

Anterior Subcapsular Opacities and Cataracts 5 Years After Surgery in the Visian Implantable Collamer Lens FDA Trial

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ABSTRACT

PURPOSE: To use the techniques of survival analysis to analyze the incidence of anterior subcapsular opacities (symptomatic and asymptomatic) and clinically significant cataract in the US Food and Drug Administration clinical trial of the Visian Implantable Collamer Lens (ICL).

METHODS: Five hundred twenty-six eyes were followed for an average of 4.7 years; 89% (468 eyes), 73% (384 eyes), and 59% (311 eyes) were seen at 3, 4, and 5 years or later, respectively. Anterior subcapsular opacities were defined as trace or more (≥ 0.6 LOCS III opacity). Clinically significant cataract required loss of 2 or more lines of best spectacle-corrected visual acuity (BSCVA), a significant increase in glare symptoms, or cataract extraction. Kaplan-Meier analyses of opacities and cataract were performed.

RESULTS: The Kaplan-Meier cumulative probability estimate for anterior subcapsular opacities over 7+ years of follow-up was 7% whereas 31 (5.9%) eyes were actually observed. Anterior subcapsular opacities generally occurred early with 58% seen in the first year, 68% in the first 2 years, and 74% in the first 3 years. The cumulative probability estimate for clinically significant cataracts over the 7+ years of follow-up was 2% whereas 7 (1.3%) were actually observed. The difference between the Kaplan-Meier estimate and the actual observed percentage is due to the fact that the former takes into account the differences in postoperative follow-up time of individual eyes. Preoperative myopia (>12.00 diopters) and patient age (>40 years) were significant factors in the development of cataract. No loss of BSCVA was observed in any eye following cataract extraction.

CONCLUSIONS: Approximately 6% to 7% of eyes develop anterior subcapsular opacities at 7+ years following ICL implantation but only 1% to 2% progress to clinically significant cataract during the same period, especially very high myopes and older patients. Visual outcome following cataract extraction was good. [*J Refract Surg.* 2007;xx:xxx-xxx.]

The most commonly reported complication with the Visian Implantable Collamer Lens (ICL; STAAR Surgical Co, Monrovia, Calif) has been the development of lens opacities.¹⁻⁴ We previously reported the rate of asymptomatic and clinically significant cataracts in the US Food and Drug Administration (FDA) trial when patients averaged 17 months of follow-up⁵ and at the completion of follow-up in the clinical trial when 369 of the 526 eyes had been followed for 3 years.⁶ In the latter report, 14 (2.7%) eyes had anterior subcapsular lens opacities of trace (LOCS III) or greater and 2 (0.4%) of these were clinically significant cataracts.

The Visian ICL is a posterior chamber phakic intraocular lens (IOL) designed to vault anteriorly to the crystalline lens. This article addresses the incidence and severity of lens opacities and clinically significant cataracts with the current V4 ICL design. The now discontinued V3 ICL design, which had substantially less vaulting away from the crystalline lens, had a greater incidence of lens opacities.^{7,8} This report documents the incidence of asymptomatic and clinically significant anterior subcapsular opacities with longer patient follow-up.

PATIENTS AND METHODS

The US FDA clinical study of the STAAR ICL for myopia was a prospective, nonrandomized clinical trial initiated in May 1997. Twelve clinical sites across the United States enrolled 526 consecutive eyes of 291 patients between November 11, 1998 and July 25, 2001. Standardized inclusion and exclusion criteria were used for study enrollment by all clinical investigators.⁹

The Visian ICL study was originally designed as a 3-year follow-up study; however, as part of the US FDA approval

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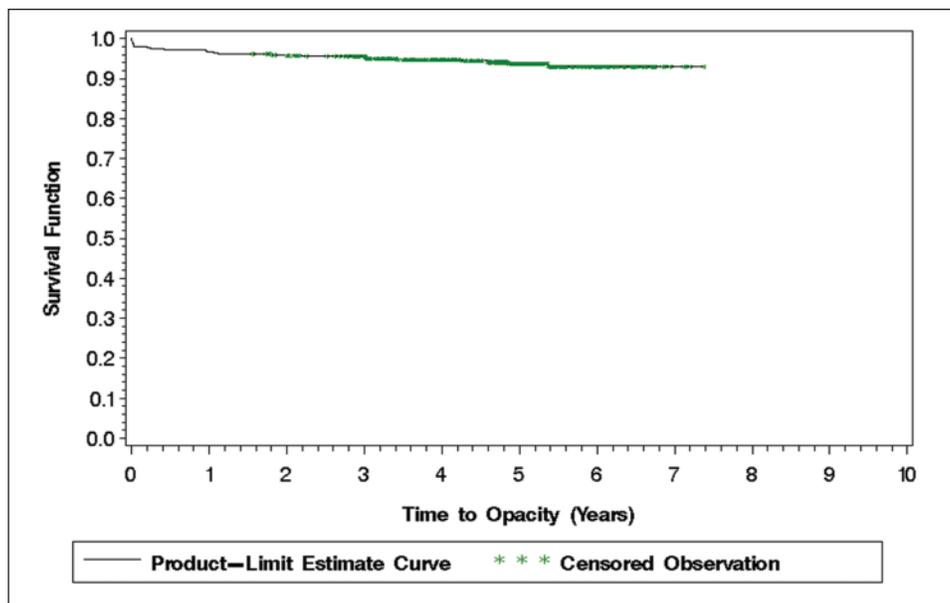


Figure 1. Kaplan-Meier survival analysis curve demonstrating the cumulative probability of not developing an anterior subcapsular LOCS opacity greater than trace.

process, 5 years of follow-up was requested. To date, of the 526 eye cohort, 468 (89%) eyes have been examined at 3 years or later, 384 (73%) at 4 years or later, and 311 (59%) at 5 years or later postoperatively. The mean age \pm standard deviation of the STAAR Myopia ICL US FDA cohort, at the time of implantation, was 36.5 ± 5.9 years (range: 22 to 45 years). Average follow-up was 4.7 ± 1.2 years (range: 1.6 to 7.4 years).

The standardized Lens Opacities Classification System (LOCS III) photographic images were used across all clinical centers in the STAAR Myopic ICL clinical investigation for the assessment of incidence, type, and severity of lens opacities. This standardized photographic grading system developed by Chylack et al¹⁰ was used to assess the development of cataracts and classifies lens characteristics into four major categories: nuclear color, nuclear opalescence, cortical appearance, and posterior subcapsular appearance. Anterior subcapsular appearance was assessed using the photographs for posterior subcapsular appearance but the slit-lamp examination localized the opacity anteriorly. Evaluations were performed with a dilated pupil and a grading score of 0.6 to 1+ (referred to as “trace” on a scale of 0 to 5.9) as the lower level of cutoff for reportability of subcapsular opacities. A score of 1+ was the smallest photographic grade in the grading system; this score represents <1% (approximately 0.7%) of the total observable area with opacity in a dilated pupil.

We previously reported, after 3 years of follow-up, the development of nuclear opacities in 5 eyes in 3 patients in this study cohort, which was believed to be unrelated to the ICL implantation. No posterior subcapsular or cortical opacities were observed. Two of these nuclear opacities had a small component of

anterior subcapsular opacities greater than trace and thus were included in the current analysis. With the current follow-up, no new opacities have been reported other than in the anterior subcapsular region and thus this report focuses solely on anterior subcapsular opacities, which appear to be the cataract type related to posterior chamber phakic IOL implantation.

Kaplan-Meier survival analysis was used to compare time course and rates of anterior subcapsular opacification and development of clinically significant cataract using SAS software (SAS Institute, Cary, NC).¹¹ The date of onset of the anterior subcapsular opacity was considered to be the first examination exhibiting any observable anterior subcapsular opacity. The date of onset of a clinically significant cataract was the first examination demonstrating an anterior subcapsular opacity associated with either a 2 or more line loss of best spectacle corrected visual acuity (BSCVA) or an increase in glare symptoms or cataract extraction.

RESULTS

Figure 1 presents the Kaplan-Meier survival analysis curve demonstrating the cumulative probability of not developing an anterior subcapsular LOCS opacity greater than trace. Figure 2 demonstrates the time curve for the development of anterior subcapsular opacities based on these probabilities. The cumulative probability estimate over the 7+ years of follow-up was 7% whereas 31 (5.9%) eyes were symptomatic and asymptomatic anterior subcapsular opacities were actually observed of the total population of 526 eyes. Trace or more anterior subcapsular opacities generally occurred early with 18 (58%) of 31 eyes initially seen in the first year, 21 (68%) eyes in the first 2 years,

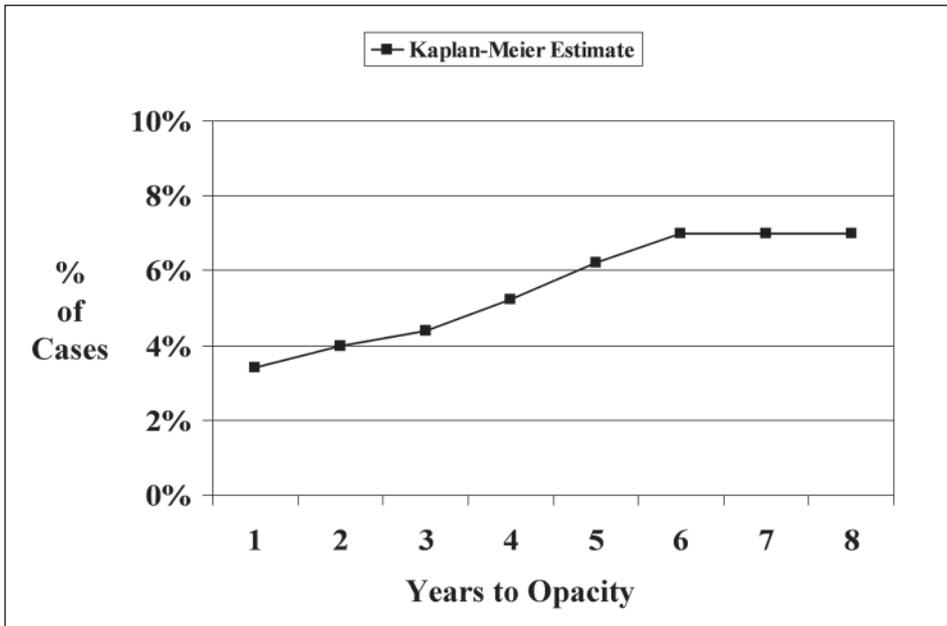


Figure 2. Kaplan-Meier estimates and time course for the development of anterior subcapsular LOCS opacity greater than trace in the 526 eye study cohort.

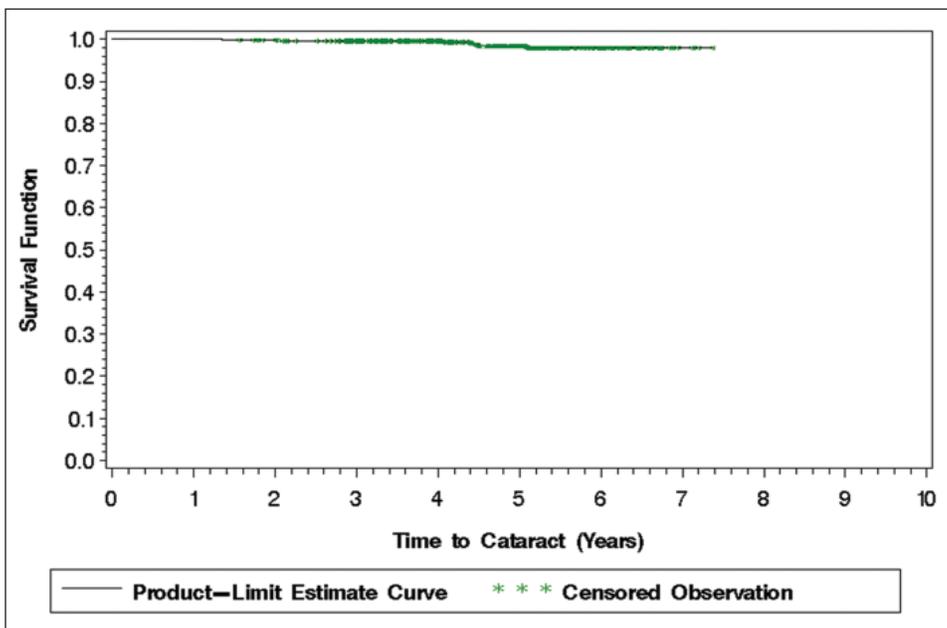


Figure 3. Kaplan-Meier survival analysis curve demonstrating the cumulative probability of not developing a clinically significant cataract.

and 23 (74%) eyes in the first 3 years. The difference between the Kaplan-Meier estimate and the actual observed percentage is due to the fact that the Kaplan-Meier estimate takes into account the differences in postoperative follow-up time of individual eyes within the 526 eye cohort.

Figure 3 presents the Kaplan-Meier survival analysis curve demonstrating the cumulative probability of not developing a clinically significant cataract. Figure 4 demonstrates the time curve for the development of clinically significant cataract based on these probabilities. The cumulative probability estimate over the 7+ years of follow-up was 2% whereas 7 (1.3%) clinically

significant cataracts were actually observed of the total population of 526 eyes.

The average preoperative spherical equivalent refraction of the 7 eyes with clinically significant cataracts was -16.40 diopters (D) (range: -12.75 to -20.00 D) whereas that of the entire US FDA cohort was -10.10 D (range: -3.00 D to -20.00 D). Although there were 7 (6.6%) clinically significant cataracts of the 106 eyes with preoperative myopia >12.00 D, there were none in the 420 eyes with preoperative myopia >12.00 D ($P < .0001$ with Fisher's exact test). Six (2.9%) of the 209 eyes of patients aged ≥ 40 years at the time of ICL implantation developed clinically significant

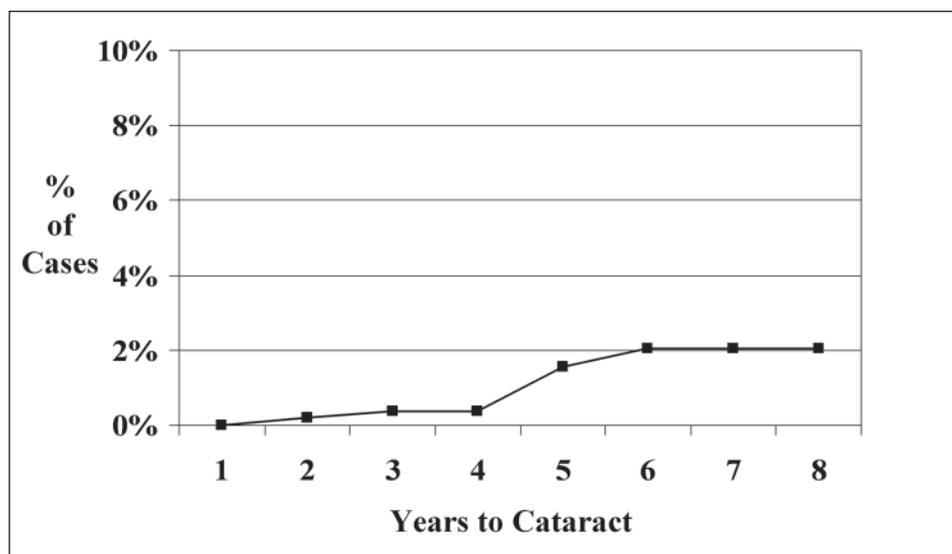


Figure 4. Kaplan-Meier estimates and time course for the development of a clinically significant cataract in the 526 eye study cohort.

cataracts whereas this occurred in only 1 (0.3%) of the 317 eyes of patients who were aged ≤ 40 years ($P < .02$ with Fisher's exact test). One of the clinically significant cataracts was due to inadvertent anterior chamber irrigation of a preservative-containing solution at surgery⁹ and was most likely not due to the ICL. All 7 clinically significant cataracts underwent cataract extraction with IOL implantation; postoperative BSCVA compared to BSCVA before ICL implantation improved by 2 lines in 1 eye, 1 line in 3 eyes, and was unchanged in the remaining 3 eyes for an average improvement of 0.7 lines of BSCVA.

DISCUSSION

Although a number of articles in the peer-reviewed literature support the relatively low rate of anterior subcapsular opacities and clinically significant cataract reported in this article (see Table 4 from Sanders and Vukich⁵), two recent European papers reported much higher rates of anterior subcapsular opacities. Gonvers et al¹² studied 75 eyes implanted with either the V3 (discontinued design) or V4 (Visian) ICL. They claimed no significant difference in outcome between the two lens designs. Twenty (27%) eyes developed symptomatic and asymptomatic anterior subcapsular opacities and of these, 2 (2.7%) were clinically significant cataracts. In their series, 46 (61%) eyes demonstrated poor vault (distance between the ICL and crystalline lens). In the US FDA trial, 87 V3 eyes were implanted as part of phase 1 and 2 data before the definitive phase 3 outcomes using the Visian (V4) model ICL (>500 eyes) and the rates of lenticular changes were previously reported.⁵ The V4 ICL was designed to provide 170 μm more vault based on height characteristics of the ICL independent of sizing considerations. In the US trial, at the time

of the previous report, the rate of symptomatic and asymptomatic anterior subcapsular opacities was 12.6% in the V3 group and 2.9% in the V4 (Visian) group ($P < .001$). The rate of clinically significant cataract was 9.2% in the V3 group and 0.8% in the V4 (Visian) group ($P < .001$). The incidence of poor vault was 23.6% in the V3 group and 4.3% in the V4 (Visian) group ($P < .001$). Given these dramatic differences in outcome between ICL designs it is surprising that Gonvers et al found no difference between V3 and V4 ICL designs although with their relatively small sample size, a type II statistical error (a false negative outcome) is likely.

Other factors that may explain the study differences include the fact that Gonvers et al did not use the sizing algorithm required in the US trial and their method resulted in ICLs being implanted that were routinely 0.5 mm smaller than would have been implanted in the United States. We have found in the US trial that implantation of smaller ICLs resulted in eyes with poorer vault. One trial investigator implanted 29% of his eyes with the smallest length ICL compared to only 4.5% of eyes for the remainder of the investigators ($P < .001$); this same investigator had an incidence of poor vault of 11% compared to 3.7% for the remainder of the investigators ($P = .02$). The mean ICL power implanted in the series by Gonvers et al was 17.60 D, implying a highly myopic population, which we have shown in our current study placed the patients at dramatically greater risk for anterior subcapsular opacities. Patient age might also have been a factor. In the 20 eyes that Gonvers et al reported with anterior subcapsular opacities, patients aged ≤ 62 years were implanted (average age 42 years). Gonvers et al also demonstrated that patients aged >40 years had three times the anterior subcapsular opacity rate as those aged <40 years ($P < .02$).

Thus inappropriate sizing, inclusion of V3 ICL data, extremely high myopia, and patient age may all have contributed to Gonvers et al's outcome. Despite all of this, their rate of clinically significant cataract was only 2.7%.¹²

Lackner et al¹³ studied 75 ICL patients (65 myopes and 10 hyperopes) implanted with 6 different ICL designs: 4 were discontinued and prototype models including the V3 model. Although the authors state that no significant difference was found among ICL designs, the probability of type II statistical error (a false negative outcome) would be very high with this sample size and number of groups. The reported clinically significant cataract rate was 17.3% and symptomatic and asymptomatic anterior subcapsular opacities were reported in 33% of eyes. Although patients were followed for as long as 7.4 years, no new symptomatic or asymptomatic anterior subcapsular opacities were observed after 2¼ years postoperatively. No information was given in the report regarding how ICL length was determined in this series. No vault was observed in 5 (6.7%) eyes and 2 (2.7%) of these developed anterior subcapsular opacities. Average myopia in this patient series was -16.23 D and patients as old as 60 years were implanted with the ICL. No possibility of surgically induced trauma was discussed although some of these opacities were seen early in the postoperative period. Differences between the US trial and the Lackner study could be due to the inclusion of hyperopic ICL designs and discontinued prototype model myopic ICLs, extremely high average myopia, and the allowance of older patients in the Lackner series as well as sizing methodology and surgical trauma uncertainties.

Our reported series constitutes the largest, most well-controlled study of the commercially available Visian ICL with a significant number of eyes (59%) followed for at least 5 years postoperatively. Generally in FDA trials a loss to follow-up rate of 10% a year is considered acceptable, therefore 59% follow-up at 5 years was reasonable especially because refractive surgery patients were asked to return 2 years after the initial agreed upon follow-up endpoint was completed. That being said, more follow-up would allow greater confidence in the conclusions of this study.

The cumulative probability estimate for the development of clinically significant cataract over the 7+ years of follow-up was 2% whereas the percentage actually observed was 1.3%. No loss of BSCVA following cataract extraction compared to before ICL implanta-

tion was observed. High myopia (>12.00 D) and increased age appeared to be risk factors. The cumulative probability estimate for the development of symptomatic and asymptomatic anterior subcapsular opacities over the 7+ years of follow-up was 7% whereas the percentage actually observed was 5.9%. These findings suggest that, with regard to cataract development and the ICL, the risk is sufficiently low to justify its use throughout its full approved myopic range and in patients aged 21 to 45 years, which is the approved age range in the United States.

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