

Multifocal intraocular lenses and cystoid macular edema: a multicenter study

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OBJECTIVE: We evaluated a large case series in order to determine the incidence and development of clinical cystoid macular edema (CME) associated with the implantation of two multifocal intraocular lenses: Acri.LISA 366D (Carl Zeiss Meditec) and AcrySof ReSTOR SN6AD3 (Alcon Laboratories, Fort Worth, Texas, USA).

SETTING: Multicenter study involving several European eye clinics.

METHODS: We performed a multicenter (European Eye Institute, Baviera Group), retrospective, comparative study of 10,390 pseudophakic eyes from 5,195 patients who underwent multifocal intraocular lens implantation between January 2009 and January 2012. The exclusion criteria included a history of diabetic retinopathy, ocular trauma, intraocular surgery, vitreous loss during cataract surgery, previous CME, uveitis and vitreoretinal disease.

RESULTS: We implanted 7,682 Acri.LISA 366D lenses and 2,708 AcrySof ReSTOR SN6AD3 lenses. The incidence of clinically significant CME was 0.12% in the Acri.LISA group and 0.18% in the Acrysof ReSTOR group. No statistically significant differences in the incidence of CME were detected between the groups ($P = 0.41$).

CONCLUSIONS: The analysis of this large number of implanted multifocal lenses confirms that the incidence of clinically relevant macular edema was not significantly different between the two lenses.

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In 1953, Irvine reported an association between the loss of visual acuity (VA) and vitreous and macular alterations after intra- or extra-capsular cataract surgery¹. In 1966, Gass and Norton used fluorescein-based and angiographic studies to evaluate patients who had undergone these procedures, and found a characteristic petaloid pattern in the macula².

The incidence of cystoid macular edema (CME) diminished after the abandonment of extra-capsular surgery and improvement in phacoemulsification techniques. Clinically significant CME, defined as a Snellen VA of 20/40 or worse and the presence of cystoid spaces in the macula with a significant increase in its thickness, has been reported to occur in 0.1%-2.3% of cases after uncomplicated phacoemulsification with an implanted monofocal intraocular lens (IOL)^{3,4}. This incidence may increase to 2.5% after posterior capsulotomy with neodymium-doped yttrium aluminium garnet laser (Nd:YAG)⁵. Other factors, such as preexisting diabetic retinopathy or uveitis may

increase the incidence to 12% during the first month after phacoemulsification, even in uneventful cataract surgery^{6,7}.

CME may be associated with other ocular diseases such as Behçet's syndrome, ocular toxoplasmosis, Eales' disease, Vogt-Koyanagi-Harada syndrome, retinal vein occlusion, scleritis, ocular trauma, retinal dystrophy, or age-related macular degeneration⁷.

To our knowledge, the present article reports the results from the largest series of CME associated with multifocal IOL implantation in different eye care centers belonging to the same medical institution (Clinica Baviera European Ophthalmological Institute). Cases were retrospectively reviewed to compare the incidence of clinical CME between two multifocal intraocular lenses with different materials and properties that could lead to a variable incidence of clinical CME.

PATIENTS AND METHODS

The current report adheres to the tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants prior to surgery. The Ethics Committee of Clinica Baviera Group approved the study protocol.

Based on the computerized medical records of Clínica Baviera European Ophthalmological Institute (a private ophthalmology institution with 66 centers throughout Europe), we designed a multicenter, retrospective and comparative study to examine a large series of patients who underwent implantation of either of two multifocal IOLs—Acri.LISA 366D (Acri.Tec AG) and AcrySof ReSTOR SN6AD3 (Alcon, Laboratories Fort Worth, Texas, USA)—between January 2009 and January 2012 (36 months).

Computerized medical records enabled those patients with a clinical history of previous ocular surgery, ocular diabetes, previous retinal vascular alteration or episodes of uveitis that could lead a higher incidence of CME to be ruled out. We also excluded those cases with surgical complications during cataract surgery that could facilitate the development of CME (e.g., posterior capsule rupture or vitreous prolapse) and patients with decreased VA throughout the postoperative period caused by corneal edema, ocular hypertension, inflammation in the anterior chamber, posterior capsule opacification, and tilt or any other alteration in the centering of the IOL.

The inclusion criteria were loss of two or more lines with best spectacle-corrected VA and CME verified by optical coherence tomography (OCT) as the only cause of the decrease in VA.

After removing patients who had any exclusion criteria, we analyzed 10,390 eyes from 5,195 consecutive patients who underwent a clear lens or cataract refractive surgery procedure with bilateral implantation of Acri.

LISA 366D (n = 7,682 eyes) or AcrySof ReSTOR SN6AD3 (n = 2,708 eyes).

In both groups, data on previous cataract or clear lens refractive surgery were verified. All centers used the same pre-surgical examination protocol: monocular and binocular best spectacle-corrected and uncorrected distance VA (recorded at 6 m under photopic conditions), monocular and binocular best corrected and uncorrected near VA (at 33 cm with a Jaeger chart), and binocular best corrected intermediate VA at 70 cm. Endothelial cell density was measured using the Specular Microscope SP300P (Topcon Corporation), and corneal topography (Orbscan II, Bausch & Lomb Inc), central ultrasonic pachymetry, and ultrasound biometry (Ocuscan RxP, Alcon Inc) were determined. The retina was studied prior to surgery under cycloplegic conditions.

All patients were instructed to administer topical moxifloxacin, tobramycin, and diclofenac 4 times daily during the 3 days before surgery. Surgical procedures were performed under topical anesthesia by experienced surgeons using the phacoemulsification technique with a clear corneal incision measuring 2.8 mm to 3.2 mm. Phacoemulsification was followed by irrigation and aspiration of the cortex, and Acri.LISA 366D or AcrySof ReSTOR SN6AD3 was implanted and centered in the capsular bag. The time between surgeries on the first and second eye was one week.

Acri.LISA 366D is a bifocal biconvex refractive-diffractive single-piece IOL with a 6.0 mm foldable acrylate aspherical optic and an overall diameter of 11.0 mm. Incident light is distributed with 65% for distance focus and 35% for near focus. The IOL has an aspherical profile to correct positive spherical aberration of the cornea. The optic is made of acrylate with 25% water content and ultraviolet wavelength-absorbing properties. The hydrophobic surface has sharp edges to reduce posterior capsule opacification. The IOL incorporates a +3.75 D near add power, corresponding to approximately +3.00 D in the spectacle plane.

AcrySof ReSTOR SN6AD3 has an aspheric profile. The apodized diffractive region is within the central 3.6 mm optic zone. The refractive part of the optic surrounds the apodized diffractive region. This area directs light to a distance focal point for larger pupil diameters and is dedicated to distance vision. It incorporates a +4.00 D near add power corresponding to approximately +3.20 D in the spectacle plane. In addition to the ultraviolet light filter, the material of this IOL includes a blue-light filter, which filters the 400–475 nm blue light wavelength.

Postoperative medication included topical tobramycin, moxifloxacin, and diclofenac 4 times daily for 2 weeks. Dexamethasone eyedrops were administered 4 times daily during the first week, 3 times daily during the second week, twice daily during the third week, and once daily during the fourth week.

Patients were scheduled for evaluation 1 day, 1 week, 1 month, and 3 months after surgery. The examination included manifest refraction, slit lamp biomicroscopy (with special emphasis on the centering and tilt of the IOLs), binocular indirect ophthalmoscopy, and tonometry. VA was measured as before the phacoemulsification refractive surgery: in monocular and binocular uncorrected and best spectacle-corrected at 6 m (distance VA), at 33 cm (near VA), and at 70 cm (intermediate VA) under photopic conditions.

Patients with significant loss of VA (> 2 lines) underwent OCT (Stratus OCT™, Carl Zeiss Meditec) to confirm the presence of clinically significant CME and rule out other possible causes. In patients with a diagnosis of CME, visits were scheduled 24 hours after starting topical and/or systemic treatment, at 1 week, at 1 month, and at 3 months to verify the effectiveness of treatment and the outcome of CME.

The statistical analysis was performed using SPSS software (version 19.0, SPSS Inc). The Chi-squared test was used to compare the incidence of CME between the two groups studied. The null hypothesis (Ho) was established as the absence of differences; the alternative hypothesis (Ha) was established as the presence of differences in the incidence of CME. We designed a 2 × 2 contingency table with 1 degree of freedom. Statistical significance was set at $P < 0.05$. If ≥ 2 expected incidence values were smaller than 5 cases, Yate's correction was applied. The unpaired t test was used to compare group means with a significance level of 0.05. The Kolmogorov-Smirnov test was used to confirm the normal distribution of the demographic samples. Continuous variables were described as mean \pm standard deviation (SD), with minimum and maximum values.

RESULTS

The study sample included 10,390 procedures: 2,708 with AcrySof ReSTOR SN6AD3 (26.1%) and 7,682 with Acri.LISA 366D (73.9%). No statistically significant differences ($p < 0.05$) were found between the groups for age or sex. Demographic characteristics are shown in Table 1.

Five cases of clinically significant CME were found in the AcrySof ReSTOR SN6AD3 group (incidence of 0.18%); 9 cases were identified in the Acri.LISA 366D group (incidence of 0.12%). No statistically significant differences were found for development of clinical CME (for a significance level of $P < 0.05$ and a Chi-squared value of 0.68, we must accept the null hypothesis: there are no differences). No statistically significant differences were observed when both groups were stratified by age, spherical equivalent refraction, or axial length of the eye (t test, $P < 0.05$). Table 2 summarizes the data from cases of CME in both groups.

Table 1. Demographic characteristics of the study groups.

	AcrySof ReSTOR+3D	Acri.LISA366
Number of MTF IOLs (n = 10,390)	2,708 (26.1%)	7,682 (73.9%)
Gender		
Female (%)	51.8	53.4
Male (%)	49.2	47.6
Age		
Mean age (y) \pm SD	52.1 \pm 8.5	56.3 \pm 10.6
IOL Power		
D \pm SD	23 \pm 1.8	22.7 \pm 2.2
MTF IOLs: multifocal intraocular lenses; D = diopters; SD = standard deviation		

Common in both groups, the main and initial symptom was a patient-reported decrease in VA without pain or other clinical manifestations. In the medical records studied, the loss of VA was recorded 48 hours after surgery to 51 days with an average of 35.2 ± 12.4 days. OCT was performed to confirm the diagnosis in each doubtful case. The OCT images revealed an average foveal thickness of 327.5 ± 28.9 microns in the Acri.LISA group and 315.6 ± 33.1 microns in the AcrySof ReSTOR SN6AD3 group. The VA at this initial clinical stage, determined on a decimal scale, was 0.28 ± 0.18 in the AcrySof ReSTOR SN6AD3 group and 0.48 ± 0.06 in the Acri.LISA 366D group. Presentation was bilateral in all cases in the AcrySof ReSTOR group and in 8 cases in the Acri.LISA 366D group (88.9%). Only one case had unilateral involvement (11.1%).

Regardless of the lens implanted, all cases of CME were treated with the topical non-steroidal anti-inflammatory drug (NSAID) ketorolac tromethamine 0.5% 4 times daily for at least 8 weeks in combination with topical corticosteroids (dexamethasone 1%) 4 times daily during the first week and reducing this dose to once per day in the following weeks. In 1 case (Acri.LISA group), an oral corticosteroid was also used (deflazacort 30 mg) for 4 weeks. Finally, in 4 of the 5 cases in the AcrySof ReSTOR group and in 3 of the 9 cases in the Acri.LISA group, oral acetazolamide (carbonic anhydrase inhibitor) was added for 1 month at 500 mg/d.

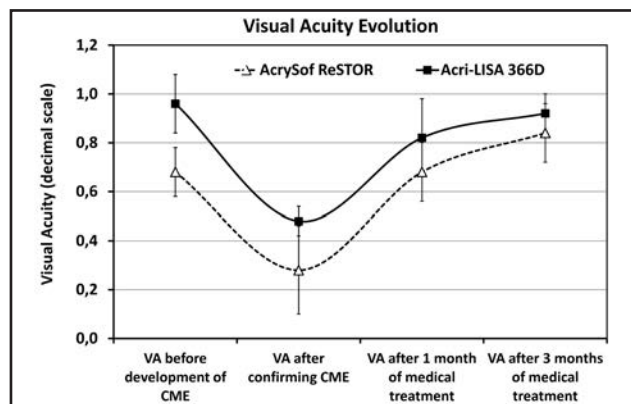
One month after beginning treatment, the mean VA had improved to 0.68 ± 0.12 in the AcrySof ReSTOR group and to 0.82 ± 0.16 in the Acri.LISA group. During the second month, all patients maintained ketorolac eye drops 4 times daily until 8 weeks with topical NSAIDs. Three months after the first CME symptom, the mean VA was 0.84 ± 0.12 in the AcrySof ReSTOR group and 0.92 ± 0.08 in the Acri.LISA group. Figure 1 summarizes the outcome for VA in both groups.

The OCT scan performed 3 months after the first CME symptom showed decreased macular thickness

Table 2. Clinical characteristics of the patients diagnosed with CME.

	AcrySof ReSTOR+3D	Acri.LISA366	P Value
CSME cases (n)	5	9	0.410 (*)
Gender			
Female (n)	2	5	0.573 (*)
Male (n)	3	4	
Mean age (y) ± SD	52.3 ± 8.64	56.23 ± 10.51	0.531 (*)
Pre-surgical mean SE (D) ± SD	+1.95 ± 3.59	+1.02 ± 2.88	0.606 (*)
max.	+5.75	+5.50	
min.	-2.25	-2.25	
OCT macular thickness			
Mean ± SD (µm)	315.6 ± 33.1	327.5 ± 28.9	0.457 (*)
Mean axial length (mm)			
Mean ± SD	23.37 ± 1.49	22.56 ± 0.82	0.208 (*)
max.	25.28	23.94	
min.	21.77	21.25	

CSME = clinically significant macular edema; sd = standard deviation; SE = spherical equivalent; D = diopters.
 (*) Chi square test with one degree of freedom
 (†) Unpaired *t* test

**Figure 1.** Chart showing visual acuity between the two groups of multifocal lenses studied. VA, visual acuity; CME, cystoid macular edema.

in both groups. The mean foveal thickness was 157.4 ± 15.2 microns in the AcrySof ReSTOR group and 163.1 ± 12.1 microns in the AcriLisa 366D group. VA did not improve in only 1 case in the Acri.Lisa group (0.4 on the decimal scale), even though the patient had received the same treatment as the others. Foveal thickness determined by OCT was 278 ± 21 microns, and total macular volume was 6.8 mm^3 in the right eye (Figure 2). This case was followed until the ninth week after the first CME symptom. As no further data were recorded in the medical record, the case was considered lost to follow-up.

DISCUSSION

In cataract surgery or clear lens surgery (refractive lensectomy), multifocal, bifocal, and accommodative intraocular lenses address the challenge of emmetropia at different focal distances. The safety of and satisfaction with multifocal lenses have been widely compared. However, as is the case in patients with pseudophakia after implantation of monofocal lenses, CME remains a frequent cause of loss of VA after uncomplicated phacoemulsification.

Many reports present the incidence of pseudophakic CME and monofocal IOLs, although very few refer to the incidence of clinical CME in eyes with multifocal IOL implants. We performed a literature search of all articles available on the Medline and Scopus databases using the keywords “cystoid macular edema” and “multifocal intraocular lens”. We reviewed original and review articles on any type of multifocal IOLs, as well as letters and case reports, from January 1995 to October 2012. The published incidence of pseudophakic clinical CME after implantation of a multifocal IOL ranges from 1% to 2%^{7,8}.

Our retrospective series of 10,390 pseudophakic eyes revealed a lower incidence of clinical CME: 0.12% after implantation of AcrySof lenses and 0.18% after implantation of Acri.LISA lenses. The finding of a lower incidence of clinical CME than in previous reports could be due to variations in patient populations with

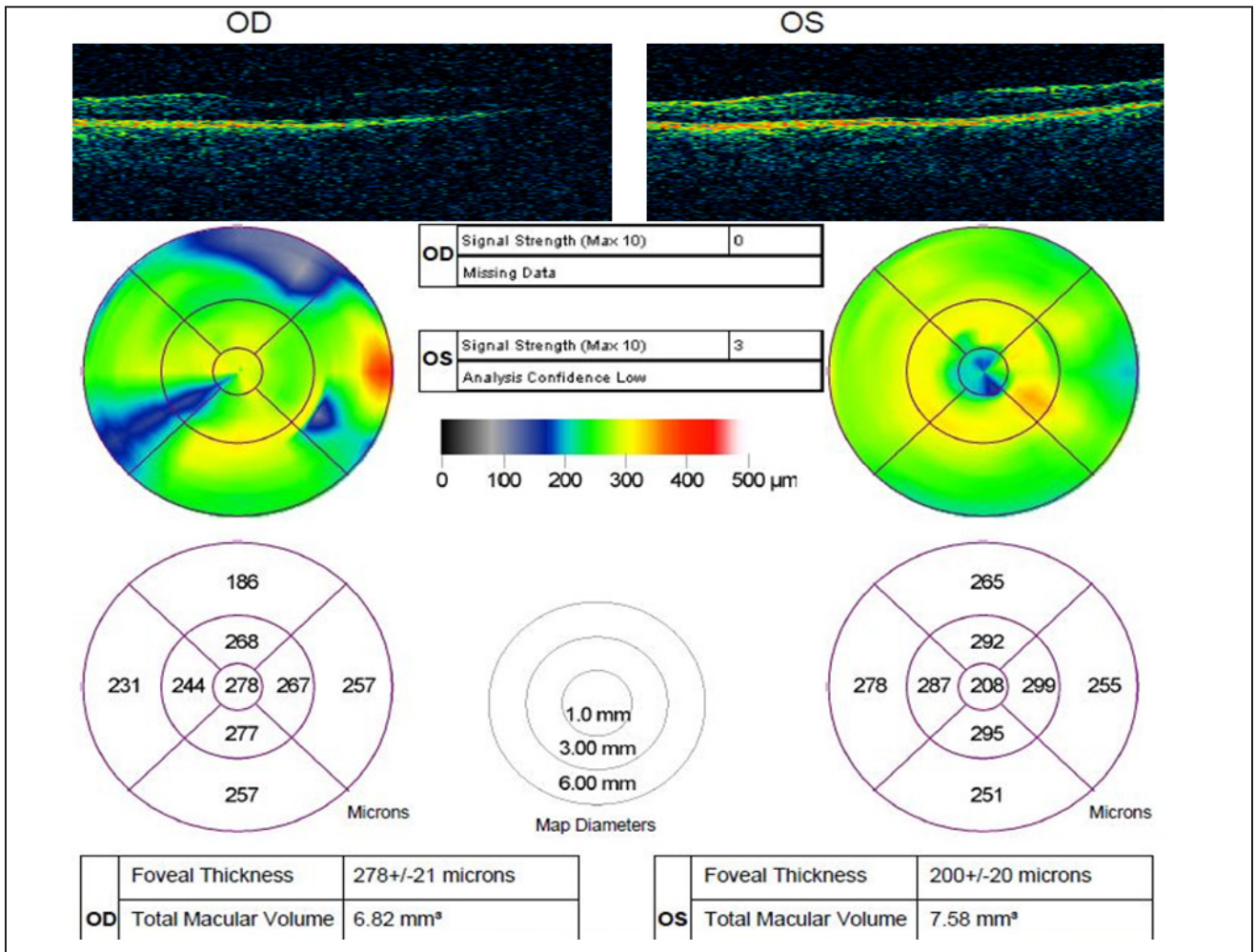


Figure 2. OCT image showing incomplete resolution of CME after medical treatment.

different risk factors and the use of different methods and criteria for evaluating macular thickening. Another factor that contributes to the uncertain incidence is the use of different prophylactic medications before and after surgery⁹. Furthermore, it is important to note that in the present study, the OCT was performed when there was a patient-reported decrease in VA, so we might have misdiagnosed cases with subclinical CME but not with clinical CME, which was the scope of our study.

When macular thickness before and after implantation is compared, our results may be limited by the absence of an OCT scan before surgery. In most eyes, macular thickness increases after cataract surgery, with no significant decrease in VA (subclinical CME). In our study, OCT was performed when VA diminished by at least 2 lines; therefore, the presence of subclinical CME may have led to underdiagnosis. However, analysis of subclinical CME is beyond the scope of this study. Eyes that develop clinically relevant CME (defined as loss of 2 or more lines of VA) show substantial increases in macular thickness. Applying an increase of at least 40% in retinal thickness from baseline in OCT may be a valid, objective,

and uniform method of defining clinically relevant CME. Preoperative and postoperative OCT evaluations in eyes at high risk for CME (diabetes, uveitis) may be warranted. These criteria were used by Kim et al. to demonstrate clinically significant CME using the OCT technique in high-risk eyes³. In our study, OCT was not performed before cataract surgery; therefore, it was not possible to compare the previous macular thickness value with the post-surgery value. In our opinion, this is not a limitation, because patients with a history that could favor development of CME were not included in the study or in the data analysis.

The second objective of this study was to identify differences between the two most widely implanted multifocal IOLs in our group of eye care centers, namely Acri.LISA and AcrySof ReSTOR SN6AD3. In this respect, differences between the properties and material of both multifocal lenses could lead to a variable incidence of CME or other retinal damage. For example, in addition to the standard UV-light filtering of the Acri.LISA IOL, AcrySof ReSTOR SN6AD3 includes a blue light-filtering chromophore which filters light in a manner

that approximates the human lens in the 400-475 nm blue-light wavelength that could activate the lipofuscin in the retinal pigment epithelium, thus preventing possible damage by photooxidation^{10,11}.

Our results may also have been affected by differences in the design of the haptics platform: L-modified haptics in AcrySof ReSTOR SN6AD3 and a plate haptic design in Acri.LISA. In theory, L-modified haptics feature a lower tensile strength and can withstand more deformation than other designs. Their greater stability in the capsular bag means that they could have less effect on the vitreous cavity during implantation and stabilization of the lens. However, the role of accommodation during the early postoperative period may facilitate development of clinical CME after diffractive IOL implantation^{12,13}.

Despite these differences, the statistical analysis revealed no significant differences in the incidence of CME ($P = 0.410$). It also showed that hydrophilic or hydrophobic acrylic material generally has appropriate uveal and retinal biocompatibility^{14,15}. However, our intensive and thorough review of the literature revealed no reports on the development of CME after implantation of Acri.LISA 366 or AcrySof ReSTOR SN6AD3; consequently, we are unable to compare our results with those of other authors.

Although spontaneous resolution can potentially occur in up to 80% of cases between 3 and 12 months after the first symptoms, treatment with NSAIDs, carbonic anhydrase inhibitors and topical corticosteroids was initiated to prevent the development of chronic symptoms and restore adequate VA as quickly as possible. Chronic and refractory CME remains a therapeutic challenge. Experimental anti-vascular endothelial growth factor agents (Anti-VEGF) should be considered for nonresponsive and persistent pseudophakic CME^{8,16-18}. The treatment-refractory case described in the present study, which was found in the Acri.Lisa group and was labeled as lost to follow-up, could have benefited from intravitreal injection of triamcinolone or treatment with Anti-VEGF.

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