meridian did not correspond to the preoperative steep axis of astigmatism as surgery was not aimed to reduce astigmatism. Furthermore, main surgical incision in the Iris group was not always located temporally (unlike the Exchange group). However, to be comparable with the Exchange group in analyses, the horizontal meridian at 0° in the Iris group was chosen as well.

We recommend suturing of out-of-the-bag dislocated 3-piece IOL to the iris if iris atrophy and history of uveitis or macular edema are absent. Eventual alternative methods should be evaluated in future randomized studies, namely, intrascleral fixating

of the haptics of pre-existing IOL, suturing pre-existing IOL through the optic part to the sclera, and IOL exchange with a retropupillar iris-claw IOL using scleral pocket incision.

6.2 STUDY II

Study II reports on 3-D IOL position after dislocated IOL suturing to the sclera as well as on IOL-induced astigmatism. This study shows that SS–AS-OCT is useful for IOL 3-D position measuring after IOL repositioning. The study findings also suggest that choice of in-the-bag dislocated IOL fixation method might depend on the level of capsular fibrosis.

Ab externo method to suture IOL to the sclera includes capsular bag, therefore, study II investigated whether status of the bag (i.e., fibrosis level) might impact the postoperative IOL position. It is known that the capsular bag changes after cataract surgery;[11,75] the change on histological level resembles fibrosis process and is more pronounced in bags with a dislocated IOL.[78] Study II indirectly confirms these findings as the capsular bag at the CCC opening was significantly thicker in eyes with dislocated IOL than in normal pseudophakia. However, fibrosis does not always develop. A total of 11% of cases in Study II did not have fibrosis or S ring. In patients without fibrosis, IOL tilt was twice as small in Group B (7°) than in Group A (15.5°) although without statistically significant difference, likely because of the low number of patients in this subgroup, 5 and 7, respectively. According to the power analysis, 27 patients are needed to find a difference of 5° IOL tilt between the groups. In conclusion, the question of whether capsular fibrosis impacts IOL position remains unanswered. A new study with more patients (at least 27) without fibrosis would answer whether the modified method is better than the traditional method for this subgroup. The majority of patients had moderate fibrosis, which prevents the prolene suture from gliding away from the haptic. This explains why the average IOL position was good with no difference between Groups A and B.

In the current study, IOL tilt after suturing to the sclera was higher than IOL tilt in normal pseudophakia. Probably, sample size >27 resulted in detection of a difference less than 5°. However, 3.75° difference from ordinary pseudophakia is of little clinical significance as it would induce only 0.27 D of astigmatism. Furthermore, the direction of IOL tilt was similar to that in normal pseudophakia and there was a mirror symmetry between right and left eyes. Therefore, IOL position after suturing to the sclera may be seen as acceptable, even if IOL tilt postoperatively exceeds 5°, the normal value for IOL tilt.

IOL tilt (8°) in Study II was similar or higher than IOL tilt using other fixation techniques.[34,91,92,130] For example, intrasclerally sutureless fixated IOLs were tilted by 8.4° ± 6.9° (range, 0.6°–35.8°).[91] Posterior iris-claw IOLs were tilted less, with a median of

5° (3.7°–6.2°).[90] Intrasclerally sutureless fixated IOL with Yamane technique were tilted even less (3.28° ± 3.00°).[130] In Study II, IOL position after IOL suturing to the sclera was not always predictable, with a number of outlying (higher) IOL tilt (tilt > 15° in 6.2% of cases at 1 month postoperatively), which was reported also with sutureless techniques[91] but not by all studies.[92,130] One study on sutureless technique presented IOL tilt as a median, which indicates non-normal distribution of the data and might include some outliers.[90] In summary, studies reporting on 3-D IOL position are too few to compare 3-D IOL position between IOL fixation methods. Notably, UBM measurements showed that postoperative IOL position after IOL suturing to the sclera might not be exactly the intended one if compared with IOL suturing to the iris;[17,38,52] this is inevitable considering the "blind" needle pass through the sclera. However, other IOL fixation methods also include inevitable events or complications, such as iris injuries and vitreous prolapse in IOL exchange.[13] The aforementioned randomized study reported that 15% of patients in the sclera-sutured IOL group had a little decentered IOL at the end of the surgery vs. 3% in the Exchange group with iris-claw IOL, but without worsening over 2 years, and the overall IOL position was reported equally good with both methods.[12]

There are 3 components of IOL position: tilt, decentration, and longitudinal position towards/away from retina. Astigmatism caused by IOL tilt was very low (0.075 D) in Study II, which was similar to that reported in a theoretical study where 4°of tilt induced 0.07 D.[70] In contrast, longitudinal change of IOL position in Study II (i.e., anterior shift) had substantial impact on refraction as it induced significant myopic shift of >1 D, a finding previously reported after IOL suturing behind the limbus at 1.8–2.0 mm,[13,42] a shorter distance than the 2.5 mm used in Study II. The ideal distance to enter the sulcus with a needle is 3 mm from the limbus,[132] as this distance may decrease risk for myopic change. Another option is to exchange the IOL if there is a risk for too large anisometropia postoperatively or when it is crucial to reach some specific refraction. Refractive predictability was reported to be better with IOL exchange, although not "perfect," as reported in Study I with a myopic shift of approximately 0.6 D (although not statistically significant) and in a randomized study with 33% of patients ending up slightly hyperopic.[42] A postoperative visual acuity of ≥ 0.5 (Snellen chart) was reported in 81.3% of Study II patients, which matches or supersedes results reported elsewhere.[13,27]

The modification Embracing the CCC may be used in situations other than in-the-bag IOL dislocation without capsular fibrosis. For example, fixating a dislocated plate-haptic IOL using only capsular tissue because this IOL is not designed for the suture loop technique. Also, the modification may serve to improve IOL centration, in addition to other techniques. Finally, for IOL re-dislocation, the modified method may be applied several times in the same patient if the CCC remains intact.

Prerequisites for the modified method are intact CCC and at least a moderate-sized CCC opening. Otherwise, the traditional Ab externo method should be used, eventually combined with excision of the fimotic CCC.

This study has a few drawbacks. First, the pupils were not always well dilated, so decentration of the IOL was not analyzed. However, within reasonable limits, the pupil size does not affect the IOL tilt measurements.[86,88] Second, a tilt of 30° was imputed in 2 cases in subgroup analysis based on fibrosis presence as the large IOL tilt was impossible to measure because the IOL was behind the iris. Third, fibrosis level was not quantified, although differentiation between a transparent capsular bag from the fibrotic with/without S ring was simple. Fourth, thickness of the CCC margin was measured rather than the equatorial part of the bag as the CCC margin was visible and possible to measure in most cases. The impression is, however, that the morphology of the CCC margin should represent the status of the entire bag at least to some extent. Many lost-to-follow-up patients can also be seen as limitation of the study, which led to recruitment of more patients than the power analysis suggested. This resulted in detection of smaller difference in IOL tilt (3.7°) than intended (5°) between the groups. However, this over-recruitment resulted in enough patients for the final analyses as many patients dropped out. If we had not recruited more patients than the power analysis suggested, we would have had too few participants at the final visit.

The strengths of this study include randomization, one-surgeon design, large sample size, and 3-D manner of IOL position quantification.

In conclusion, the modified method Embracing the CCC is one more alternative for IOL fixation that might be advantageous when the capsular bag is not fibrotic. Pre-existing IOL suturing to the sclera results in good IOL position and IOL induced astigmatism is generally low. The surgery is rapid, has few complications, and can be performed with local anesthesia in almost all cases. SS–AS-OCT is useful in measurement of 3-D IOL position and can be valuable in future studies evaluating IOL fixation methods.

6.3 STUDY III

Study III showed that surgical treatment does not necessarily stop UGH syndrome, however, it improves visual acuity. The study also shows that IOP≥22 mmHg at the first hemorrhage predicts a need for IOP-lowering treatment after resolution of UGH syndrome, and neither UGH syndrome duration nor surgical treatment impact this aspect. The study reports that IOL-donesis may cause UGH syndrome, and that iris defects are not specific to UGH syndrome unless they are shaped like haptic or optic's

edge. Blood thinners generally are not a risk factor, although the impact of Waran® on UGH development should be investigated further.

According to the results of Study III (n=71), there is no ideal surgery to treat UGH: neither IOL exchange nor minimally invasive surgery were fully effective. In contrast, other studies report that various surgical and conservative treatments of UGH syndrome have been successful, however, these studies were mainly case reports. [95,97,99–101,104,105,109,113,133] For example, one study reported that IOL suturing to the iris stopped UGH syndrome,[105] but study III found that IOL suturing to the iris was not effective in 1 of 3 cases. Haptic amputation was also reported as a successful treatment,[133] but Study III found haptic amputation to be ineffective in 3 of 8 surgeries as the sharp end of the remaining part of the haptic may produce a new malicious contact with the iris.

Although surgery was not always effective in Study III, visual acuity and IOP improved significantly in operated cases. However, improvements were little from clinical aspect and IOL surgery did not prevent from IOP-lowering therapy in the long run. Although conservative treatment in this study did not improve IOP results or visual acuity, UGH syndrome did not re-occur in ≥1 year in 6 patients. Some studies report conservative treatment as effective,[104] whereas others do not.[112] However, neither of the treatments guarantee that UGH syndrome has ceased: resolution of UGH syndrome might be mistaken for a pause between UGH episodes. In Study III, the longest time between 2 hemorrhages was 2.7 years, and re-occurrence after the first surgery took 2.3 years at the longest.

Secondary glaucoma is a complication of UGH, which can cause blindness. In Study III, IOP increase requiring therapy (or therapy change) was observed not only under the UGH manifestation but also after UGH resolution. The latter finding indicates that UGH syndrome can irreversibly increase the IOP. Furthermore, initiation or increase of IOP-lowering therapy was seen twice as often under ongoing UGH manifestation than in the Dislocated group, which may be explained by iritis, hemorrhage and pigment dispersion probably exaggerating the IOP-increasing effect. Other studies also report that IOP increases during active UGH syndrome,[94,97,100–102,105,112,116] but Study III is the first to systematically analyze IOP issues, including the period after UGH resolution.

Clinical opinion that long duration of UGH syndrome negatively impacts IOP was not supported by Study III. Other factors might be more important such as the number of episodes, the extent of the hemorrhage, and the intensity of iritis; however, these are difficult to quantify. The IOP at the first hemorrhage was a risk factor for the need for IOP-lowering treatment after the resolution of UGH syndrome, according to results in the current study. The reason for this relationship should be investigated further. Limitations of these analyses are as follows. One may wonder whether the first hemorrhage was really the first one, with prior hemorrhages remaining undiagnosed.

Probably, however, the first hemorrhage was indeed the first one, since even small hemorrhages usually result in sudden and marked symptoms, and patients seek the doctor. Another limitation is a risk to include patients with undiagnosed primary glaucoma. Risk for missing primary glaucoma that started ***soon*** *after* cataract operation is not big because all patients underwent ophthalmological examination before and after their cataract procedure, which was performed in average of 6 years before the UGH syndrome. However, it may be more difficult to find undiagnosed primary glaucoma ***a few years*** *after* cataract surgery. In this study, all cases with IOP increase that started ***after cataract surgery*** were analyzed as "secondary to UGH syndrome", because it is hardly possible that primary glaucoma would have started ***during*** *UGH* or *directly* ***after*** *UGH resolution*. There were no patients in this study with normal IOP during UGH, whose IOP started to increase after UGH resolution. PEX are associated with open angle glaucoma development, but there was no data on PEX or other risk factors for primary glaucoma in medical charts. In conclusion, increased IOP in UGH group seemed to be related to UGH syndrome, not with eventual undiagnosed primary glaucoma.

Study III found a large variety of iris-IOL contact signs. Absence of iris-IOL contact on slit-lamp examination (2 cases in this study) is rare, however, it does not rule out UGH syndrome. Study III found one type of IOL malposition–i.e., IOL with one haptic or the entire 1-piece IOL in the sulcus–only in cases with UGH, which is a known risk factor for developing UGH syndrome.[134–136] Such IOL implantations should be avoided. However, even those IOL malpositions sometimes do not cause UGH syndrome.

Surprisingly, the iris-IOL contact itself does not always result in UGH, which was shown in Study III. In the Dislocated group, the preoperative IOL position deviated greatly from the normal, sometimes with iris defects (and only 4 of 19 patients underwent some other surgery previously), although these patients did not develop UGH (Fig. 7). One may hypothesize that a specific contact between the iris vessel and the IOL is required to develop UGH, and that the IOL should be mobile at least to some degree.

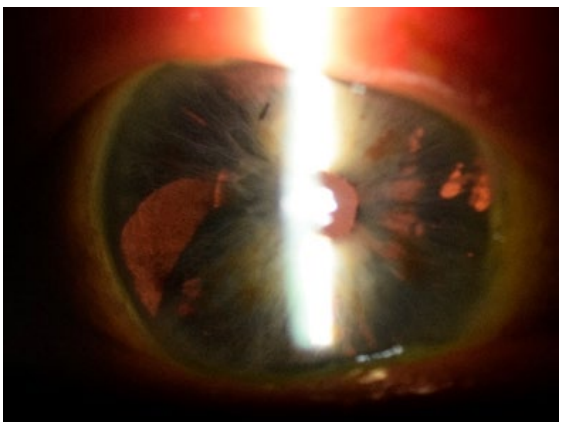


Figure 7. Iris defects in eye with dislocated IOL without a history of UGH syndrome. Photo: Laura Armonaite

One mechanism of UGH syndrome, zonular laxity, causes IOL mobility (IOL-donesis), which has been reported also in previous studies.[100,105] In Study III, isolated IOL-donesis was seen in 22.5% of cases at the beginning of UGH syndrome. Notably, patients in the UGH group with IOL-donesis waited for the surgery 4 times longer than patients with TIDs–i.e., it seems that clinicians tend to underestimate the importance of IOL-donesis for UGH development. In contrast, the shape of TID was more important than just presence/absence of TID–the haptic or optic edge formed TID should be seen as specific to UGH syndrome, as opposed to other forms of TIDs. To our knowledge, study III is the first study to systematically classify and analyze iris-IOL contact signs and TID shapes, while other studies only mention TID as a part of UGH syndrome.[97,99,103,105,109,134,135] It has been known that TID may be absent in UGH syndrome, [104,113] a finding confirmed in Study III.

In the current study, patients with UGH syndrome did not use blood thinners more frequently than the control group, except of Waran® (warfarin). Mechanism of inhibiting blood clotting system is different in direct and indirect anticoagulants and antiplatelets. Waran® has less predictable effect on anticoagulation and therefore needs monitoring of INR; bleeding during treatment with Waran® was 5 times more frequent than without Waran® therapy.[137] Probably the iris-IOL contact is more important for developing UGH syndrome than a status of a blood coagulation system; however, the latter might be more important if a patient uses Waran® (Study III). A new study with analysis of INR value in Waran® users may answer the question.

In Study III, clinical examination was more useful for diagnosing UGH syndrome than UBM or AS-OCT. UBM usually visualizes haptics well.[17, 38, 52] In cases with a loose IOL, the haptic probably moves away from the iris under UBM examination, which is performed while the patient is in a supine position. This might explain why UBM could not detect iris-IOL contact in many patients in the current study. In other types of IOL malpositions, UBM is reported to be useful[98,136] and might be useful also in loose IOL cases if performed in different head positions.[108] UBM fail to detect iris-IOL contact rarely (e.g., in only 1 of 10 patients where IOL was placed in the sulcus).[98] In contrast, AS-OCT (also SS–AS-OCT) fail to detect iris-IOL-haptic contact always as it cannot visualize IOL part under the iris; only the tilt of the IOL optic part can be detected. However, authors of the other study preferred AS-OCT to UBM in diagnosing UGH syndrome.[138]

One of limitation of Study III is retrospective design, which usually includes missing or inaccurate data, inability to determine the incidence and causative relationships when testing hypotheses. For example, data on visual field or macular edema were absent in many patients in this study. In addition, IOL-iris signs were what an ophthalmologist saw on slit-lamp examination but not necessarily the actual status of the eye. Only a randomized study can answer which UGH syndrome treatment is most effective. However, randomization is not possible to conduct as incidence of the syndrome is very

low. The latter problem was solved with retrospective design that made it possible to collect 71 cases of UGH syndrome, which gave a full picture of UGH and allowed statistical analyses of hypotheses.

Regarding IOP-lowering therapy after the resolution of UGH, one may wonder whether these patients continued the therapy only because the drops were "forgotten" to be discontinued by an ophthalmologist. To check this, additional inspection of the material was performed. In available material of 13 cases, it was the ophthalmologist who made the decision to continue IOP-lowering therapy on every follow-up. In 5 of these cases, IOP increased despite existing glaucoma therapy or when the therapy was discontinued. Secondary glaucoma with glaucomatous optic discs and visual field defects was diagnosed in 4 patients. One patient became severely ill and died after the last visit. In 3 other cases, glaucoma therapy was continued by the ordination of the ophthalmologist although the detailed motivation could not be found.

In summary, clinical manifestation of UGH syndrome varies greatly and can mimic other ocular diseases. UGH syndrome should be treated surgically, but the final choice between surgical or conservative treatment should be made individually on each patient. Long follow-up (several years or lifelong) is necessary, since IOP increase might be permanent after UGH syndrome resolution in many patients, and a long pause between UGH episodes might be mistaken for resolution of UGH. A new study would answer which type of IOL surgery is most effective in UGH syndrome treatment and whether Waran® use is associated with UGH development in eyes with iris-IOL contact.

7 Conclusions

Study I: Out-of-the-bag dislocated IOL suturing to the iris is a safe and effective method with less corneal SIA and fewer postoperative appointments than IOL exchange.

Study II: The 3-D IOL tilt after in-the-bag dislocated IOL suturing to the sclera is approximately 8° in the inferotemporal direction in most cases and differs on average by 3.75° from the normal IOL position. This difference has little clinical significance as IOL-induced astigmatism from IOL tilt is low, 0.075 D for each degree of IOL tilt. However, postoperative myopic shift is common if IOL is sutured to the sclera 2.5 mm behind the limbus. The modification Embracing the CCC is a novel alternative for IOL fixation to the sclera that might be used also for cases with a non-fibrotic capsular bag. SS–AS-OCT is useful for quantifying the 3-D IOL position.

Study III: Surgical treatment of UGH syndrome is effective in 77% of patients. Various types of IOL malposition can cause UGH syndrome, and absence of visible iris-IOL contact on examination does not rule out this condition. IOL-donesis is a risk factor for developing UGH syndrome. Presence of iris defects is not specific to UGH syndrome, unless they are formed like a haptic or optic edge. Patients with UGH syndrome used Waran® more frequently than patients in the Dislocated group. Approximately half of patients with UGH syndrome may need IOP-lowering therapy in the long run after UGH resolution; the predictors for this therapy is IOP≥22 mmHg at the first hemorrhage, but not UGH duration or IOL surgery. All patients with UGH need a long follow-up time after UGH resolution.

8 Points of perspective

After finishing this thesis, I think it would be valuable to further deepen knowledge on several topics. Studies I and II analyzed the pre-existing IOL repositioning. It would be useful to evaluate the alternative treatment, for example, IOL exchange with sutureless methods in a new randomized study. So far, only one randomized study has compared pre-existing IOL fixation using sutures and sutureless IOL exchange; the study found that long-term visual results and complications did not differ between the groups[12] except for better refraction predictability and tendence (with borderline significance) for more IOP decrease in the exchange group. However, the latter group had tendency for larger SIA and more iris injuries and intraoperative vitreous prolapse.[12,13,39,42, 139,140] It is difficult to generalize these conclusions because a very experienced surgeon performed all surgeries, which can be seen as both strength and a limitation of the study. Therefore, more randomized studies are needed to evaluate which method has better outcomes– sutureless IOL exchange or fixation of the pre-existing IOL using sutures.

Out-of-the-bag dislocated 3-piece IOL suturing to the iris showed good results in Study I. Two alternatives should be evaluated in future studies: pre-existing IOL suturing to the sclera through the optic edge and pre-existing IOL fixation into scleral tunnels.

There were too few patients without capsular fibrosis in Study II; however, obvious tendency for better IOL position was observed using the method Embracing the CCC. A new study including more patients without capsular fibrosis would answer whether the modified method is better than the traditional one in terms of IOL position in this subgroup. The other applications of the modified method should also be studied further, such as plate-haptic IOL suturing to the sclera or correcting position of the already sutured IOL using other methods.

Study II showed that SS–AS-OCT is useful in quantifying IOL tilt larger than normal, although accuracy and repeatability of this measurement, especially in eyes with small pupils, should be investigated in future research as well as the capacity of this SS–AS-OCT to measure ocular tissues. Furthermore, theoretically, polar vector methods to calculate corneal astigmatism can be applied to calculate IOL-induced astigmatism, which was employed in Study II. A more thorough investigation of these methods would be useful.

To my knowledge, Study III is the largest study on UGH syndrome to date. The study' size enabled testing of various hypotheses and perform statistical analyses. Further investigations on IOP increase despite UGH resolution and the mechanism could be useful. Additionally, analysis with included INR value would clarify whether Waran® is a risk factor for developing intraocular hemorrhage in eyes with iris-IOL contact and whether treatment with Waran® should be adjusted in these patients. IOP increase and

secondary glaucoma should be studied also in patients with dislocated IOL without UGH.

Many types of surgeries were included in Study III, but none was completely effective in stopping UGH syndrome. A new study should be conducted to answer which type of IOL surgery is most effective (or at least more effective) in treating UGH syndrome.

Surgery of dislocated IOLs is not a standardized mass-production surgery; it rather resembles intellectually creative process, and comprises endless opportunities to develop surgical techniques and to perform scientific research.

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