

Predicting Extended Wear Complications from Overnight Corneal Swelling

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PURPOSE. To examine the hypothesis that the corneal overnight swelling response (ONSR) is a predictor of ocular complications in contact lens extended wear (EW).

METHODS. The Berkeley Contact Lens Extended Wear Study (CLEWS) was a randomized, concurrently controlled clinical trial in which more than 200 subjects in EW with rigid gas-permeable (RGP) lenses were observed for 1 year. After adapting to EW, subjects were randomized to either medium or high oxygen-permeable (Dk) RGP lenses and underwent clinical assessments, keratometry, and corneal pachometry at 3-month intervals.

RESULTS. The ONSR was directly related to lens Dk ($P = 0.01$) and exhibited substantial variability across subjects. The probability of remaining free of complications over time was not significantly lower for subjects with a mild ONSR compared with those with greater edema ($P = 0.84$). The risk of development of keratopathy was not significantly related to the ONSR (relative risk = 1.00).

CONCLUSIONS. The corneal ONSR is not a good predictor of ocular complications in 1 year of RGP EW. Lenses that cause little or no corneal edema are not necessarily safer for overnight wear. (*Invest Ophthalmol Vis Sci.* 2001;42:3150-3157)

Extended wear (EW) of contact lenses is associated with several types of adverse ocular response, some of which can lead to loss of vision.¹⁻⁴ Corneal hypoxia is thought to be an important factor in the development of many contact lens-related complications. For example, several clinical studies have reported greater incidences of microbial keratitis,⁴ acute red eye,⁴ epithelial microcysts,⁵⁻⁷ and endothelial polymegethism^{3,5} associated with hypoxic exposure in overnight lens wear. Laboratory studies have shown that corneal swelling,^{8,9} stromal acidosis,^{10,11} and impaired corneal hydration control^{3,11} occur when the cornea is experimentally subjected to hypoxia. A hypoxic environment also facilitates binding of the bacterium *Pseudomonas aeruginosa* to the corneal epithelium,^{12,13} promotes epithelial cell loss,^{4,12} and contributes to increased epithelial permeability.¹⁴ These results have led researchers to conclude that the risk of developing an adverse response is related to the hypoxic dose to which the cornea is

exposed during contact lens wear.³ Indeed, this belief has resulted in an industry-wide effort to develop lens materials that permit greater oxygen availability at the corneal surface in the hopes of reducing the risk of complications.

The likely connection between hypoxic dose and risk of contact lens-associated keratopathy (CLAK) has prompted researchers to monitor corneal swelling response as a means of assessing the impact of closed-eye contact lens wear on the cornea. There are several possible pathways by which corneal swelling can occur in overnight lens wear. If the oxygen transmissibility of a lens is inadequate to maintain normal corneal metabolism, lactate accumulates, creating an osmotic imbalance that causes the cornea to swell. The mechanical effects of a contact lens may include disruption of the epithelial cell layer, which could allow increased fluid uptake in the stroma. Corneal edema has also been linked to epithelial cytochrome P450 metabolites of arachidonic acid, in a rabbit model of closed-eye hydrogel lens wear.^{15,16}

In addition to the known pathways leading to edema in closed-eye lens wear, other considerations have contributed to the use of the corneal swelling response as a quantitative measure of the impact of contact lens wear. The corneal overnight swelling response (ONSR) is directly related to hypoxic dose yet varies considerably among lens wearers, thereby reflecting individual differences in sensitivity to hypoxic exposure.¹⁷⁻²⁰ In addition, edema due to contact lens wear is known to be associated with changes in corneal morphology and physiology such as polymegethism and pleomorphism of the endothelial cell layer,^{21,22} corneal striae,^{17,23} and impaired epithelial barrier function.²⁴ Although swelling of the cornea occurs naturally (e.g., during sleep) and thus is unlikely to pose a risk for complications directly, it does provide a clear indication of hypoxic stress and may also reflect adverse changes in corneal morphology and physiology in response to contact lens wear. For these reasons, it has become widely accepted that the degree of corneal swelling provides an indication of the impact of overnight contact lens wear on the cornea and hence is likely to be related to the risk of ocular complications.

Previous studies have suggested that for safe overnight wear, a contact lens should not induce more than approximately 8% swelling if the cornea is to recover to a normal level during day wear.⁸ In current practice, most clinicians considering the prescription of lenses for EW have come to expect contact lens manufacturers to provide corneal swelling data, and the US Food and Drug Administration (FDA) requires overnight swelling results from manufacturers as part of the approval process for EW lenses.¹⁸ The majority of studies addressing the clinical effects of contact lens wear also report corneal swelling data, and there are numerous statements in the literature to the effect that reduced corneal swelling response is a feature of "safer" lenses, and that monitoring corneal swelling can help to ensure the patient's safety in EW.^{13,18,19,25-28} It has been generally assumed that contact lenses that induce greater overnight corneal swelling pose a greater risk for development of keratopathy, and conversely

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that complications are less likely with lenses that induce little or no swelling. Although indirect evidence from many sources supports this assumption, to our knowledge there has not been a rigorous, longitudinal evaluation of corneal swelling response as a predictor of risk for CLAK.

The Berkeley Contact Lens Extended Wear Study (CLEWS) provides an opportunity to test this hypothesis directly. CLEWS was a randomized, concurrently controlled clinical trial in which 201 subjects were observed for 1 year of EW with rigid gas-permeable (RGP) lenses in a wide range of FDA-approved oxygen transmissibilities (Dk/t). In this article we use the clinical observations and corneal swelling data from CLEWS to estimate the risk of complications associated with the subject-specific edematous response to contact lens-induced hypoxia. The CLEWS data also permit us to examine more closely the assumption that ONSR can be used as a measure of contact lens safety for EW.

METHODS

Overview of CLEWS

The Berkeley Contact Lens Extended Wear Study was a single-center, randomized, concurrently controlled clinical trial structured in three stages. In stage 1 prospective subjects were oriented to the goals and procedures of the study and then examined to determine study eligibility and suitability for RGP lens fitting. In stage 2 subjects underwent a period of adaptation to contact lens wear, beginning with daily wear and progressing to full-time EW of 6 nights per week. Those who were able to achieve full-time EW then proceeded to stage 3, in which they were randomly assigned either medium- or high-Dk lenses (Paflufocon B or D; Paragon Vision Sciences, Mesa, AZ) for 12 months of full-time EW. These contact lenses are made from a siloxane-fluorocarbon polymer, with average Dk of 45×10^{-11} and 92×10^{-11} (cm²/sec)(ml O₂/ml · mm Hg) for the Paflufocon B and D lenses, respectively. The central thickness of the lenses averaged 0.17 mm and varied from 0.12 to 0.22 mm in both Dk groups, giving a range of Dk/t of 21 to 38 and 43 to 77 (cm · ml · O₂)/(sec/ml · mm Hg) for the Paflufocon B and D lenses, respectively. Of the 201 CLEWS subjects who successfully adapted to EW, 98 were randomized to the high-Dk group and 103 to the medium-Dk group. A stratified block randomization scheme was employed to ensure a balance of age and gender in the two study groups, as well as a balanced allocation of subjects to the two lens types throughout the course of the study. An in-depth discussion of the design and conduct of the CLEWS clinical trial and the primary clinical outcomes have been reported previously.^{29,30} All research was approved by the University of California Berkeley Committee for Protection of Human Subjects and adhered to the tenets of the Declaration of Helsinki for research involving human subjects; informed consent was obtained from all subjects.

Measurement Procedures and Analysis Variables

Pachometry measurements were taken to assess both the ONSR with the study lenses and the recovery of the cornea to open-eye steady state (OESS) thickness after experimentally induced edema. We used a modified Haag-Streit optical pachometer equipped with small light-emitting diodes to improve the patient's fixation and alignment. The instrument and calibration techniques have been described previously.³¹

Baseline overnight swelling measurements were made after the first successful week of EW adaptation, during which all subjects wore the same high-Dk lenses, but before randomization to the study lenses. Subjects reported for baseline (pre-randomization) measurements after discontinuing all lens wear for 1 week. The ONSR was also assessed 1 week after randomization, and at the 3-, 6-, 9-, and 12-month study visits. For these post-randomization visits, subjects slept with lenses on

for 4 to 6 nights before the ONSR assessment and reported to the laboratory wearing the lenses.

For the baseline ONSR assessment, afternoon (PM) OESS corneal thickness measurements were taken on each eye a minimum of 4 hours after awakening. Subjects were instructed to place a patch over the right eye before sleep that night that was not removed until 1 to 2 minutes before pachometry readings began the following morning (AM). An identical procedure was used in all post-randomization ONSR visits, except that subjects wore their lenses until immediately before the PM measurements and reinserted them immediately after, keeping their lenses on for overnight patching. Subjects failing to attend the AM visit or who did not keep the eye patched correctly until reaching the laboratory were rescheduled for the next available AM visit. If the subject was unable to reschedule within 1 week of the PM visit, then both the PM and AM visits were rescheduled.

The baseline (i.e., pre-randomization, no lens) ONSR reflects the normal physiological swelling that occurs when the eyes are closed in sleep. Because randomized subjects reported for follow-up visits with the assigned study lenses in place, the uncorrected ONSR (ONSR_u) includes the combined effects of the closed-eye state and contact lens-induced hypoxia. We also used a corrected ONSR (ONSR_c) by subtracting the baseline ONSR (closed-eye, no lens) from the post-randomization ONSR (closed-eye, with lens) readings. The ONSR_c thus reflects the actual overnight swelling response to the lenses, over and above the normal swelling occurring during sleep. Although the corrected ONSR_c variable is preferred, in that it more accurately reflects the swelling response to the lens, this correction has not been widely employed, and therefore we present analyses using both variables for comparison with previous studies.

The recovery of the cornea from experimentally induced edema was assessed at baseline (before randomization), after discontinuing lens wear for 1 week. For the corneal recovery assessment, low-Dk stress lenses were inserted in both eyes, and the subject lay supine with eyes closed for 1 hour to induce corneal edema. The lenses were then removed and pachometry measurements were taken throughout the day as the cornea recovered to OESS thickness. The eye to be measured first was randomly selected for each subject. We employed a nonlinear model of corneal recovery³² from which we obtained estimates of the swelling response to the stress lens and the late-afternoon OESS thickness. For analysis, we use the stress lens swelling response (SLSR), expressed in percentage increase over OESS thickness, which provides another measure of the subject-specific reaction to hypoxia at baseline, and as such may be a predictor of subsequent keratopathy in EW.

In this article we examine each of these corneal swelling response variables as a predictor of initial onset of CLAK. For analysis CLAK is defined as a suite of adverse ocular responses, including moderate to severe grades of 17 possible slit lamp findings (e.g., microcysts, corneal staining, infiltrates, striae), substantial changes in corneal curvature or refractive error, unresolvable pain-related symptoms, persistent lens binding, or multiple concurrent slit lamp findings. This definition of CLAK was based on survey responses from six optometrists not associated with CLEWS who were asked to indicate for each adverse condition the level of severity they thought would require intervention (e.g., changing lens parameters, prescribing medications, discontinuing lens wear). We elected to use this composite outcome because the incidence of any specific, serious complication (e.g., corneal ulcer) was very low or null over 1 year of RGP EW, and the majority of complications that did arise were diagnosed early and successfully treated by CLEWS clinicians. It is of interest to determine whether this composite CLAK outcome can be predicted, because it reflects the earliest signs of adverse response to lens wear, unacceptable ocular health, and conditions that may seriously threaten vision unless identified and treated by a clinician. An in-depth discussion of the criteria for defining CLAK has been presented previously.³⁰

Statistical Methods

The relationships between ONSR and lens Dk and Dk/t were analyzed using a mixed model approach (SAS Proc Mixed; SAS, Cary, NC).³⁵ We employed mixed effects analysis of variance models with fixed effects for time in EW after randomization, hypoxic dose expressed as Dk or Dk/t, and hypoxia-time interactions plus a single subject-level random effect. In our mixed models we specified a compound symmetric covariance structure and assumed a common covariance in the repeated measurements on a subject and independence between subjects.

Survival analysis methods were employed to assess the risk of complications associated with the level of corneal swelling. Many CLEWS subjects with pachometry data were observed for varying periods up to 12 months without development of an adverse condition. For example, a subject may have moved from the area, may have been unwilling to continue the time commitment required by the study, or may have been terminated for noncompliance (unrelated to any problem wearing the study lenses). These subjects provided censored observations and contributed less than 12 subject-months at risk for CLAK.

To account for censoring, the probability of remaining free of complications over time was estimated using the Kaplan-Meier method (Proc LIFETEST; SAS).³³ Kaplan-Meier provides a nonparametric estimate of the survival function, which gives the probability of surviving at least to a specified time without experiencing an adverse event. In using this method, we assume that survival and censoring times are independent and that the probability of survival is constant within each time interval in which a complication was observed. Subjects were stratified by level of corneal swelling, and the Kaplan-Meier survival curves for the strata were compared by log-rank test. The relative risk of keratopathy associated with the level of corneal swelling response was derived from Cox proportional hazards regression models (Proc PHREG; SAS³³). Cox proportional hazards models provide an estimate of the hazard function, which gives the instantaneous risk of development of a complication at a specified time, given survival to that time. A ratio of the hazard estimates for two different levels of corneal swelling provides a measure of the relative risk of complications associated with the swelling response. The Cox approach takes censoring of observations into account and assumes that the hazard rates in two strata are related by a multiplicative constant.

RESULTS

Overview

The first section that follows describes the baseline characteristics of the CLEWS subjects in the medium- and high-Dk groups, establishes that they were subject to distinctly different levels of oxygen availability at the cornea, and summarizes the outcomes for each corneal swelling variable by Dk group. In the second section, we confirm that the ONSR does represent a subject-specific reaction to hypoxic stress, in that it was directly related to the level of oxygen available on average, while exhibiting variability among subjects. Further, we determine whether the corneal swelling response changed over time and whether such a trend could be dependent on the level of oxygen. In the final section, we assess the risk of initial onset of keratopathy as predicted by the different measures of corneal swelling response.

Subjects, Treatment, and Outcomes

Because pachometry measurements were taken on nonrandom subsets of the larger CLEWS subject group, it was necessary to ensure that subjects with pachometry data did not differ substantially between Dk groups in their baseline demographic and ocular characteristics. The average age of CLEWS subjects

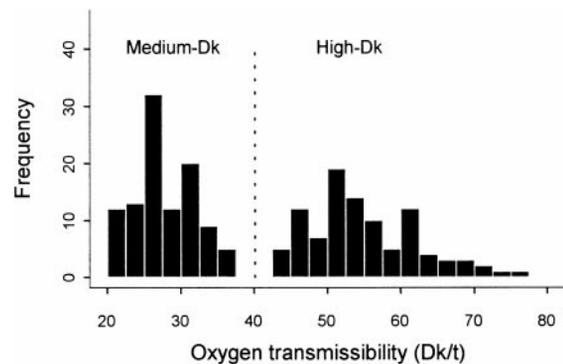


FIGURE 1. Histogram of Dk/t in the medium- and high-Dk lens groups. Disjoint distributions confirm that the two study groups received different hypoxic doses. Dk/t units are 10^{-9} (cm · ml · O₂)/(sec · ml · mm Hg).

was 23 years, there were approximately 56% males and 44% females, Caucasian and Asian North Americans accounted for approximately 75% of the ethnic makeup, and refractive errors averaged approximately 2.75 diopters in the direction of myopia. For the CLEWS subjects with pachometry measurements, we found no clinically important differences between the two Dk groups in these baseline characteristics, nor did the pachometry subgroups differ from the larger CLEWS subject group from which they were selected. We may therefore conclude that any apparent group differences in outcomes we find will not be due to confounding by these variables and that our corneal swelling results will be generally applicable to the larger CLEWS study population.

With the medium- and high-Dk lenses used in CLEWS, two distinct levels of oxygen would be available to the cornea if all other lens parameters were held constant. However, the amount of oxygen reaching the cornea is more closely related to Dk/t, which is a function of the permeability of the material and the thickness of the lens. Because study lenses of varying central thickness were made to achieve the correct vertex power for each subject, there was a resultant range of Dk/t across subjects within each Dk group. The histogram shown in Figure 1 reveals a bimodal distribution of Dk/t with a clear separation between the two Dk groups. Because the distributions of Dk/t in the two study groups are completely disjoint, we may conclude that the subjects in the medium- and high-Dk groups participating in pachometry measurements received distinctly different hypoxic doses.

Table 1 shows the means and 95% confidence intervals (CI) for each of the corneal swelling variables, along with the number of subjects with available data, stratified by Dk group. Pre-randomization SLSR was comparable in the two Dk groups (~17% above OESS, on average). Baseline overnight swelling was approximately 2.3% in both groups, whereas post-randomization overnight swelling was greater on average in the medium-Dk group for all the ONSR variables. The first ONSR_c taken shortly after randomization was 4.8% for the medium-Dk group on average with subjects ranging from 0% to 14%, whereas the high-Dk group averaged 2.4% ONSR_c with corneas in individual subjects swelling from 0% to 9%. The first uncorrected ONSR_{uc} averaged 6.6% with corneal swelling ranging from 1% to 17%, and 5.1% with corneal swelling ranging from 0% to 10% in the medium- and high-Dk groups, respectively. ONSR readings began after the stress lens measurement was discontinued from the CLEWS trial, and many subjects had already completed part of the 12-month follow-up period before ONSR data collection began. Therefore, not all subjects

TABLE 1. CLEWS Corneal Swelling Results

	Medium Dk			High Dk		
	<i>n</i>	Mean Swelling (%)	95% CI	<i>n</i>	Mean Swelling (%)	95% CI
ONSR _c						
First	20	4.77	(3.01, 6.54)	13	2.43	(0.65, 4.21)
Median	20	4.40	(2.83, 5.97)	13	2.00	(0.82, 3.17)
ONSR _{uc}						
First	40	6.55	(5.32, 7.78)	35	5.09	(4.29, 5.88)
Median	40	6.21	(5.09, 7.33)	35	4.96	(4.33, 5.58)
SLSR	58	16.69	(15.61, 17.78)	59	16.74	(15.29, 18.20)

Shown are the first ONSR after randomization, the median pre-CLAK ONSR, and the SLSR. ONSR variables are shown both uncorrected and corrected for baseline (no lens) swelling.

with uncorrected post-randomization ONSR_{uc} ($n = 75$) had an ONSR_c corrected for baseline ($n = 33$).

In summary, our pachometry subgroups with medium- and high-Dk lenses were well matched in baseline characteristics, received distinctly different hypoxic doses, and exhibited correspondingly different levels of corneal swelling response on average. In addition, a post hoc analysis found that the risk of keratopathy did not differ significantly between subjects with and without pachometry data ($P = 0.27$) and that the reasons for missed visits (e.g., vacation travel) and censoring (e.g., moving out of area) were not related to ocular outcomes. We therefore had the conditions necessary to test our study hypothesis and evaluate the use of the corneal swelling response as a predictor of subsequent CLAK.

Hypoxic Dose and Corneal Swelling Response

Before assessing the risk of keratopathy associated with the level of corneal edema, we want to confirm that the ONSR represents a subject-specific physiological reaction to hypoxic stress and thus may be useful as a predictor of CLAK. In this section we verify that the ONSR was directly related to hypoxic dose and exhibited variability among our subjects and that repeated ONSR measurements before initial onset of CLAK did not systematically change over time.

Figure 2 shows the trend in pre-CLAK ONSR_c (corrected for baseline), stratified by Dk group. The ONSR_c was significantly greater in the medium-Dk group ($P = 0.01$) when adjusted for time in EW and group-time interactions, indicating that overnight corneal swelling is directly related to the oxygen permeability (Dk) of the lens in our subjects. There was no significant time effect on ONSR_c ($P = 0.52$), which suggests that our subjects did not adapt (i.e., show a systematic increase or decrease in swelling response) to continued hypoxic exposure over time. There was no significant interaction between time in EW and Dk ($P = 0.76$), suggesting that the ability of our subjects' corneas to adapt to hypoxic exposure over time was not dependent on the level of hypoxia. With no interaction term, the fixed-effects parameter estimates and their standard errors changed only slightly. Similar results were found for pre-CLAK ONSR_{uc} (uncorrected), with a significant Dk group effect ($P = 0.05$) and no significant time effect ($P = 0.63$) or group-time interaction ($P = 0.84$).

We repeated these models using the lens-specific Dk/t in place of the Dk group categorization. Figure 3 shows that when the oxygen transmissibility (Dk/t) is considered on an individual basis, a significantly greater ONSR_c is predicted for greater hypoxic dose ($P = 0.01$). Adjusting for the minimal effects of time in EW and hypoxic dose-time interactions, our models show that a decrease in Dk/t of 25 units (which is

approximately the difference in mean Dk/t between our two study groups) results in an increase in overnight corneal swelling of approximately 2%. With Dk/t as a predictor, we did not find the effects of time in EW ($P = 0.93$) or hypoxic dose-time interactions ($P = 0.86$) to be significant. With no interaction term, the precision of the Dk/t parameter estimate was reduced further to $P < 0.01$, whereas the effect of time in EW was still insignificant ($P = 0.49$). Similar results were found for pre-CLAK ONSR_{uc}, with a significant Dk/t effect ($P = 0.03$) and no significant time effect ($P = 0.86$) or group-time interaction ($P = 0.96$).

From these results we conclude that our subjects, on average, exhibited greater overnight corneal swelling with increasing hypoxic dose, although with considerable individual variability in response. In addition, it appears that the repeated ONSR measurements before onset of CLAK did not increase or decrease linearly over time, and therefore it is reasonable to use an average of these early ONSR measurements as a possible predictor of subsequent CLAK. In the final section that follows we estimate the relative risk of CLAK as predicted by the five different measures of corneal swelling response: the SLSR, the first ONSR_c and ONSR_{uc} taken after randomization, and the medians of all ONSR_c and ONSR_{uc} measurements taken before initial onset of CLAK.

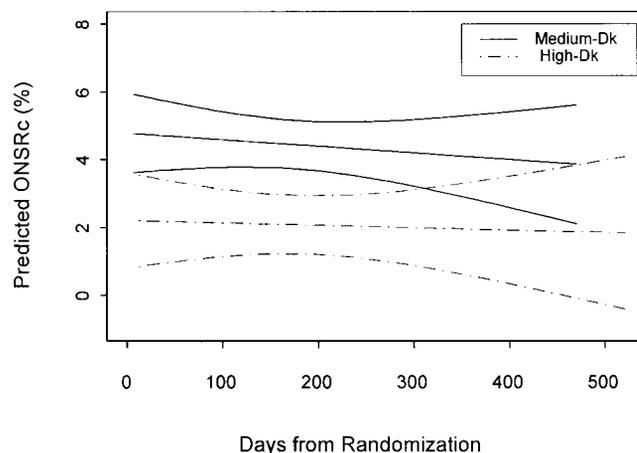


FIGURE 2. Predicted ONSR_c over time in the medium- and high-Dk lens groups, with approximate 95% confidence bounds. The medium-Dk group exhibited significantly more overnight corneal swelling than the high-Dk group.

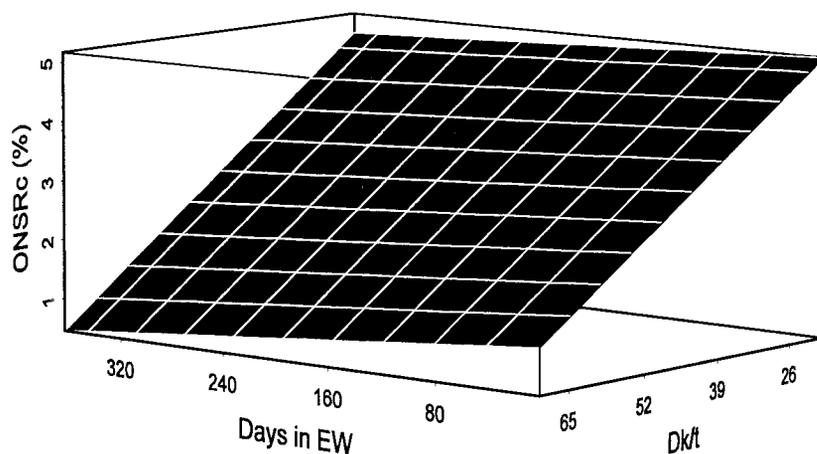


FIGURE 3. Predicted $ONSR_c$ over time as a function of lens Dk/t. Significantly greater overnight corneal swelling occurred with lower oxygen levels. The minimal effects of time in EW and oxygen-time interaction were not significant.

Corneal Swelling Response and Keratopathy

Table 2 shows, for each corneal swelling variable, the number of subjects in each group that had a CLAK event before 12 months or were censored before initial onset of CLAK for reasons unrelated to lens wear. The majority of subjects in both Dk groups had at least one adverse event during the 12-month EW follow-up period, although only one subject with medium-Dk lenses who had persistent lens adherence was forced to completely discontinue lens wear. In all other cases, the complication was treated successfully and lens wear was eventually resumed. The most commonly observed adverse conditions included redness and staining of the conjunctiva, central and peripheral corneal staining, infiltrates, striae, endothelial polymegethism, persistent lens adherence, and reported symptoms of red eye, foreign-body sensation, and general discomfort or pain. Most of these complications were observed across Dk groups, with the exception of striae, infiltrates, and polymegethism, which occurred mostly in the medium-Dk group. There were no indications of microbial keratitis, neovascularization, or corneal ulcers in any of our subjects, primarily because of early diagnosis of adverse conditions and intervention by CLEWS clinicians.

Using the Kaplan-Meier method, we estimated the probability of remaining free of CLAK over time and compared the homogeneity of survival curves by log-rank test for subjects stratified on the overall median ONSR. Figure 4 shows that subjects exhibiting less than the overall median ONSR were no less likely to experience CLAK than were subjects in the upper half of the ONSR range. There was no significant difference in the probability of remaining free of CLAK between subjects with high or low corneal swelling, for either the first post-randomization $ONSR_c$ ($P = 0.22$) or the $ONSR_{uc}$ ($P = 0.78$). We repeated these analyses for the median pre-CLAK $ONSR_c$

and $ONSR_{uc}$ and the SLSR with similar nonsignificance in each case.

In addition to a median-based stratification, we compared the survival curves for subjects above and below a threshold based on the widely accepted safe overnight swelling level of 8% (uncorrected). For our $ONSR_c$ variables, this corresponds to a threshold of approximately 5.7% after correction for baseline swelling, which averaged 2.3%. In these analyses, we found no significant differences in probability of remaining free of CLAK between subjects with overnight swelling above or below the thresholds. Log-rank tests of homogeneity of the survival curves showed no significant differences between the high and low strata for the first post-randomization $ONSR_c$ ($P = 0.84$), the first $ONSR_{uc}$ ($P = 0.90$), the median pre-CLAK $ONSR_c$ ($P = 0.53$), or the median pre-CLAK $ONSR_{uc}$ ($P = 0.61$).

Cox proportional hazards models allowed us to estimate the relative risk of development of a complication associated with the level of corneal swelling. Table 3 shows the estimated risk ratios and 95% risk limits associated with a 1% increase in the first post-randomization $ONSR_c$ and $ONSR_{uc}$. A risk ratio equal to 1 would indicate no difference in risk of CLAK with increased corneal swelling, whereas a risk ratio of more than 1.00 reflects a higher risk predicted by greater corneal swelling. The risk ratios shown in Table 3 are very close to (and not significantly different from) 1.00, as were the risk ratios obtained using the other three corneal swelling variables, both as independent predictors and as adjustments to the effects of hypoxic dose (Dk/t). Table 3 also shows that the risk of keratopathy was not significantly greater with corneal swelling above a threshold of 8% for $ONSR_{uc}$ or 5.7% for $ONSR_c$. The 95% risk limits permit us to rule out all but fairly minor elevations in risk of keratopathy associated with increases in corneal swelling. For example, an 8% increase in $ONSR_{uc}$ results in a relative risk of 1.00, with an upper limit of approximately 1.76. In this case a modest elevation in risk for high levels of swelling is within the upper confidence limit and thus cannot be completely ruled out; however, our best estimate is still that there is no increased risk.

In summary, we found no significant difference in the probability of remaining free of CLAK over time between subjects with high or low overnight corneal swelling, nor did we find any indication of increased risk of CLAK with greater overnight edema. Kaplan-Meier survival curves for time-to-CLAK were relatively homogeneous for strata based on either the median swelling or an 8% threshold, for all corneal swelling response measures. In addition, the estimates of the relative risk from all our models are consistent with the hypothesis that corneal swelling does not predict initial onset of CLAK. The confidence

TABLE 2. Number of CLEWS Subjects with Pachometry Data, Failing due to CLAK, and Leaving the Study for Reasons Unrelated to Lens Wear without Having a CLAK Event (Censored)

	Medium Dk			High Dk		
	$ONSR_c$	$ONSR_{uc}$	SLSR	$ONSR_c$	$ONSR_{uc}$	SLSR
Pachometry subjects	20	40	58	13	35	59
Subjects with CLAK	20	39	48	11	31	52
Censored	0	1	10	2	4	7

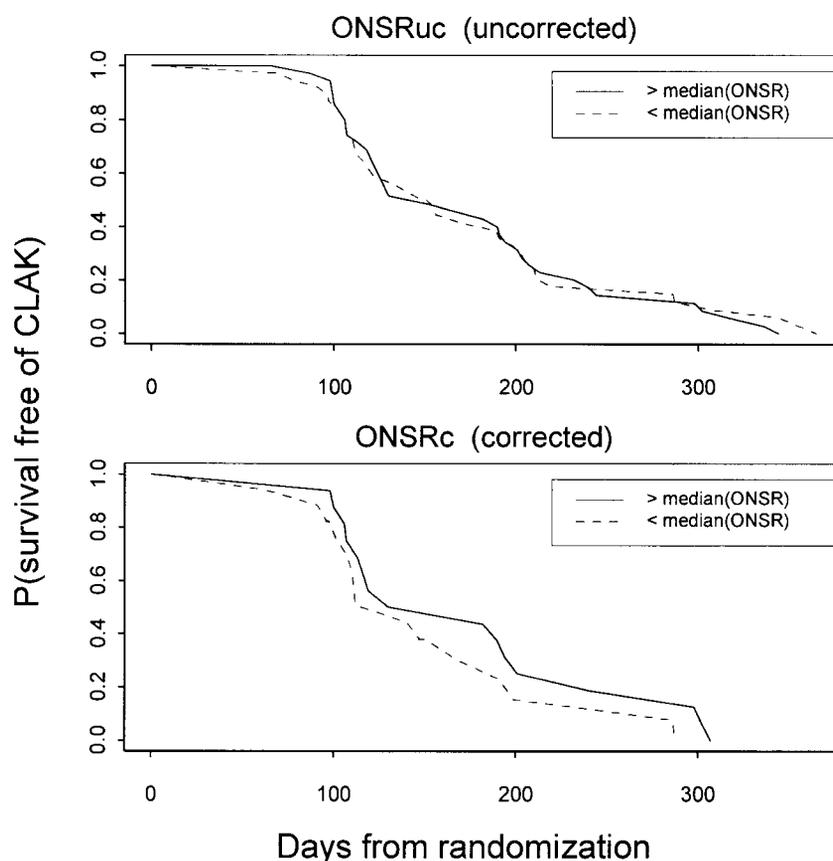


FIGURE 4. Estimated probability of remaining free of CLAK over time, as predicted by ONSR. Subjects whose corneas swelled less than the median ONSR (both uncorrected and corrected) were no less likely to experience complications than subjects with greater corneal swelling.

bounds on the risk ratios permit us to rule out all but minor elevations in risk associated with increases in corneal swelling, with point estimates suggesting no increase in risk.

DISCUSSION

The CLEWS clinical trial provided an opportunity to examine contact lens-induced corneal swelling and development of keratopathy in 201 subjects wearing RGP EW lenses. In this analysis, we sought to determine whether the ONSR could serve as a surrogate for risk of onset of keratopathy in overnight lens wear, as has been commonly assumed. There is ample indirect evidence to suggest that the ONSR could serve as a measure of contact lens safety in EW; however, in this analysis we have shown that corneal swelling does not provide useful predictive information for the initial onset of CLAK in 1 year of RGP EW. We quantified the corneal swelling response to contact lens-induced hypoxia in several different ways and considered each variable as a separate predictor of CLAK and as a subject-specific adjustment to the effect of hypoxic dose.

TABLE 3. Risk Limits from Cox Proportional Hazards Models of Time to Initial Onset of CLAK as a Function of Increased Overnight Corneal Swelling

Predictor	% Increase	Risk Ratio	95% Risk Limits	
			Lower	Upper
First ONSR _{uc}	1.0	1.00	0.93	1.07
	8.0	1.00	0.56	1.76
First ONSR _c	1.0	0.96	0.86	1.07
	5.7	0.78	0.41	1.48

In no case did we find an elevated risk of initial keratopathy associated with greater corneal swelling.

Do these results completely invalidate the use of overnight corneal swelling as a measure of contact lens safety? First, it must be kept in mind that our results apply to the specific conditions obtaining in CLEWS, and inferences cannot necessarily be drawn to substantially different study populations, lens types other than RGP, different Dk/t ratings, longer observation periods, or other wearing schedules (e.g., daily wear). Second, although corneal swelling was not associated with our composite keratopathy outcome, it is possible that distinguishing metabolically related complications such as striae and endothelial polymegethism from the mechanical effects of the lens on the ocular surface would reveal a stronger predictive relationship. However, because the CLEWS incidence rates for specific complications with 1 year of RGP wear were very low, such a detailed analysis would require further study with larger sample sizes or longer observation periods. Third, there are two facets to the use of corneal swelling as a diagnostic measure for the safety of overnight lens wear, and the CLEWS data permit us to adequately address only one of them. Ideally, a diagnostic such as corneal swelling should possess both specificity and sensitivity relative to the outcome of interest—that is, both a low rate of false positives (i.e., substantial edema but no complications) and a low rate of false negatives (i.e., complications without substantial edema). In this analysis, corneal swelling had poor sensitivity as a risk measure, because a large number of subjects who did not display greater corneal swelling nevertheless developed complications. However, because the majority of subjects in both Dk groups had at least one adverse event of some sort, we did not have a substantial control group without complications and therefore cannot draw definitive conclusions about the specificity of corneal

swelling to CLAK cases. In other words, we cannot reliably estimate the rate of false positives, because so few subjects remained free of complications.

In spite of these analytical limitations, it is clear that measuring overnight corneal swelling on a single occasion in a small group of subjects is of little use in assessing the safety of RGP lenses for overnight wear. Although it is not known whether greater corneal swelling is specific to lenses that pose a higher risk of keratopathy, we have shown in this article that the swelling response to overnight lens wear has poor sensitivity and many subjects who do not display greater edema will nevertheless develop lens-related complications. It is possible that lenses that result in substantially greater overnight swelling pose a greater risk for keratopathy (although we cannot tell from the CLEWS data); however, a lower ONSR does not imply a lesser risk for complications or a safer contact lens.

Although the usefulness of corneal swelling in predicting keratopathy appears to be limited, some means of reliably assessing the safety of a lens for EW is clearly needed. Several alternative measures of risk are suggested by recent studies, such as epithelial permeability,^{14,34,35} rate of tear exchange under the contact lens,³⁶⁻³⁸ and profiles of contact lens movement over the ocular surface.^{36,39,40} Evaluation of fluorescein staining patterns and bacterial culture from eye wash samples may also contribute predictive information. It is interesting that all these assessments reveal differences between RGP and soft contact lens (SCL) EW, because many serious types of complications associated with SCL (e.g., corneal ulcer) are observed in the absence of corneal edema,⁴¹ whereas no such adverse responses were observed, even among our medium-Dk RGP subjects whose corneas swelled substantially. This suggests that tear exchange and hypoxic or mechanical effects on the corneal epithelium could be more closely related to the mechanisms of keratopathy than the corneal edema induced by increased lactate concentration and thus may prove to be better predictors of keratopathy (perhaps in conjunction with oxygen ratings and/or corneal swelling in some cases).

In summary, it is clear that the degree of contact lens-induced corneal swelling is not a good predictor of risk for development of keratopathy in overnight wear, at least for RGP lenses in the FDA-approved range of Dk/t. In assessing the safety of RGP lenses for EW, the degree of induced corneal swelling need not be considered a major risk factor, except possibly in cases in which lenses tend to induce extreme edematous reactions in some subjects. Statements in the past literature (scientific, educational, promotional, and regulatory) relating to lens safety or risk of complications that have been based partly on overnight corneal swelling results must be viewed with these limitations in mind.

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